Acupuncture for Chronic Migraine and Chronic Tension-type Headache

Final Evidence Report

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Acupuncture for Chronic Migraine and Chronic Tension-type Headache

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision-makers, clinicians, patients, and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Aggregate Analytics, Inc. is a contract research organization whose team has over fifteen years of experience in performing health technology assessments, comparative effectiveness reviews, and systematic reviews for a variety of clients based on accepted methodologic standards for such research. AAI's mission is to assist healthcare professionals and organizations in the objective synthesis and generation of evidence to improve future healthcare delivery by providing timely, methodologically rigorous, transparent services and quality evidence synthesis products.

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Abbreviations

AE:	Adverse event
CI:	Confidence interval
CM:	Chronic migraine
CTTH:	Chronic tension-type headache
HA:	Headache
F/U:	Follow-up
HI:	Headache Index
MD:	Mean difference
MIDAS:	Migraine Disability Assessment
NC:	Not calculable
NR:	Not reported
NS:	Not statistically significant
RCT:	Randomized controlled trial
RD:	Risk difference
RoB:	Risk of bias
RR:	Risk ratio
SD:	Standard deviation
SF-36:	Short Form-36
SMD:	Standardized mean difference
SIP:	Sickness Impact Profile
UC:	Usual care
VAS:	Visual Analog Scale
WL:	Waitlist

Executive Summary

Introduction

Headache disorders are associated with substantial impact on the physical, psychological, and social well-being of patients, in addition to being associated with substantial healthcare costs. Headache disorders 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.

Headache is considered primary when a disease or other medical condition does not cause the headache. Tension-type headache is the most common primary headache. It is characterized by a dull, non-pulsatile, diffuse, band-like (or vice-like) pain of mild to moderate intensity in the head, scalp, or neck. There is no clear cause of tension-type headaches even though it has been associated with muscle contraction and stress. Migraines are the second most frequently occurring primary headaches. Migraine headache is characterized by recurrent unilateral pulsatile headaches lasting 4- 72 hours; nausea, vomiting and sensitivity to light and sound are frequent co-existent symptoms. The two major subtypes are common migraine (without aura) and classic migraine (with aura or neurological symptoms). Migraine and tension headache attacks are classified as episodic if they occur less than 15 days per month. Headaches are considered chronic if they occur 15 or more days each month for at least 3 months or more than 180 days a year. Episodic migraine and tension-type headache may evolve to become chronic. Chronic tension-type headache (CTTH) and chronic migraine (CM) features differ but the two may coexist.

Usual management of tension-type headache and migraine includes pharmacotherapy, psychological therapy and physical therapy. While abortive therapy for acute episodes is necessary for both CTTH and CM, the focus of management for CCTH and CM is on preventive treatments. Primary goals of preventive therapy are to reduce the number, severity and/or duration of acute episodes and reduce disability. A variety of interventions may be used to manage CM and chronic tension-type headache. Acupuncture may be part of the management of chronic headache that also includes medications. Acupuncture is commonly used in headache disorders. In 2006, a US survey found that 9.9% of patients that had used acupuncture used it to treat headache disorders. This report will focus on use of acupuncture for the prevention of CTTH and CM. Acupuncture has been used for thousands of years and involves the insertion of solid, filiform needles that are thin and flexible into the body (with or without manual or electrical stimulation) to stimulate acupuncture points, including trigger points, and other tissues to promote health and treat organic or functional disorders directly or indirectly.

Policy Context/Reason for Selection

A Health Technology Assessment (HTA) titled, *Treatment of chronic migraine and chronic tension-type headache*, was published on April 14, 2017, by the Health Care Authority (HCA). Acupuncture was one of the interventions investigated for the treatment for chronic headache. The Findings and Coverage Decision was adopted on July 14, 2017 and revised on July 13, 2018. At that time, the Health Technology Clinical Committee decided not to cover acupuncture for chronic migraine or for chronic tension headache. Since then, additional studies have been published on the use of acupuncture for these

headache types. For these reasons, an update report specific to the use of acupuncture was requested by the Health Technology Assessment Program.

Objectives

The primary aim of this assessment was to systematically review and synthesize published evidence on the efficacy, safety, and cost-effectiveness of acupuncture compared with standard active treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults. This re-review followed the same basic Key Questions, definitions, and scope as the prior report as they apply to acupuncture.

Key Questions and Scope

Specific key questions, as formulated by the HCA/Agency for the original report, have been modified to reflect the focus of this update on the use of acupuncture for chronic migraine, chronic tension-type, and chronic daily headache:

In adults with chronic migraine, chronic tension-type, or chronic daily headache:

1. What is the evidence of the short- and long-term **efficacy and effectiveness** of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
2. What is the evidence regarding short- and long-term **harms and complications** of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
3. Is there evidence of **differential efficacy, effectiveness, or safety** of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
4. What is the evidence of **cost-effectiveness** of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?

A summary of the inclusion and exclusion criteria (i.e., scope) is provided below; detailed inclusion and exclusion criteria can be found in Table 4 of the full report. Again, the scope of the report remained the same as the prior HTA except for acupuncture as the sole intervention of interest.

Scope:

Population: Adults with chronic migraine (with or without aura) or chronic tension-type headache. Chronic headache is defined as 15 or more days each month for at least 3 months or more than 180 days a year (International Classification of Headache Disorders, 3rd edition definition). 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 in the original report and chronic daily headache was defined as combined migraine and tension headache.

Interventions: Acupuncture

Comparators: Standard/usual active treatment(s), sham, placebo, waitlist or no treatment.

Outcomes: Primary clinical outcomes are: 1) Proportion of responders (e.g., at least 50% reduction of headache frequency from baseline for 3-4 months following treatment); 2) Complete cessation/prevention of headache; reduction in mean number of episodes and/or headache days; 3) Function/disability with a focus on validated measures (e.g., Migraine Disability Scale [MIDAS]); 4) Harms, treatment-related adverse events, treatment discontinuation due to adverse events. Economic outcomes are incremental cost effectiveness ratio (ICER) or similar outcome.

Studies: Studies must report at least one of the primary outcomes**.** Focus was on studies with the least potential for bias such as high-quality systematic reviews of randomized controlled trials (RCTs) which focus on the population of interest for this review and high-quality (low risk of bias) RCTs for Key Questions 1-2. For Key Question 3, RCTs that stratified on baseline patient characteristics and evaluated effect modification were included. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, cost-benefit studies) were sought for Key Question 4.

Timing: Focus was on intermediate (>8 weeks to <12 weeks) and long term (≥ 12weeks) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Methods

The scope of the original report and final key questions and been refined based on input from clinical experts and public comments received. For the 2017 report, clinical expert input was sought to confirm critical outcomes on which to focus; these remained the same for this update review. For this update, public comments received following topic posting for a stand-alone review for acupuncture and on draft key questions were reviewed and considered. At the request of the HTA program, the general scope of this re-review (e.g., headache definitions and population inclusion criteria) remained the same as the prior HTA with the exception that acupuncture is the sole intervention of interest.

The terminology and criteria related to headache classification has evolved over the last few decades and there is inconsistency in how headaches are described in the literature and clinically. Consequently, the terminology used in clinical studies has also varied. For the purposes of the original review and this update report, we have classified studies of patients presenting with a coexistence of migraine and tension type headache that, in combination, occur >15 days per month, as patients with chronic daily headache, which is generally consistent with the terminology used by authors. While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more headache days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions and timeframes (e.g., 28-day period or 30-day period for a month). Given these variations, for the purposes of this report, trials reporting populations with a mean of ≥12 headache days per month or ≥12 headache episodes or attacks per month or equivalent were considered to meet the criteria for chronic headache.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments. For the systematic review portion of the report, studies were selected for inclusion based on pre-specified criteria detailed in the full report. In addition to citations from structured formal searches, citations

suggested by stakeholders were also evaluated against the stated inclusion/exclusion criteria. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[7] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Review*.[1] Based on these quality criteria, each study chosen for inclusion for a Key Question was given a risk of bias (RoB) rating of "low", "moderately low", "moderately high" or "high" based on the degree to which valid methods for patient selection, inclusion, allocation to treatment were used as well as the comparability of intervention groups, attrition and use of appropriate means for controlling bias. These are described in detail in the full report. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et. al. in conjunction with consideration of epidemiologic principles that may impact findings.[11]

An overall Strength of Evidence (SOE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. The SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[3-5] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1] The strength of evidence was based on the highest quality evidence available for the primary outcomes. Briefly, bodies of evidence consisting of RCTs were initially considered as High strength of evidence. The strength of evidence could be downgraded based on the limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting/publication bias). When assessing the SOE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned (*a priori*) and whether a test for homogeneity or interaction was done. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome or the body of evidence has unacceptable efficiencies precluding judgment. If no evidence was identified, this was stated as such.

Evidence on acupuncture from the prior report was combined with new evidence. Determination of SOE considered the whole body of available evidence.

We report following primary outcomes here:

- The proportion of treatment responders is a primary outcome of interest; it was variable defined across trials (e.g., 50% or 35% of patients with reduction in headache days or headache score).
- Reduction in mean frequency of headache was the most common outcome reported. Studies reported this as frequency of attacks/episodes, overall headache days or headache days for a specific headache type (e.g., migraine days).
- Function/disability measured by validated measures.

Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using Mantel-Haenszel and DerSimonian-Laird methods and focused on the primary outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Sensitivity analyses were considered excluding outlying data and related to clinical heterogeneity.

Results

The prior report identified and included six trials (across 9 publications)[2,8,13,14,16-18,20,21] of acupuncture for the treatment of chronic migraine or chronic tension-type headache. No trials evaluating acupuncture for chronic daily headache were included in the prior report. This update added three trials[6,9,10] to the evidence base for a total of nine trials. All newly included trials assessed acupuncture for chronic migraine. No trials evaluating acupuncture for chronic tension-type headache or chronic daily headache and no formal economic studies that met inclusion criteria were identified by our update search. The table below provides a summary of the evidence base for this update.

Number of studies included for each headache type

Comparisons	2017 Report	2022 Update	Total
CHRONIC MIGRAINE			
Acupuncture vs. UC/Sham/WL	1 RCT[17,18]	2 RCTs[6,9]	3 RCTs (across 4 publications)[6,9,17,18]
Acupuncture vs. Pharmacological treatment*	1 RCT[20,21]	1 RCT[10]	2 RCTs (across 3 publications)[10,20,21]
Acupuncture vs. Botulinum toxin*	None identified.	1 RCT[10]	1 RCT[10]
TOTAL			5 RCTs (across 7 publications) [6,9,10,17,18,20,21]
CHRONIC TENSION-TYPE HEADACHE			
Acupuncture vs. Sham	2 RCT[8,16]	None identified.	2 RCTs[8,16]
Acupuncture vs. Physical Training†	1 RCT (2 publications)[13,14]	None identified.	1 RCT (across 2 publications) [13,14]
Acupuncture vs. Physiotherapy	1 RCT[2]	None identified.	1 RCT[2]
Acupuncture vs. Relaxation Training†	1 RCT (across 2 publications)[13,14]	None identified.	1 RCT(2 publications)[13,14]
TOTAL			4 RCTs (across 5 publications)[2,8,13,14,16]
CHRONIC DAILY HEADACHE			

	None identified.	None identified.	None identified.

*One study (Naderinabi 2017)[10] had 3 arms: acupuncture, Botulinum toxin, and sodium valproate.

†One study (Soderberg 2006, 2011)[13,14] had 3 arms: acupuncture, physical training, and relaxation training.

Below is a summary comparing key findings from the 2017 and 2022 update report. The 2022 report included only acupuncture as the intervention of interest; otherwise, the scope of the report remained the same as the prior HTA. Key findings for all populations are presented below.

Results summaries comparing key findings between the 2017 report and the 2022 update

Key Results From 2017 HTA Report	Results From This 2022 Updated Report
Evidence of efficacy and safety of acupuncture for adults with chronic migraine, chronic tension-type headache and chronic daily headache:	**Evidence of efficacy and safety of acupuncture for adults with chronic migraine, chronic tension-type headache and chronic daily headache:**
Chronic Migraine	
Efficacy	**Efficacy**
Treatment responders Short-term (1 week): More acupuncture patients experienced **≥50% reduction in headache days (*any* and *moderate/severe)* per month** from baseline compared with topiramate in one RCT (SOE: Low for both outcomes).	***Treatment responders*** Short-term (1 week): No new evidence identified.
Long-term (36 weeks): More acupuncture patients experienced **≥50% reduction in headache days (*any, mild, and moderate/severe*) per month** and **≥35% improvement in *headache score**** from baseline compared with UC in one RCT (SOE: Low for all outcomes).	Long-term (24–36 weeks): More acupuncture patients experienced **≥50% reduction in *any* headache days per month** from baseline compared with WL and/or UC based on pooled estimates across two RCTs at 24 and 36 weeks (moderate SOE); and **≥50% reduction in *moderate/severe* and *mild* headache days per month** and **≥35% improvement in *headache score**** compared with UC in one RCT at 36 weeks (SOE: Low for all outcomes).
Reduction in Headache Frequency Short-term (1 week): Acupuncture was associated with a greater reduction in **mean headache days (*any and moderate/severe*) per month** from baseline compared with topiramate in one RCT (SOE: Low).	***Reduction in Headache Frequency*** Short-term (1–8 weeks): Acupuncture was associated with a greater reduction in **mean headache days per month** from baseline compared with sham plus UC and active controls (topiramate, sodium valproate, and Botulinum toxin A) based on pooled estimates across three RCTs, and in ***moderate/severe* headache days per month** compared with topiramate at 1 week in one RCT (low SOE for both outcomes); evidence from one RCT of acupuncture vs. sham plus UC was insufficient to draw conclusions regarding **reduction in headache episodes/attacks per month** from baseline at 4 weeks.
Long term (36 weeks): Acupuncture was associated with a greater reduction in **mean headache days (*any,***	Long-term (12–36 weeks): Acupuncture was associated with a greater **reduction in mean headache days per**

Key Results From 2017 HTA Report	Results From This 2022 Updated Report
***mild or moderate/severe*) per month** from baseline compared with UC in one RCT (SOE: Low).	**month** from baseline compared with sham plus UC and active controls (waitlist and/or usual care, sodium valproate, and Botulinum toxin A) based on pooled estimates across three RCTs (SOE: Moderate), and in ***moderate/severe* and *mild* headache days per month** compared with usual care at 36 weeks in one RCT (SOE: Low for both outcomes); there was no difference between acupuncture and waitlist/UC groups in **reduction in headache episodes/attacks per month** from baseline at 24 weeks in one RCT (SOE: Low).
Function/disability Short-term (1 week): Acupuncture was associated with a greater reduction in **MIDAS scores†**, suggesting improved function, compared with topiramate in one RCT (SOE: Low). Long-term: No evidence identified.	***Function/disability*** Short-term (1 week): No new evidence identified. Long-term (24 weeks): There was no difference between acupuncture and waitlist/UC groups in **MIDAS scores†** in one RCT (SOE: Low).
Safety	**Safety**
Any serious AEs (to include death) There is insufficient evidence to draw conclusions. No serious adverse events occurred in any group (acupuncture, topiramate, UC) as reported by two RCTs (1 to 36 weeks follow-up); no further information was provided. No deaths occurred in either the acupuncture or topiramate group as reported by one of these (small) trials at 1 week.	***Any serious AEs (to include death)*** No new evidence identified.
AEs leading to study withdrawal There was no difference between acupuncture versus topiramate in the short term in one RCT (3 cases in the topiramate group at 1 week) (SOE: Low) and acupuncture versus usual care in the long term in a second RCT (1 case in the acupuncture group at 36 weeks) (SOE: Insufficient) It is unclear, however, whether there was sufficient sample size to detect a difference.	***AEs leading to study withdrawal*** No new evidence identified. We reviewed previous assessments and, for this update, felt it was more appropriate to consider all AEs together. Based on our reassessment, there was no difference between groups in the short and long term across two RCTs, one comparing acupuncture with usual care (1 case in the acupuncture group at 36 weeks post-treatment) and the other with topiramate (3 cases in the topiramate group at 1 week) (SOE: Low). It is unclear, however, whether there was sufficient sample size to detect a difference.
Any minor AEs/side effects Fewer minor AEs occurred following acupuncture compared with topiramate at 1 week in one RCT. All events were mild and self-limiting (SOE: Low).	***Any minor AEs/side effects*** Fewer minor AEs occurred following acupuncture compared with topiramate, sodium valproate and Botulinum toxin A across two RCTs with 1- and 12-week

Key Results From 2017 HTA Report	Results From This 2022 Updated Report
	follow-up. All events were mild and self-limiting (SOE: Low).
Treatment-related Headache No difference between groups in the frequency of headache post-treatment in one RCT (5 cases in 4 patients following acupuncture and no cases in the usual care group) (SOE: Low). It is unclear whether sample size played a role in these findings.	***Treatment-related Headache*** No new evidence identified.
Other adverse events No evidence identified.	***Other adverse events*** Evidence was considered insufficient to draw conclusion for the following adverse events/side effects: *Hematoma, facial hematoma* (2 RCTs; auricular acupuncture versus sham plus UC and acupuncture versus waitlist plus UC); *ear swelling, ear pain, erythema, and ear infection* (1 RCT; auricular acupuncture versus sham plus UC)
Differential effectiveness There is insufficient evidence that the effect of acupuncture vs. usual care (1 RCT) or topiramate (1 RCT) is modified by patient (e.g., age, sex) or headache characteristics (e.g., baseline number of headache days, baseline headache score, chronicity).	**Differential effectiveness** No new evidence identified
Cost-effectiveness One poor to moderate quality CUA comparing acupuncture to usual care in patients with chronic migraine suggests that acupuncture may be cost effective for a time horizon of one year at a willingness to pay threshold of £30,000 with a probability of 84% based on data available from the associated RCT. ICERs ranged from £801/QALY (for a 10-year time horizon) to £12,333/QALY if a GP provided the service. However, this study had numerous limitations and differences between the UK and US medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.	**Cost-effectiveness** No new evidence identified
Chronic Tension-Type Headache	
Efficacy ***Treatment responders*** <u>Short term (4-6 weeks) and long term (52 weeks)</u>: There was no difference between acupuncture and sham acupuncture in the proportion of patients achieving **>33% or >50% improvement from baseline on the**	No new evidence identified

Key Results From 2017 HTA Report	Results From This 2022 Updated Report
Headache Index at either timepoint in one small trial (SOE: Insufficient for both times) ***Reduction in headache frequency*** Short term (4-6 weeks) and long term (26-52 weeks): There were no differences between acupuncture and sham in **mean reduction in headache episodes per month** based on the pooled estimate across two small trials at short-term or in one of the trials at long-term follow-up (SOE: Insufficient for both times). Long-term (12-26 weeks): There were no differences between acupuncture and physical training/exercise or between acupuncture and relaxation training in the frequency of **headache-free periods and headache-free days per week** in one trial (SOE: Insufficient for both outcomes and comparisons). ***Function/disability*** Short-term (4 to 9 weeks)‡: The acupuncture was associated with greater improvement on the Sickness Impact Profile score category for sleep and rest, but not with respect to the psychosocial categories, compared with physiotherapy in one quality trial (SOE: Insufficient). **Safety** A few patients in the acupuncture group had a **slight vasovagal reaction** in one trial that compared acupuncture with physiotherapy; no other complications were noted, and no data was provided (SOE: Insufficient). **Differential effectiveness** No evidence identified **Cost-effectiveness** No evidence identified	
Chronic daily headache	
No evidence identified	No new evidence identified

CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MIDAS = Migraine Disability Assessment; QALY = quality adjusted life years; RCT = randomized controlled trials; SOE = strength of evidence; UC = usual care; WL = waitlist.
*Defined as the summed total of headache severity recorded 4x/day on a 6-point Likert scale; this was the study protocol definition of responder.
†The MIDAS assesses how severely migraines affect a patient's life and includes questions about the frequency and duration of headaches, as well as how often these headaches limit the patient's ability to participate in activities at work, at school, or at home.
‡This trial reported follow-up as a range; most of the time would be considered short term for the purposes of this report.

KQ1 Summary of Results (Efficacy):

General findings for each headache type for the primary outcomes are briefly summarized by timeframe and comparator below. The SOE tables that follow summarize effect sizes, general conclusions and additional information for the primary outcomes. Detailed findings, including results for secondary outcomes are found in the full report. For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame or comparator. Not all trials reported all outcomes at each time frame of interest.

Across RCTs, headache types and comparators, most patients were female, with mean ages ranging from 33 to 49 years (pooled mean age 44 years). The mean number of migraine days per month at study entry ranged from 12 to 27. In general, a large proportion of study participants reported previous use of prophylactic medications and a few trials permitted concurrent use of them. Almost all trials allowed the use of rescue medication. Overuse of medications was variably defined and variably reported across trials; some trials excluding patients with medication overuse, and one reported a large proportion of participants with overuse. Given the evolution of criteria and recognition of medication overuse over the past two decades, the prevalence across studies is unclear as is the impact of it on findings. Where provided we report data on medication overuse.

Regarding the overall quality of included RCTs, the majority (n=7)[2,6,8,10,13,16,17] were rated moderately high risk of bias (poor quality RCTs); two trials, both in chronic migraine, were rated moderately low risk of bias (moderate or fair quality RCT).[9,21] No trial was rated low risk of bias (good quality). Common methodological limitations across the trials included unclear randomization and allocation concealment methods, high (or unclear) loss to follow-up, and baseline differences between intervention groups. In trials with active controls (i.e., not sham), the inability to blind patients to interventions received was a further limitation. One economic study (in chronic migraine) met inclusion criteria and was rated poor to moderate quality; this study was included in the prior review.[18] Detailed descriptions of study quality are provided below for each headache type and comparator set and in Appendix E.

The majority of trials compared acupuncture with active alternate treatments that might be used to treat headache conditions.[2,10,13,14,20,21] Three trials (1 chronic migraine[6] and 2 chronic tension-type headache[8,16]) employed sham as control groups. These types of controls provide valuable information regarding treatment efficacy for pain conditions by controlling for factors such as the natural course of the condition, the effects of placebo or unmeasured effects, and measurement error but do not provide comparative information regarding other treatments that may be used clinically.

Overall, SOE for most efficacy outcomes was considered low or insufficient across headache types, interventions and comparators. Efficacy outcomes for which there was moderate quality evidence (in favor of acupuncture) were confined to reduction in headache days (both proportion with ≥50% reduction [i.e., treatment responders] and mean reduction in headache days from baseline) at long term (12 to 36 weeks post-treatment) for chronic migraine. In general, for chronic migraine, acupuncture was associated with reductions in the number and severity of headache days per month over the short and long term and in disability over the short term compared with sham and active treatments (i.e., usual care, waitlist, pharmacologic therapy, Botulinum toxin A); the SOE was primarily low. For chronic tension headache, there was insufficient evidence across four trials at moderately high risk of bias to draw conclusions regarding the efficacy of acupuncture compared with sham and with active treatments (i.e.,

exercise, physiotherapy, relaxation). Evidence on safety, differential effectiveness/safety and cost effectiveness are limited. The SOE tables below and more detailed SOE evaluation in Section 5 of the report provide additional information. It is important to note that, across most studies, acupuncture was most likely used in addition to usual care which may have included medications as well as use of various modalities such as physical or physiotherapy and massage.

Results are organized by outcome below.

Chronic Migraine

Our updated search identified three new RCTs[6,9,10] of acupuncture for treatment of chronic migraine for a total of five trials (across 7 publications)[6,9,10,17,18,20,21] for this review. The results from the 2017 report were re-evaluated for accuracy and edits have been made for consistency with this updated review. In general, results indicated that acupuncture was beneficial for reducing the number and severity of acute headache episodes over the short and long term compared with sham and active treatments and in reducing disability over the short term compared with pharmacologic therapy; the strength of evidence was primarily low. Most trials were rated moderately high risk of bias (i.e., poor quality).

Treatment Responders

- In the short-term (1 week), more acupuncture patients experienced **≥50% reduction in *any* headache days** and **in *moderate to severe* headache days** from baseline compared with topiramate in one RCT[21] (low SOE for both outcomes).
- In the long-term (24–36 weeks), more acupuncture patients experienced **≥50% reduction in *any* headache days** from baseline compared with waitlist and/or usual care across 2 RCTs[9,17] at 24 and 26 weeks post-treatment (moderate SOE) and in both ***moderate to severe* and *mild* headache days** compared with usual care in one RCT[17] at 36 weeks post-treatment (low SOE for both outcomes).
- In the long-term (36 weeks), more acupuncture patients a **≥35% improvement in *headache score*** from baseline compared with usual care in one RCT[17] (low SOE).

Reduction in Headache Frequency

- In the short-term (1–8 weeks), acupuncture was associated with a greater **reduction in mean headache days per month** from baseline compared with sham/UC and active controls (topiramate, sodium valproate, and Botulinum toxin A) across 3 RCTs[6,10,21] and in ***moderate to severe* headache days per month** compared with topiramate in one RCT[21] (low SOE for both outcomes).
- In the long-term (12–36 weeks), acupuncture was associated with a greater **reduction in mean headache days per month** from baseline compared with sham/UC and active controls (waitlist and/or usual care, sodium valproate, and Botulinum toxin A) across 3 RCTs[9,10,17] (moderate SOE) and in ***moderate to severe* and *mild* headache days per month** compared with usual care in one RCT[17] (low SOE for both outcomes).

- In the short-term (4 weeks), data from one RCT[6] comparing auricular acupuncture with sham plus usual care were insufficient to draw conclusions regarding **reduction in headache episodes/attacks per month** from baseline.
- In the long-term (24 weeks), there was no difference between patients randomized to acupuncture versus waitlist/usual care in **reduction in headache episodes/attacks per month** from baseline in one RCT[9] (low SOE).

Migraine Disability Assessment (MIDAS)

- In the short-term (1 week), acupuncture was associated with a greater reduction in **MIDAS scores**, suggesting improved function, compared with topiramate in one RCT[21] (low SOE).
- In the long-term (1 week), there was no difference between patients randomized to acupuncture versus waitlist/usual care in **MIDAS scores** in one RCT[9] (low SOE).

Chronic Tension-Type Headache

Our updated search did not identify new RCTs of acupuncture for treatment of chronic tension-type headache (CTTH) that met the inclusion criteria. The results from the 2017 report were re-evaluated for accuracy and edits have been made for consistency with this updated review. Differences in reported outcomes and length of follow-up across trials precluded pooling of data across studies of acupuncture for CTTH for most outcomes. All four trials[2,8,13,14,16] were rated moderately high risk of bias (i.e., poor quality) and strength of evidence for all efficacy outcomes was insufficient.

Treatment Responders

- Only one trial reported this outcome. There was no difference between acupuncture and sham acupuncture either short-term (4-6 weeks) or long-term (52 weeks) in the proportion of patients **achieving >33% or >50% improvement** from baseline on the Headache Index (HI) in one small trial (insufficient SOE for both times).[16]

Reduction in Headache Frequency

- There were no differences between acupuncture and sham based on the pooled mean **reduction in headache episodes per month** across two small trials at short-term (4-6 weeks) follow-up[8,16] or in one of the trials longer-term (26-52 weeks) (insufficient SOE for both timepoints).
- In one trial,[13,14] at longer-term (12 and 26 weeks), no differences were seen between the acupuncture and physical training/exercise or between acupuncture and relaxation training in **the number of headache-free periods or in headache-free days per week** (insufficient SOE for all outcomes and comparisons).

Function

- Short-term (4 to 9 weeks), one trial reported that the acupuncture group improved significantly more than the physiotherapy group on **Sickness Impact Profile (SIP) score** category for Sleep and Rest but not with respect to the psychosocial categories[2] (insufficient SOE).

Chronic Daily Headache

- No trials were identified that met the inclusion criteria.

KQ2 Summary of Results (Safety)

All included comparative studies were evaluated for harms and complications. In general, adverse events were poorly reported and most studies too small to detect rare events. The overall SOE for most efficacy outcomes was considered low or insufficient across timeframes and comparators. A summary of safety outcomes for all interventions and comparators is provided below and in the summary strength of evidence tables in this section. Section 5 of the report provides additional detail of SOE determination for each outcome.

Chronic Migraine

Serious adverse events

- There is insufficient evidence to draw conclusions regarding the risk of **any serious adverse events (to include death)** for acupuncture compared with active control treatments. No serious adverse events occurred in any group (acupuncture, topiramate, UC) as reported by two RCTs with follow-up ranging from short to long term (1 to 36 weeks post-treatment)[17,21]; no data and no further information was provided. No deaths occurred in either the acupuncture or topiramate group as reported by one of these (small) trials at 1 week post-treatment.[21]
- There was no statistical difference between groups across the short and long term in the risk of **adverse events leading to study withdrawal** across two RCTs, one comparing acupuncture with usual care (1 case in the acupuncture group at 36 weeks post-treatment)[17] and the other with topiramate (3 cases in the topiramate group at 1 week post-treatment)[21] (low SOE). It is unclear, however, whether there was sufficient sample size to detect a difference.

Any minor adverse events/side effect

- Statistically fewer minor adverse events or side-effects occurred following acupuncture versus topiramate and versus Botulinum toxin A across two RCTs with 1- and 12-week follow-up periods post-treatment.[10,21] All events were mild and self-limiting. One these RCTs also compared acupuncture with sodium valproate[10], and though a direct comparison was not made for this outcome, it can be inferred from the data provided that acupuncture had fewer side effects overall over 12 weeks (low SOE).

Treatment-related Headache

- There was no statistical difference between groups in the frequency of headache post-treatment in one RCT[17]: there were five cases in four patients following acupuncture and no cases in the usual care group (low SOE). It is unclear whether sample size played a role in these findings.

Other adverse events

Evidence was considered insufficient to draw conclusion for the following adverse events/side effects:

- **Hematoma, facial hematoma**: auricular acupuncture versus sham/usual care (1 RCT)[6] and traditional acupuncture versus waitlist/usual care (1 RCT)[9]
- **Ear swelling, ear pain, erythema, and ear infection:** auricular acupuncture versus sham/usual care (1 RCT) [6]

Chronic Tension-Type Headache

- Over the short- (4 weeks) and intermediate-term (9 weeks), one trial that compared acupuncture with physiotherapy reported that a few patients in the acupuncture group had a **slight vasovagal reaction[2]**; no other complications were noted, and no data was provided (insufficient SOE).
- Adverse events were not reported for the following comparisons included for efficacy: acupuncture versus sham (2 RCTs)[8,16]and acupuncture versus physical training and versus relaxation (1 RCT).[13,14]

Chronic Daily Headache

- No trials were identified that met the inclusion criteria in either the original review or for this update report.

KQ3 Summary of Results (Differential Efficacy and Safety)

To evaluate differential efficacy and safety (heterogeneity of effect, interaction) RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. When assessing the quality of evidence for studies performing subgroup analysis, we also considered sample size, whether the subgroup analysis was preplanned (a priori) with a relevant hypothesis provided, whether a test for interaction was done and performance of multiple analyses. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis generating, and additional confirmatory evidence should be sought.[12,15,19] Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. If a comparison is not

listed below there was either no evidence identified that met the inclusion criteria or the included trials did not provide information on differential efficacy or harms.

Chronic Migraine

Acupuncture versus Active Control

- Acupuncture vs. Usual Care (1 RCT)[17]:
    - Baseline headache score modified the treatment effect such that those with more severe symptoms at baseline showed greater improvement with acupuncture vs. usual care; all other variables (headache diagnosis, age, sex, chronicity) did not modify the treatment effect (insufficient strength of evidence).
- Acupuncture vs. Topiramate (1 RCT, 2 publications)[20,21]:
    - Baseline headache days (overall and in patients with moderate/severe at baseline) may modify treatment effect such that patients with higher (≥20 days/mo.) compared with lower (<20 days/mo.) frequency showed greater improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect (insufficient strength of evidence).

Chronic Tension-Type Headache and Chronic Daily Headache

- No trials formally evaluating the differential efficacy or safety of acupuncture in these headache populations that met inclusion criteria were identified in either the original review or for this update report.

KQ4 Summary of Results (Cost-Effectiveness)

For the treatment of chronic migraine, one study, included in the 2017 report, compared acupuncture with usual care.[18] No new full economic studies comparing acupuncture with other treatments for chronic migraine, chronic tension-type headache or chronic daily headache were identified for this update. The results for acupuncture versus usual care for chronic migraine described below are excerpted from the prior report.

Chronic Migraine

One poor to moderate quality cost-utility analysis[18] comparing acupuncture to usual care suggests that acupuncture may be cost effective for a time horizon of one year at a willingness to pay threshold of £30,000 with a probability of 84% based on data available from the associated RCT (included in this HTA report).[17] In the base case, incremental cost-effectiveness ratios (ICERs) ranged from £801/quality-adjusted life years (QALY) (for a 10-year time horizon) to £12,333/QALY if a general practitioner provided the service.

The primary limitations of this study include lack of comparison to more active treatments, limited availability of data for benefits and harms beyond one year and limited sensitivity analyses around model inputs. Given the chronic nature of chronic migraine, it is assumed that continued treatment may needed, however the circumstances for continuation or discontinuation are not clear. Lack of clarity

regarding the components of usual care and differences between the United Kingdom and United States (U.S.) medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.

Chronic Tension-Type Headache and Chronic Daily Headache

- No trials performing formal economic analysis evaluating acupuncture in these headache populations that met inclusion criteria were identified in either the original review or for this update report.

Strength of Evidence Summaries

The following summaries of evidence for primary outcomes have been based on the highest quality of studies available. ***Detailed SOE tables, including reasons for downgrading are found in section 5 of the report***. Summaries for each key question are provided in the tables below and are sorted by time frame and/or comparator. Details of other (secondary) outcomes are available in the report.

Strength of Evidence Summary: Efficacy of Acupuncture versus Sham and Active Control for Chronic Migraine

Outcome	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
Responders: Proportion with ≥50% reduction in *any headache days* from baseline	1–36 wks.	**3 RCTs** Vickers 2004 (UC) Musil 2018 (WL+UC) Yang 2011 (Topiramate)	443	RoB[1] (-1), Inconsistency Unknown (Short term), Imprecision (-1) (Short term)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** RR 4.20 (95% CI 1.80 to 9.80) RD 48% (95% CI 28% to 69%) Long-term (24-36 wks.) **2 RCTs, N=377 (vs. UC/WL)** Pooled RR 2.14 (95% CI 1.56 to 2.95), I^2=0% Pooled RD 29% (95% CI 0% to 58%), I^2=86% Any time point (1-36 wks.) or comparator **3 RCTs, N=443 (vs. topiramate, UC/WL)** Pooled RR 2.35 (95% CI 1.70 to 3.24), I^2=11% Pooled RD 35% (95% CI 11% to 59%), I^2=85% Conclusion: More acupuncture participants experienced ≥50% reduction in number of migraine days compared with active controls over the short and long term.	⊕⊕○○ LOW (Short term) ⊕⊕⊕○ MODERATE (Long-term)

Outcome	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
Responders: Proportion with ≥50% reduction in *moderate/ severe headache days* from baseline	1–36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	RoB[1] (-1), Inconsistency Unknown, Imprecision (-1) (Short term)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** RR 2.50 (95% CI 1.44 to 4.34) RD 45% (95% CI 24% to 67%) Long-term (24-36 wks.) **1 RCT, N=301 (vs. UC)** RR 1.48 (95% CI 1.06 to 2.07) RD 13% (95% CI 2% to 23%) Any time point (1-36 wks.) or comparator **2 RCTs, N=367 (vs. topiramate, UC)** Pooled RR 1.83 (95% CI 1.11 to 3.04), I^2=60% Pooled RD 28% (95% CI –4% to 60%), I^2=86% Conclusion: More acupuncture participants experienced ≥50% reduction in number of *moderate or severe* migraine days compared with active controls over the short and long term	⊕⊕○○ LOW (Short and Long term)
Responders: Proportion with ≥50% reduction in *mild headache days* from baseline	36 wks.	**1 RCT** Vickers 2004 (UC)	301	RoB[1] (-1), Inconsistency Unknown	RR 1.9 (95% CI 1.3 to 2.9) RD 16.9% (95% CI 7.2% to 26.6%) Conclusion: More acupuncture participants experienced ≥50% reduction in number of *mild* migraine days compared with usual care over the long term	⊕⊕○○ LOW
Responders: Proportion with ≥35% improvement in *headache score from baseline**	36 wks.	**1 RCT** Vickers 2004 (UC)	301	RoB[1] (-1), Inconsistency Unknown	RR 1.7 (95% CI 1.3 to 2.2) RD 21.9% (95% CI 11.0% to 32.8%) Conclusion: More acupuncture participants experienced ≥35% improvement in headache score from baseline compared with usual care over the long term	⊕⊕○○ LOW
Reduction in *any headache days* per month†	1–8 wks.	**3 RCTs** Habibabadi 2021 (Sham+UC) Naderinabi 2017	296	RoB[1] (-1), Inconsistency[2] (-1)	Pooled MD –2.80 (95% CI –4.19 to –1.42), I^2=44% Conclusion: Acupuncture was associated with a greater reduction in mean headache days compared with active controls	⊕⊕○○ LOW

Outcome	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
		(Sodium valproate; Botulinum toxin A) Yang 2011 (Topiramate)			(sham/UC, topiramate, sodium valproate, and Botulinum toxin A) at short term.	
	12–36 wks.	**3 RCTs** Vickers 2004 (UC) Musil 2018 (WL+UC) Naderinabi 2017 (Sodium valproate; Botulinum toxin A)	527	RoB[1] (-1)	Pooled MD –3.54 (95% CI –5.15 to –1.94), I^2=30% Conclusion: Acupuncture was associated with a greater reduction in mean headache days compared with active controls (sham/UC, WL/UC, sodium valproate, and Botulinum toxin A) at long term.	⊕⊕⊕○ MODERATE
Reduction in *moderate/ severe headache days* per month	1–36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1) (Short term)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** MD –2.30 (95% CI –3.68 to –0.92) Long-term (36 wks.) **1 RCT, N=301 (vs. UC)** MD –1.50 (95% CI –2.69 to –0.31) Any time point (1-36 wks.) or comparator **2 RCTs, N=367 (vs. topiramate, UC)** Pooled MD –1.84 (95% CI –2.74 to –0.94), I^2=0% Conclusion: Acupuncture was associated with a greater reduction in mean headache days of *moderate or severe intensity* compared with active controls at short and long term.	⊕⊕○○ LOW (Short and Long term)
Reduction in *mild headache days* per month (adjusted for baseline)	36 wks.	**1 RCT** Vickers 2004 (UC)	301	RoB[1] (-1), Inconsistency Unknown	MD –1.6 (95% CI –2.6 to –0.5) Conclusion: Greater reduction in mild headache days with acupuncture vs. usual care long term.	⊕⊕○○ LOW
Reduction in *headache episodes/attacks* per month	4 wks.	**1 RCT** Habibabadi 2021 (Sham+UC)	80	RoB[1] (-2)‡, Inconsistency Unknown, Imprecision[3] (-1)	MD –6.12 (95% CI –9.91 to –2.33) Conclusion: Greater reduction in headache episodes/attacks with acupuncture vs. sham/UC short term.	⊕⊕⊕○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
	24 wks.	**1 RCT** Musil 2018 (WL+UC)	76	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	MD –0.90 (95% CI –2.05 to 0.25) Conclusion: No difference between groups (acupuncture and WL/UC) in headache episodes/attacks long term.	⊕⊕◯◯ LOW
Migraine Disability Assessment (MIDAS)§	1–24 wks.	**2 RCTs** Musil 2018 (WL+UC) Yang 2011 (Topiramate)	124	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** MD –12.00 (95% CI –17.58 to –6.42) Long-term (24 wks.) **1 RCT, N=58 (vs. UC+WL)** MD –13.60 (95% CI –32.01 to 4.81) Any time point (1-24 wks.) or comparator **2 RCTs, N=124 (vs. topiramate, UC+WL)** Pooled MD –12.13 (95% CI –17.47 to –6.80), I^2=0% Conclusion: Greater reduction in mean MIDAS scores, suggesting improved function, was seen in the acupuncture group compared to active controls over the short, but not the long, term; this may be a clinically important difference.	⊕⊕◯◯ LOW (Short and Long term)

CI = confidence interval; MD = mean difference; MIDAS = Migraine Disability Assessment; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; UC = usual care; wks. = weeks; WL = waitlist.

*Defined as the summed total of headache severity recorded 4x/day on a 6-point Likert scale; this was the study protocol definition of responder

†It is unclear what constitutes a clinically meaningful difference in headache days or what would be consider a mild to substantial improvement; this estimate could be considered imprecise if the confidence interval ranged from mild to substantial.

‡This trial appeared to exclude patients who experienced certain adverse event/side effects and it is unclear what impact that loss-to-follow-up may have had on efficacy outcomes.

§The MIDAS assesses how severely migraines affect a patient's life and includes questions about the frequency and duration of headaches, as well as how often these headaches limit the patient's ability to participate in activities at work, at school, or at home.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.

3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: Efficacy of Acupuncture versus Sham for Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Tension Type Headache: Acupuncture vs. Sham						
Responders Proportion with >33% and >50% improvement from baseline on the HI*	4 wks.	1 RCT (Tavola 1992)	30	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	<u>>33% improvement on the HI</u> RR 1.4 (95% CI 0.9, 3.2) RD 26.7% (95% CI –3.5%, 56.8%) <u>>50% improvement on the HI</u> RR 1.1 (95% CI 0.6, 2.3) RD 6.7% (95% CI –29.0%, 42.4%) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	⊕OOO INSUFFICIENT
	52 wks.			RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	<u>>33% improvement on the HI</u> RR 1.1 (95% CI 0.6, 2.3) RD 6.7% (95% CI –29.0%, 42.4%) <u>>50% improvement on the HI</u> RR 1.5 (95% CI 0.5, 4.3) RD 13.3% (95% CI –20.1%, 46.7%) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	⊕OOO INSUFFICIENT
Reduction in headache *episodes* per month	4-6 wks.	2 RCTs (Tavola 1992, Karst 2000)	69	RoB[1] (-1), Inconsistency[2] (-1), Imprecision[3] (-1)	Pooled MD –1.94 (95% CI –6.74, 2.85, I^2= 61%) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions. No difference between acupuncture and sham acupuncture in reduction of headache episode per month.	⊕OOO INSUFFICIENT
	26-52 wks.	1 RCT (Tavola 1992)	30	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	Authors state that the frequency of headache episodes continued to decrease through 26 and 52 weeks post-treatment with no statistical differences between groups; no data provided.	⊕OOO INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					Conclusion: Insufficient evidence precludes firm conclusions.	

CI = confidence interval; MD = mean difference; HI = Headache index; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; wks. = weeks.
*Authors definition: headache index = intensity (sum of the intensity of the crises in a month/number of crises) X duration (sum of the hours of headache in a month/number of crises) X frequency (the number of crises in a month)/30.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: Efficacy of Acupuncture versus Active Control: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N	Reasons for Downgrading*	Conclusion	Quality
Chronic Tension Type Headache: Acupuncture vs. Physical Training/Exercise						
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-1)	12 weeks: mean 6.25 and median 0.25 (range, 0.00–28.00) (n=30) versus mean 7.46 and median 5.00 (range, 0.00–28.00) (n=30); p=NS 26 weeks: mean 7.58 and median 0 (range, 0.00–28.00) (n=30) versus mean 9.37 and median 9.38 (range, 0.00–28.00) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	⊕○○○ INSUFFICIENT
Headache-free *days* per week				RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-1)	12 weeks: mean 1.18 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.23 and median 0.50 (range, 0.00–7.00) (n=30); p=NS 26 weeks: mean 1.56 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.66 and median 1.00 (range, 0.00–7.00) (n=30); p=NS	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading*	Conclusion	Quality
					Conclusion: Insufficient evidence precludes firm conclusions.	
Chronic Tension Type Headache: Acupuncture vs. Physiotherapy						
Reduction in headache episodes†	4-9 wks.	1 RCT (Carlsson 1990)	62	RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-2)	Authors state headache frequency was significantly (<0.001) reduced in both groups 4 to 9 weeks after treatment; however, no data were provided and no information regarding the between group difference was provided. Conclusion: Insufficient evidence precludes firm conclusions.	⊕OOO INSUFFICIENT
Sickness Impact Profile (SIP)				RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-2)	Authors state that the acupuncture group improved significantly (p<0.05) more than the physiotherapy group in the SIP category Sleep and Rest but significantly less with respect to the psychosocial categories Emotional Behavior, Work, Eating, and Recreation and Pastimes; overall SIP score and the Psychosocial dimension were improved in both groups but between group differences are unclear. No data was provided to support these statements. Conclusion: Insufficient evidence precludes firm conclusions.	⊕OOO INSUFFICIENT
Chronic Tension Type Headache: Acupuncture vs. Relaxation Training						
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-1)	12 weeks: mean 6.25 and median 0.25 (range, 0.00–28.00) (n=30) versus mean 7.67 and median 2.0 (range, 0.00–29.00) (n=30); p=NS 26 weeks: mean 7.58 and median 0 (range, 0.00–28.00) (n=30) versus mean 8.29 and median 2.0 (range, 0.00–29.00) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	⊕OOO INSUFFICIENT
Headache-free *days* per week				RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-1)	12 weeks: mean 1.18 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.58 and median 0.13 (range, 0.00–7.25) (n=30); p=NS	⊕OOO INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading*	Conclusion	Quality
					26 weeks: mean 1.56 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.73 and median 0.13 (range, 0.00–7.25) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	

NS = not statistically significant; RCT = randomized controlled trial; SIP = Sickness Impact Profile; wks. = weeks.
*Though both RCTs were rated as moderately high risk of bias, they each suffered from a variety of methodological limitations that makes them at higher risk of bias compared with other RCTs.
†Headache frequency was measured on a 1 to 5 scale: almost never, once or twice a month, once a week, several times a week, and daily.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: Safety of Acupuncture versus Sham and Active Control for Chronic Migraine

Outcome*	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
Chronic Migraine						
Serious adverse events	1 to 36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-2)	No serious adverse events occurred in any group (acupuncture, topiramate, UC); data and information not provided. Conclusion: Without knowing what constitutes a serious adverse event and the rarity of such events, it is unknown whether there was sufficient sample size to detect such events; firm conclusions are difficult.	⊕◯◯◯ INSUFFICIENT
Discontinuation due to adverse events	1 to 36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011	367	RoB[1] (-1), Imprecision[3] (-1)	**Acupuncture vs. UC (1 RCT):** 0.6% (1/161) vs. 0% (0/140) **Acupuncture vs. Topiramate (1 RCT):**	⊕⊕◯◯ LOW

Outcome*	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
		(Topiramate)			0% (0/33) vs. 9.1% (3/33) Conclusion: Although no statistical difference between groups in either trial, it is unclear whether there was sufficient sample size to detect a statistical difference.	
Death	1 wk.	**1 RCT** Yang 2011 (Topiramate)	66	RoB[1] (-1,) Inconsistency Unknown, Imprecision[3] (-2)	No deaths occurred in either group (acupuncture vs. topiramate). Conclusion: Small sample size and short follow-up makes the detection of rare events difficult; insufficient evidence preclude firm conclusions.	⨁◯◯◯ INSUFFICIENT
Any side effect (minor, self-limiting)	1 to 12 wks.	**2 RCTs** Yang 2011 (Topiramate) Naderinabi 2017 (Sodium valproate; Botulinum toxin A)	216	RoB[1] (-1), Imprecision[3] (-1)	**Acupuncture vs. Topiramate (1 RCT):** RR 0.09 (95% CI 0.02, 0.36) • Acupuncture: 6% (2/33); all due to local insertion of needles (pain, paresthesia, ecchymosis) • Topiramate: 66% (22/33); most common included paresthesia (48%), difficulty with memory (36%), dyspepsia (36%), fatigue (24%), dizziness (21%), somnolence (18%), and nausea (12%) **Acupuncture vs. Botulinum toxin (1 RCT):** RR 0.27 (95% CI 0.08, 0.92) • Acupuncture: 6% (3/50); bleeding or subcutaneous hematoma • Botulinum Toxin A: 22% (11/50); ptosis, facial masking or asymmetry **Acupuncture vs. Sodium Valproate (1 RCT):** • Acupuncture: 6% (3/50); bleeding or subcutaneous hematoma • Sodium Valproate: frequency of any non-serious AEs NR but authors list a variety of side effects that occurred (i.e., anorexia, weight gain, tremor, somnolence, insomnia, alopecia) and ranged from 4% to 18% of patients. Conclusion: Statistically fewer side-effects occurred following	⨁⨁◯◯ LOW

Outcome*	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
					acupuncture versus topiramate and versus Botulinum toxin A. For sodium valproate, though not a direct comparison, it can be inferred that acupuncture had fewer side effects than sodium valproate with the data provided.	
Hematoma, facial hematoma	4 to 12 wks.	**2 RCTs** Habibabadi 2021 (Sham+UC) Musil 2018 acupuncture group only (WL+UC)	159	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1)	**Acupuncture vs. sham/UC, 1 RCT:** • No cases of hematoma in either group; however, authors state that patients were excluded from the study if they developed redness or infection at the site of the needle implant **Acupuncture vs. WL/UC, 1 RCT:** • One case of facial hematoma in acupuncture group: 1.3% (1/79) • NR in WL/UC group Conclusion: The evidence is insufficient to draw conclusions regarding the risk of hematoma following acupuncture. Methodological concerns in one trial [Habibabadi 2021] regarding the exclusion of patients due to side effects further limit our confidence in the results.	⊕◯◯◯ INSUFFICIENT
Headache	Unclear	**1 RCT** Vickers 2004 (UC)	301	RoB[1] (-1), Inconsistency Unknown	2.5% (4/161) [5 cases] vs. 0% (0/140) Conclusion: No statistical difference between groups; it is unclear whether sample size played a role.	⊕⊕◯◯ LOW
Ear swelling, Ear pain, Erythema Ear infection	4 wks.	**1 RCT** Habibabadi 2021 (Sham+UC)	80	RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-1)	No events occurred in the sham/UC group. In the auricular acupuncture group, the frequency of **ear swelling** ranged from 3% (1/40) to 10% (4/40) and **ear pain** from 5% (4/240) to 18% (7/40) across 1-, 2-, 3-, and 4-week follow-ups. No cases or **erythema or ear infection** were reported, *however, authors state that patients were excluded from the study if they*	⊕◯◯◯ INSUFFICIENT

Outcome*	Follow-up	RCTs	N	Reason for Downgrading	Conclusion	Quality
					developed redness or infection at the site of the needle implant Conclusion: Ear swelling, ear pain and erythema are common, likely expected, AEs following auricular acupuncture; however, the evidence is considered insufficient to draw conclusions. Methodological concerns regarding the exclusion of patients due to side effects further limit our confidence in the results.	

CI = confidence interval; MD = mean difference; MIDAS = Migraine Disability Assessment; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; UC = usual care; wks. = weeks; WL = waitlist.

*Neither study provided information on what constituted a serious adverse event or adverse events that caused discontinuation.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: Safety of Acupuncture versus Active Control: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N	Reasons for Downgrading*	Conclusion	Outcome
Chronic Tension Type Headache: Acupuncture vs. Physiotherapy						
Vasovagal reaction	4-9 wks.	1 RCT (Carlsson 1990)	62	RoB[1] (-2), Inconsistency Unknown, Imprecision[3] (-2)	Authors state that a few patients in the acupuncture group had a slight vasovagal reaction; no other complications were noted. Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

RCT = randomized controlled trial; wks. = weeks.

*Though rated as moderately high risk of bias, this trial suffered from a variety of methodological limitations that makes it at higher risk of bias compared with other RCTs.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: Differential Efficacy and Harms for Chronic Migraine

Exposure	Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Migraine: Acupuncture versus Usual Care							
Baseline headache score; Headache type/diagnosis; **Age;** **Sex;** **Chronicity**	Headache score	36 wks.	1 RCT (Vickers 2004)	301	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1), HTE-related[5, 7] (-2)	Baseline headache score modified the treatment effect such that those with more severe symptoms at baseline showed significantly greater improvement with acupuncture vs. usual care (interaction p=0.004). Type of headache (chronic migraine or CTTH) did not modify treatment effect (no interaction); the small number of CTTH patients likely precluded detection of effect. Age, sex, and chronicity did not modify the treatment effect.	⊕◯◯◯ INSUFFICIENT
Chronic Migraine: Acupuncture versus Topiramate							
Baseline headache days; **multiple other demographic and headache characteristics**	≥50% reduction from baseline in moderate/ severe headache days	36 wks.	1 RCT (Yang 2013)	66	RoB[1] (-1), Inconsistency Unknown, Imprecision[3] (-1), HTE-related[5, 7] (-2)	Baseline headache days (overall and moderate/severe at baseline) may modify treatment effect; patients with higher (≥20 days/mo.) versus lower (<20 days/mo.) frequency showed greater improvement with acupuncture but not with topiramate overall (interaction	⊕◯◯◯ INSUFFICIENT

Exposure	Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
						p=0.002) and in those with moderate/severe headache days at baseline (interaction p=0.007).* Other variables explored did not modify the treatment effect (see full report)	

CTTH = chronic tension-type headache; HTE = heterogeneity of treatment effect; mo. = month; RCT = randomized controlled trial; wks. = weeks.
*Interaction was examined by logistic regression; the dichotomized outcome i.e., dependent variable was whether or not the reduced moderate/severe headache days was ≥50% of the baseline level.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

The following apply specifically to heterogeneity of treatment effect (HTE):

5. Subgroup analysis not preplanned (and/or no hypothesis), not considered in sample size calculation or unknown
6. Statistical test for homogeneity or interaction not performed
7. Multiple comparisons made

Executive Summary References

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1 Appraisal

1.1 Background and Rationale

Headache disorders are associated with a substantial impact on the physical, psychological, and social well-being of patients, in addition to being associated with 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.
Headache is considered primary when a disease or other medical condition does not cause the headache. Tension-type headache is the most common primary headache. It is characterized by a dull, non-pulsatile, diffuse, band-like (or vice-like) pain of mild to moderate intensity in the head, scalp, or neck. There is no clear cause of tension-type headaches even though it has been associated with muscle contraction and stress. Migraines are the second most frequently occurring primary headaches. Migraine headache is characterized by recurrent unilateral pulsatile headaches lasting 4- 72 hours; nausea, vomiting, and sensitivity to light and sound are frequent co-existent symptoms. The two major subtypes are common migraine (without aura) and classic migraine (with aura or neurological symptoms). Migraine and tension headache attacks are classified as episodic if they occur less than 15 days per month. Headaches are considered chronic if they occur 15 or more days each month for at least 3 months or more than 180 days a year. Episodic migraine and tension-type headache may evolve to become chronic. Chronic tension-type headache (CTTH) and chronic migraine (CM) features differ but the two may coexist.

Usual management of tension-type headache and migraine includes pharmacotherapy and nonpharmacologic approaches (e.g., acupuncture, neuromodulation, trigger management, psychotherapy, physical therapy and lifestyle changes).. While abortive therapy for acute episodes is necessary for both CTTH and CM, the focus of management for CCTH and CM is on preventive treatments. The primary goals of preventive therapy are to reduce the number, severity, and/or duration of acute episodes and reduce disability. Acupuncture may be part of the management of chronic headache that also includes medications. This report will focus on the use of acupuncture for the prevention of CTTH and CM. Acupuncture has been used for thousands of years and involves the insertion of solid, filiform needles into the body (with or without manual or electrical stimulation) to stimulate acupuncture points, including trigger points, and other tissues to promote health and treat organic or functional disorders directly or indirectly.

1.1.1 Policy Context

A Health Technology Assessment titled, *Treatment of chronic migraine and chronic tension-type headache*, was published on April 14, 2017, by the Health Care Authority. Acupuncture was one of the group of interventions investigated for the treatment of chronic headaches. Findings and Coverage Decision was adopted on July 14, 2017, and revised on July 13, 2018. At that time, the Health Technology Clinical Committee decided not to cover Acupuncture for chronic migraine or chronic tension headache. Since then, additional studies have been published on the use of acupuncture for these headache types. For these reasons, an update report specific to the use of acupuncture was requested by the Health Technology Assessment Program.

1.1.2 Objectives

The primary aim of this assessment is to systematically review and synthesize published evidence on the efficacy, safety, and cost-effectiveness of acupuncture compared with standard active treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults. This re-review will follow the same basic Key Questions, definitions, and scope as the prior report as they apply to acupuncture.

1.2 Key Questions

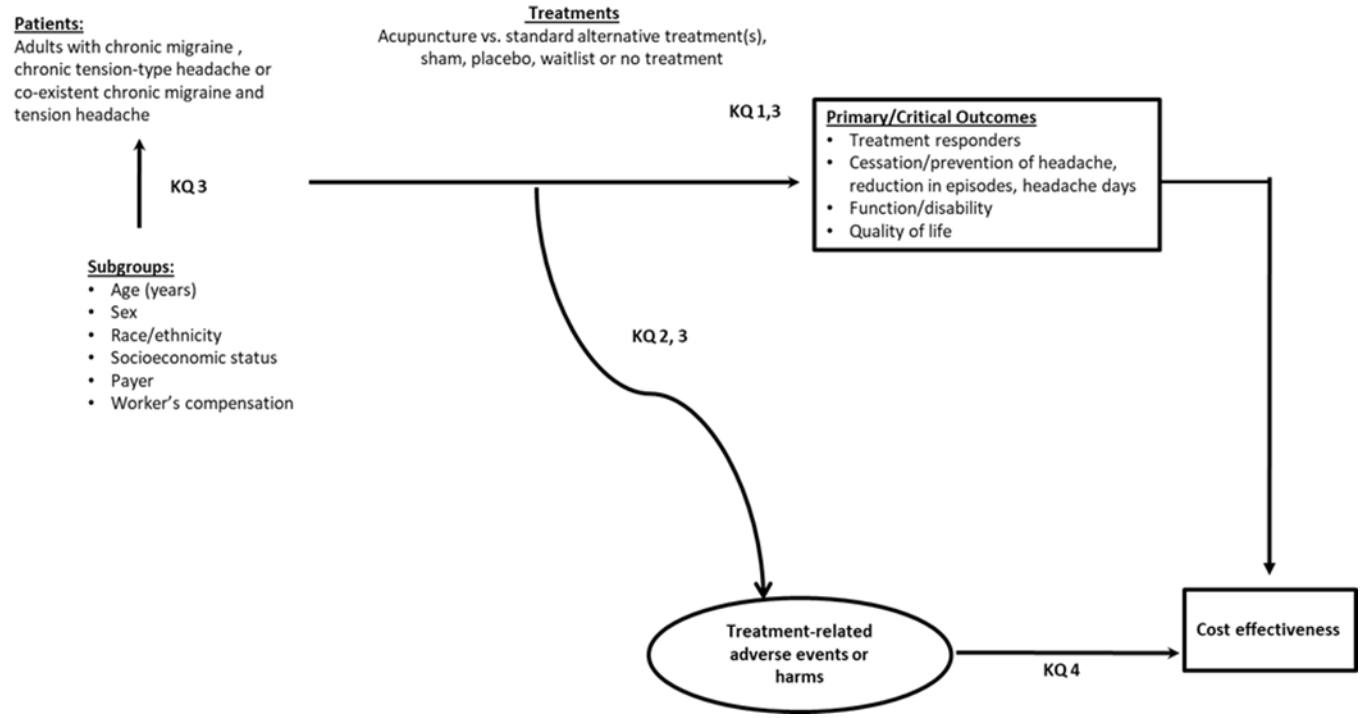
Specific key questions, as formulated by the HCA/Agency for the original report have been modified to reflect the focus of this update on the use of acupuncture for chronic migraine, chronic tension-type, and chronic daily headache:

In adults with chronic migraine, chronic tension-type, and chronic daily headache:

5. What is the evidence of the short- and long-term efficacy and effectiveness of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
6. What is the evidence regarding short- and long-term harms and complications of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
7. Is there evidence of differential efficacy, effectiveness, or safety of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
8. What is the evidence of cost-effectiveness of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?

The figure below (Figure 1) presents the analytic framework for the re-review.

Figure 1. Analytic framework



KQ = key question

1.3 Outcomes Assessed

The primary clinical outcomes of interest for this report are listed below. For the 2017 report, clinical expert input was sought to confirm critical outcomes on which to focus; these remained the same for this update review:

- Proportion of responders (e.g., at least 50% reduction of headache frequency from baseline for 3–4 months following treatment): Responders were variably defined by authors and a variety of measures and thresholds were reported.
- Cessation/prevention of headache: The most commonly reported outcomes related to reduction in mean number of episodes and/or headache days in general. Some trials reported on episodes or headache days specific to a given headache type.
- Function/disability: We focused on validated measures (e.g., burden of migraine [BURMIG]; Headache Activities of Daily Living Index [HADLI]; Headache Disability Index/Inventory [HDI]; Headache Disability Questionnaire [HDQ]; Headache Impact Test [HIT-6]; Migraine Disability Scale [MIDAS]) such as those listed in the table below.
- Harms, treatment-related adverse events, treatment discontinuation due to adverse events

Economic outcomes are cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality-adjusted life-year (QALY), incremental cost-effectiveness ratio (ICER) outcomes.

Table 1 below includes outcome measures reported by the included studies to evaluate treatment outcomes and is arranged alphabetically. The table is intended as a general reference of measures. We acknowledge that the table contains measures that evaluate different constructs and domains. Information on the minimal clinically important difference (MCID) was obtained for the population being evaluated if available and if the results revealed a statistically significant difference between treatment and comparator.

Table 1. Outcome measures for outcomes used in included studies

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
Beck Depression Inventory Score[22]	Patient	21 symptom-attitude categories consisting of 4 to 5 self-evaluative statements that are ranked numerically 0 – 3 points: • Mood • Pessimism • Sense of failure • Lack of satisfaction • Guilty feeling • Sense of punishment • Self-hate • Self-accusations • Self-punitive wishes • Crying spells • Irritability • Social withdrawal • Indecisiveness • Body image • Work inhibition • Sleep disturbance • Fatigability • Loss of appetite • Weight loss • Somatic preoccupation • Loss of libido	0 – 63 points	Higher score = greater depression	NR
Clinical Global Impression (CGI)[59]	Patient†	3 subscales: • Severity of illness (1 – 7 points) • Global improvement (1 – 7 points) • Efficacy index (1 – 4 points)	-4 to 4 points‡	Higher score = less disability	
Headache Index (HI) Score[90]	Patient	Weekly sum of daily 11-box ordinal scale (0 = no pain, 10 = unbearable pain)	0 – 70 points	Lower score = lesser pain	NR
Hospital Anxiety and Depression	Patient	Anxiety: 7 questions with a four-point (0—3) response scale	Anxiety: 0—21 points	Greater number = greater	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
Scale (HADS)[106]		Depression: 7 questions with a four-point (0—3) response scale	Depression: 0—21 points	severity of disorder: • 0—7 points = normal • 8—10 points = indicative of presence of disorder • ≥ 11 points = probable presence of disorder	
Migraine Disability Assessment Scale (MIDAS)[112]	Patient	Five items (number of days reported for each), assesses how many days of work/school, productivity (2 items; one for work/school and one for household work), ability to do household work, and participation in social activities were impacted due to headache-related reasons.	0—270 points	Greater number of points = greater headache-related disability: • Grade I, little or no disability: 0—5 points • Grade II, mild disability: 6—10 points • Grade III, moderate disability: 11—20 points • Grade IV, severe disability: ≥ 21 points	NR
Minor Symptom Profile Questionnaire (MSEP)[108]	Patient	24 total items ranked on a visual analog scale with three major dimensions and 9 independent items: • Contentment (7 items): Happiness, tranquility, self-control, decisiveness, self-	0 –10 cm or 0 – 100 mm	Lower score = positive feelings	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
		confidence, mental fatigue, and general well-being • Vitality (5 items): Enthusiasm, initiative, endurance, concentration, and responsiveness • Sleep (3 items): nocturnal sleep, quality of sleep, and insomnia • Dreams • Sexual interest • Muscular tension • Numbness • Self-consciousness • Sociability • Appetite • Sweating • Physical competence			
Mood Adjective Check List (MACL)[39]	Patient	71 adjectives describing mood and feeling grouped in 6 bipolar dimensions: • Pleasantness/unpleasantness • Activation/deactivation • Calmness/tension • Extroversion/introversion • Positive/negative social orientation • Confidence/lack of confidence	1 – 4 points	Higher score = high emotional well-being	
Sickness Impact Profile (SIP)[26]	Patient	12 categories (136 statements): • Physical dimension categories ○ Ambulation ○ Body care ○ Movement • Psychosocial dimension categories ○ Emotional behavior ○ Social interaction ○ Alertness behavior ○ Communication • Independent categories ○ Eating ○ Work ○ Sleep and rest ○ Home management ○ Recreation and pastime	0 – 100 points (subscale score)	Higher score = greater disability	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
Short Form-36 (SF-36)[123,124]	Patient	8 subscales (36 items): • Role-functioning • Role limitations due to physical health problems • Bodily pain • General health • Vitality • Social functioning • Role limitations due to emotional problems • Mental health In addition, the following scores may be reported for the SF-36: • Mental Component Score (MCS) (35 items) • Physical Component Score (PCS) (35 items)	0 – 100 (subscale score) 0 – 100 (component score) Total score not used	Lower score = greater disability	NR
VAS (Visual Analogue Scale) for pain	Generic	• Pain	0 –10 cm or 0 – 100 mm	No pain: 0 Worst pain imaginable: 10	Varied population presenting pain in ED: 12 mm

ED = Emergency Department; MCID = minimal clinically important difference; NR = not reported.

*MCIDs were only looked for if an outcome was statistically significant in any of the results of this report, those outcomes for which there was a statistically significant result but we could not locate a MCID in the literature are reported as NR; all others are left blank.

1.4 Washington State Utilization Data

Acupuncture for chronic migraine and chronic tension-type headaches

Washington State agency utilization data

Population

Administrative claims and encounter data for acupuncture for chronic migraine and chronic tension-type headaches from the following Washington State health programs were assessed: the Public Employees Benefit Board (PEBB) and School Employees Benefit Board (SEBB) Uniform Medical Plan (UMP), Medicaid managed care (MC) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid claims and encounters for adults 18 years of age and older. Denied claims or rejected encounters are excluded. Individuals eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/SEBB UMP experience includes claims for non-Medicare services.

Acupuncture Procedures

The assessment includes only procedures and services specific to acupuncture that had a line-level diagnosis of migraine or other headache syndromes (ICD-10 categories G43 & G44), with a date of service between January 1, 2017, and December 31, 2020.

Claims and encounters with qualifying procedures or services according to current procedural terminology (CPT) code or level II healthcare common procedure coding system (HCPCS) during the period were extracted for analysis.

Table 2. Utilization of acupuncture and related procedures and services, by state health program (2017-2020)

Medicaid	2017	2018	2019	2020	Total (unique)
Fee for service (FFS)					
Individuals with at least one acupuncture-related procedure/service	-	-	-	-	-
Managed care (MC)					
Individuals with at least one acupuncture-related procedure/service	16	16	15	23	**62**
Female, count	NR	NR	NR	NR	**49**
Male, count	NR	NR	NR	NR	**13**
Number of encounters with acupuncture	150	94	160	276	**680**
Average encounters with acupuncture	9	6	11	13	**11**
Amount paid, acupuncture	$1,980	$480	$5,012	$8,508	**$15,980**
Individuals	16	16	15	23	**62**
Average payments per individual	$124	$30	$334	$370	**$258**
Amount paid, acupuncture and related procedures	$3,768	$1,542	$6,082	$10,002	**$21,394**
Public Employees Benefit Board/School Employees Benefit Board Uniform Medical Plan (PEBB/SEBB UMP)					
Individuals with at least one acupuncture-related procedure/service	314	161	166	208	**687**
Female, count	268	142	147	186	**603**
Male, count	46	19	19	22	**84**
Number of encounters with acupuncture	6,180	2,900	2,726	3,874	**15,680**
Average encounters with acupuncture	20	18	16	19	**23**
Amount paid, acupuncture	$216,886	$107,877	$96,875	$111,785	**$533,424**
Individuals	314	161	166	208	**687**
Average payments per individual	$691	$670	$584	$537	**$776**
Amount paid, acupuncture and related procedures	$270,615	$128,008	$116,251	$146,890	**$661,763**
Washington State Department of Labor and Industries (L&I)					
Individuals with at least one acupuncture-related procedure/service	-	-	-	-	-
Washington State – Combined Medicaid, PEBB/SEBB UMP, L&I					
Individuals with at least one acupuncture-related procedure/service	330	177	181	231	**749**

Medicaid	2017	2018	2019	2020	Total (unique)
Female, count	NR	NR	NR	NR	**652**
Male, count	NR	NR	NR	NR	**97**
Number of encounters with acupuncture	6,330	2,994	2,886	4,150	**16,360**
Average encounters with acupuncture	19	17	16	18	**22**
Amount paid, acupuncture	$218,866	$108,357	$101,888	$120,293	**$549,404**
Individuals	330	177	181	231	**749**
Average payments per individual	$663	$612	$563	$521	**$734**
Amount paid, acupuncture and related procedures	$274,382	$131,390	$125,029	$157,713	**$688,515**

Data notes: NR = not reported; small numbers suppressed to protect patient privacy. Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. Amount paid reflects all claims submitted with the procedure code for the same date of service, and includes professional, facility, and ancillary claims (such as durable medical equipment). Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than one year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations.

Table. Codes and cost by HCPCS/CPT code (maximum allowable), by state health program and setting

Code	Description	Medicaid FFS		L&I	
		Non-facility	Facility	Non-facility	Facility
S8930	Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient	NC	NC	NC	NC
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient	NC	NC	NC	NC
97811	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)	NC	NC	NC	NC
97813	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient	NC	NC	NC	NC
97814	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)	NC	NC	NC	NC

Data notes: NC = Not Covered. Medicaid FFS from 10-1-2020 Physician-Related Services Fee Schedule and OPPS Fee Schedule (accessed December 22, 2021; webpage). L&I from 2020 provider fee schedule (accessed December 22, 2021). PEBB/SEBB UMP fees are not publicly available (proprietary).

2 Background

2.1 Epidemiology and Burden of Disease

Headache disorders are associated with a 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.[15]

In a systematic analysis of the 2017 Global Burden of Disease report, headache disorders represented the second highest cause of years of life lost to disability (YLD).[11,111] The 2018 National Health Interview Survey (NHIS) reported the age-adjusted prevalence of migraine or severe headache to be 15.9% across all U.S. adults.[3,35] The 2016 National Hospital Ambulatory Medical Care Survey ranked headache/pain in the head as the fifth most common patient-reported reason for emergency department visits, accounting for 2.8% of total visits.[34,35] The survey recorded 6.8 million outpatient visits due to headache or migraine, representing 0.8% of all outpatient visits.[34,35] Higher rates of headache disorders are reported for females; the NHIS found that 20.7% of females reported a headache episode compared to 9.7% of males across three months in 2015.[3]

Primary headaches are headache disorders that are not caused by another disease or medical condition. These are the most common form of headaches, of which tension-type headaches (TTH) and migraine have the highest prevalence. Chronic forms of these primary headaches have the highest burden on both the patient and the healthcare system.

Tension-type headache (TTH) is the most common headache type worldwide.[11,53,120] The 2016 Global Burden of Disease (GBD) report ranked TTH as the third most prevalent disease out of all the GBD causes of disease examined.[10] TTH is associated with considerable disability, with a reported 60% of afflicted individuals citing negative impacts on work and social engagement.[16] The 2017 GBD study reported a 15.6% increase in years lived with disability from TTH between 2007 to 2017.[11] Prevalence of the chronic form of TTH range from 0.9% to 2.2%.[16] Data on the economic impact of TTH are limited but an analysis done in Europe found TTH was responsible for 5,433 million € in total healthcare costs in 2010.[93]

Although TTH is the most common primary headache type, most individuals who present for care do so for migraine headache. Migraine headaches are the second most common type of primary headache. In terms of years of life lived with disability, migraine ranked second globally.[10] Prevalence estimates of chronic migraine (CM) range from 1.4% to 2.2% of the world population.[89] CM is more prevalent in females than males, with both genders experiencing peak prevalence in their 40's.[37] Estimates of annual US costs from emergency department visits to treat migraine range from $646 million to $1.94 billion.[19] Estimates of indirect costs of migraines, which are primarily due to reduced work productivity and missed workdays,[25] range from $5.6 to $17.2 billion worldwide,[45] with a 1999 study from the US estimating indirect costs of migraine to be $13.3 billion.[69]

The public health and economic burdens of chronic primary headache are high. Treatment and prevention of them are of public health importance. Usual management of tension-type headache and migraine include pharmacotherapy and non-pharmacologic approaches, most commonly including

psychological therapy, acupuncture, botulotoxin a, and neuromodulation. . In chronic headache disorders, including chronic tension-type headache (CTTH) and chronic migraine (CM), the focus of treatment is on preventative measures.

2.2 Headache Classifications and Types

This report focuses on patients with chronic migraine (CM), chronic tension-type headache (CTTH), and chronic daily headache. While CM and CTTH are explicitly classified in the 2013 International Classification of Headache Disorders, 3rd edition (ICHD-3)[5] the terminology, definitions, and criteria have evolved over the past two decades.[73,125] The terminology related to chronic migraine in particular and coexistent migraine and tension-type headache varies substantially across clinical practice, the literature,[16] and available patient information. For instance, one source indicates that the term "chronic migraine" has gradually replaced terms such as "transformed migraine" and "chronic daily headache"[125] while other sources suggest that combined tension-type and migraine headaches have been referred to as mixed tension migraine,[9] mixed headache syndrome, transformed migraine, chronic migraine, and chronic daily headache as well as co-existent migraine and tension headache.[4,75] In addition, the pathophysiology of migraine and tension-type headaches are not well understood and some have suggested that they exist along a continuum. Context concerning how terms are used in this report is provided below.

The current principal classifications of headache are based on the International Classification of Headache Disorders, 3rd edition (ICHD-3); deviations from this are noted below and/or in the methods section. The criteria were originally designed to ensure coherent patient populations for research in headache disorders,[125] but also provide a basis for clinical diagnosis.

The ICHD-3 classifies headaches as primary or secondary.[5] Primary headaches, as mentioned previously, are not caused by an underlying disease while secondary headaches are a result of a recognized disease process or other medical condition. Primary headaches include tension-type headaches (TTH), migraines, and trigeminal autonomic cephalgia (such as cluster headaches).[5] TTH and migraines are the disorders included in this report and are two of the most common primary headaches.[99] Common causes of secondary headache are cerebrovascular disease, infection, musculoskeletal disorders, and intracranial space-occupying lesions.[54] Medication overuse headache are another common type of secondary headache. Secondary headaches are not evaluated in this report.

Headaches are also classified according to their frequency in the ICHD-3. Individuals with episodic headaches experience 0 to 14 headache days per month[73] whereas chronic headaches result in 15 or more headache days per month for at least 3 months or more than 180 headache days in a year. The chronic forms of TTH and migraine are the diagnoses of interest for this report. For this report, we have also classified studies of patients presenting with the coexistence of migraine and tension-type headache as patients with chronic daily headache (CDH), so long as the headaches occur in combination in 15 or more days per month. This is not listed as an official classification.

2.2.1 Chronic Migraine

Although migraine is the most common cause of recurrent severe headache, patients may present differently. Migraine diagnosis is made using clinical history and the exclusion of other headache

disorders. Patients are generally asked to maintain a headache diary to assist with the identification of triggers, frequency duration, and severity. Migraine headaches are classified into two subtypes, migraine without aura and migraine with aura. Patients presenting migraine without aura have symptoms occurring unilaterally in a pulsating quality and attacks ranging from 4 to 72 hours. Attacks are moderate to severe in intensity, aggravated by routine physical activity, and associated with nausea, sensitivity to light, and/or sensitivity to noise. The diagnostic criteria from ICHD-3 for migraine without aura are as follows[5]:

I. ≥ 5 attacks fulfilling criteria II-IV
II. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
III. Headache has ≥ 2 of the following characteristics:
    a. Unilateral location
    b. Pulsating quality
    c. Moderate or severe pain intensity
    d. Aggravation by or causing avoidance of routine physical activity
IV. During headache at least one of the following occurs:
    a. Nausea and/or vomiting
    b. Photophobia and phonophobia
V. Not better accounted for by another ICHD-3 diagnosis

Patients presenting migraine with aura have similar symptoms to patients with migraine without aura but have the added presence of an aura. An aura is a disturbance caused by hyper-excited nerves in the brain[4] resulting in visual, sensory, speech, and/or language, motor, brainstem, or retinal symptoms. About 20% of migraine patients are estimated to experience aura.[125] The diagnostic criteria from ICHD-3 for migraine with aura are as follows[5]:

I. ≥ 2 attacks fulfilling criteria II and III
II. One or more of the following fully reversible aura symptoms:
    a. Visual
    b. Sensory
    c. Speech and/or language
    d. Motor
    e. Brainstem
    f. Retinal
III. Headache has ≥ 2 of the following characteristics:
    a. At least one aura symptom that spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession
    b. Each individual aura symptom lasts 5-60 minutes
    c. At least one aura symptom is unilateral
    d. The aura is accompanied, or followed within 60 minutes, by headache
IV. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

The pathophysiology of migraine is complex. Historically, researchers believed migraine to be a vascular disorder with pain caused by the dilation of blood vessels, though more recent research suggests that migraine is caused by a primary neuronal dysfunction that leads to a sequence of changes intracranially

and extracranially.[46] Episodic migraine, EM, (0-14 headache days/month) and chronic migraine, CM, (≥ 15 headache days/month for 3 or more months) appear to be part of the spectrum of migraine disorders but manifest as distinct clinical entities with different epidemiologic and symptom profiles, functional consequences and disabilities, comorbidities and patterns of treatment response.[73] It is estimated that EM may progress to CM at a rate of 2.5% per year[31] with CM remitting to EM at an estimated 2-year transition rate of 26%.[81] Certain classes of medication used to treat episodic migraine appear to increase the risk of developing CM including barbiturates and opiates while evidence regarding others such as triptans or NSAIDS appears to be mixed, with some sources reporting that they do not appear to be associated.[31,73] The American Migraine Prevalence and Prevention study suggests that while a combination of NSAIDS and triptans was not associated with increased risk of CM, triptan monotherapy was significantly associated and risk tended to increase with increasing days of use. The same study reported that NSAIDS appeared to be protective in those with fewer than 10 headache days per month but increased the risk of CM in those with ≥10 headaches per month.[79]

Factors associated with CM include female sex, lower household income, and lower socioeconomic status (SES),[37,126] in addition to potentially modifiable risk factors such as overuse of acute headache medication,[104] depression,[29] obesity,[28] anxiety, caffeine consumption, and snoring.[78] Triggers may include alcohol, hormonal changes, bright or flashing lights, lack of sleep or too much sleep, particular foods or odors, and skipping meals. Progression of frequent, episodic acute migraine attacks to chronic migraine has been termed transformed migraine or chronic daily headache in some literature.

2.2.1.1 Chronic Migraine Usual Care/Comparators

In general, management of primary headache is divided into pharmacologic and non-pharmacologic approaches (e.g., acupuncture, neuromodulation, trigger management, and lifestyle changes). Non-pharmacologic approaches are key for patients with chronic migraine that are medication refractory (i.e., tried and failed multiple pharmacologic treatments), but also for patients who cannot tolerate medications due to side effects, medical illness, or other comorbid states.[100] Additionally, some patients may simply prefer non-drug treatment options.[96] Lifestyle changes focus on regularity of sleep and meals, increasing exercise, and decreasing stress. Trigger management is done by identifying triggers, often using a headache diary, and subsequently minimizing exposure to those. Addressing possible comorbidities such as depression[125] is an important part of the lifestyle change component of management. Usual management of chronic migraine includes psychological therapy as well as pharmacological treatment.[91]

Management of acute episodes for chronic migraine generally focuses on pharmaceutical agents. Acute treatment starts with non-steroidal anti-inflammatory drugs (NSAIDs) or mixed analgesics,[6] drugs that have either one or more types of analgesics or an analgesic combined with another medicine. If migraines are unresponsive to this first-line defense, migraine-specific agents such as triptans, ergotamine, or, more recently, lasmiditan are used.[6] Triptans are serotonin receptor agonists that act to relieve swelling and narrow blood vessels.[9] Ergotamine is also a vasoconstrictor and serotonin agonist,[2] but it targets different receptors.[6] Lasmiditan is a novel and effective antimigraine treatment that has high affinity and selectivity for serotonin 5-HT_{1F} receptors and lacks the vasoconstrictor activity inherent with triptans, thereby making them safer for patients with cardiovascular and/or cerebrovascular diseases.[119]

Common prophylactic treatments for CM are also largely based on pharmaceutical agents, including anti-calcitonin gene-related peptide (CGRP) treatments, beta-blockers, tricyclic antidepressants, calcium channel blockers, angiotensin blockers, anticonvulsants, vitamins, and minerals.[51,125] In 2018, the United States Food and Drug Administration (US FDA) approved the first anti-CGRP migraine treatments specifically to prevent migraine. CGRP is a protein around the brain that causes intense inflammation in the coverings of the brain (the meninges) when released. Anti-CGRP treatments contain Gepants, a small molecule that serves as CGRP antagonist and effectively blocks the CGRP receptor, restricting the blood vessels from constricting and thereby preventing migraine.[12,115] Currently, there are four US FDA-approved drugs acting on the CGRP, or its receptor – erenumab, galcanezumab, fremanezumab, and eptinezumab – the first three of which are intended for self-injection at home.[97]

Beta-blockers, such as propranolol and metoprolol, may treat migraine by reducing adrenergic activity and decreasing neuronal hyper-excitability. Tricyclic antidepressants, including amitriptyline, decrease uptake affinity for norepinephrine and serotonin while also downregulating beta-adrenergic receptors. Like beta-blockers, these are proposed to treat migraine by decreasing neuronal hyper-excitability. Calcium channel blockers such as flunarizine are thought to reduce cortical spreading depression (CSD), a proposed cause of migraine, by inhibiting calcium influx and inhibiting serotonin and glutamate release. The angiotensin blocker candesartan has been used in migraine prophylaxis, but the mechanism remains unclear. Topiramate and sodium valproate are anticonvulsants and two of the most commonly used drugs for the prevention of migraine. Topiramate has been shown to inhibit sodium and calcium channels, inhibit glutamate-mediated neurotransmission, and modulate trigeminovascular signaling, although it has not been determined which mechanism is most vital for migraine prophylaxis.[33] These anticonvulsants have been shown to effectively prevent migraine when compared to placebo.[85] Vitamin B2 has been used to address mitochondrial dysfunction, an issue associated with some types of migraine,[101] while magnesium is a mineral that has been used to target CSD.[51]

Common non-pharmacologic treatment options include Botulinum Toxin A (Botox®) and neuromodulation. The US FDA approved Botulinum Toxin A (Botox®) for the prophylactic treatment of CM in 2010. It has been shown that Botulinum Toxin A is effective in the reduction of headache frequency and severity in patients with CM.[50] Neuromodulation devices have been studied as safe and well-tolerated strategies for the acute and preventive treatment of migraine. There are currently four US FDA-approved devices available.[68] All provide electrical stimulation to extracranial sensory afferent fibers above their depolarization thresholds but below the perceived pain threshold, which activates the central descending inhibitory pathways to inhibit pain.[32] These devices include remote electrical neuromodulation (REN) device, external trigeminal neurostimulation (eTNS) device, single-pulse transcranial magnetic stimulation (sTMS) device, and non-invasive vagal nerve stimulation (nVNS) device pain.[32,57]

Prophylactic treatment is administered when acute treatments have not been effective and the frequency of migraine attacks interferes with day-to-day life (i.e., the patient has four or more headaches a month or at least eight headache days a month).[62,125] Choosing the appropriate preventative agent is based on contraindications, precautions, side effects, compliance issues, patient preference, and cost. Once an agent is chosen, a 2-to-3-month trial period is used to assess the efficacy of the regime.

2.2.2 Chronic Tension-Type Headache

Clinical history and patient presentation form the basis of diagnosing CTTH. Like migraine, patients may be asked to use a diary to record factors that potentially contribute to the disorder, as well as frequency, duration, and severity of attacks. CTTH is characterized by a dull, non-pulsatile, diffuse, band-like bilateral pain of mild to moderate intensity in the head, scalp, or neck. Unlike migraine, TTH does not generally have the clinical features of nausea, sensitivity to noise and light, and unilateral pain.[84] The ICHD-3 diagnostic criteria for chronic tension-type headache are summarized as follows[5]:

I. Headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year), fulfilling criteria II-IV
   II. Lasting hours to days, or unremitting
   III. ≥ 2 of the following characteristics
      a. Bilateral location
      b. Pressing or tightening (non-pulsating) quality
      c. Mild or moderate-intensity
      d. Not aggravated by routine physical activity
IV. Both of the following:
      a. No more than one of photophobia, phonophobia, or mild nausea
      b. Neither moderate or severe nausea nor vomiting
V. Not better accounted for by another ICHD-3 diagnosis

There is no clear cause of tension-type headaches, but there are numerous risk factors and associated comorbidities. Unlike migraine, the relationship between SES or obesity and CTTH is ambiguous.[30] Stress is widely accepted to be a contributing factor to TTH,[71] with CTTH patients presenting higher reported levels of stress and a decreased ability to cope with stress.[41] Population studies have reported correlations between TTHC and anxiety, depression, and mood disorders[67,110] with one study reporting that patients with CTTH were 3 to 15 times more likely to receive a diagnosis of an anxiety or mood disorder.[67,111]

2.2.2.1 Chronic Tension-Type Headache Usual Care/Comparators

Management of acute attacks and prophylaxis are the two pillars of CTTH treatment. The treatment for acute attacks utilizes pharmaceutical agents while prophylactic tactics include both pharmacological and non-pharmacological approaches.

Pharmacological treatments for acute TTH are most commonly the analgesics NSAIDs, typically ibuprofen, and acetaminophen. If analgesics are insufficient at mitigating acute attacks, they can be reinforced with sedating antihistamines, such as promethazine or diphenhydramine, or with antiemetic agents, such as metoclopramide and prochlorperazine. Combining aspirin or acetaminophen with caffeine and butalbital is a further line of defense for acute treatment, although this combination has been strongly linked to promoting chronic daily headache.[49]

The most common pharmacological prophylactic treatment of CTTH are tricyclic antidepressants, with amitriptyline as the most frequently prescribed.[24] The mechanism of amitriptyline has not been fully elucidated, but it's been possible that its inhibition of serotonin reuptake influences the central nervous

system (CNS) and allows for better pain control.[40] Other selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, venlafaxine, and fluoxetine[84] have also been used prophylactically but their efficacy is still debated.[53]

Of nonpharmacological treatments used preventatively, physical therapy may be used,[23] focusing on muscles and joints of the peripheral nervous system.[8,109] The treatment typically includes postural correction, cervical range of motion exercises, isometric strengthening of the neck, self-mobilization exercises of the cervical spine, and whole-body stretching and reconditioning.[82] Physical therapy often includes exercise and physical training. Psycho-behavioral treatments, including EMG biofeedback, cognitive-behavioral therapy, and relaxation training,[24] are also frequently recommended for CTTH. EMG biofeedback is used to help patients recognize and control muscle tension using electrical signals to measure muscle activity.[55] Cognitive behavioral therapy teaches patients to identify thoughts that increase stress and trigger headaches.[24] Relaxation training is based on recognizing and controlling tension that occurs during daily activities.[24]

Similar to chronic migraine, prophylactic treatment is administered when acute treatments have not been effective and the frequency of migraine attacks interferes with day-to-day life.[125]

2.2.3 Chronic Daily Headache, Mixed Headache, Co-existent Migraine and Tension Headache

As mentioned previously, there is substantial variability across sources with the definitions and uses of the terms describing different forms and types of headache disorders, some of which have been used interchangeably. For purposes of this report, we have classified studies of patients presenting with the coexistence of migraine and tension-type headache that, in combination, occur > 15 days per month, although this is not listed as an official classification. We have used the classification of CDH as provided by the study authors. Studies using CDH as a general descriptive term, fitting these parameters have reported that CDH is estimated to occur in 4% of the general population.[16]

The combination of TTH and migraine is one of the most common types of headaches seen in clinical practice and other terms used include mixed tension migraine, mixed headache syndrome, and co-existing migraine and tension headache. Symptoms and triggers vary across patients but generally include symptoms and triggers that characterize tension headache and migraine separately. One headache type may be more prominent and an individual diagnosis of either migraine or TTH may be given.[75] The pathophysiology of combination headache is not well understood but it is believed that typically, patients initially have episodic migraine that causes tension, triggering a tension-type headache.

Medication overuse may contribute to the daily occurrence of headache. Medication over-use headache (MOH), also called rebound headache, is classified in the ICHD-3 as a secondary headache and is commonly associated with CM and CCTH[16] and is frequently described with them although the pathophysiology is not clear. The terminology and criteria for medication overuse have also evolved as has the recognition of its potential impact on patients. Before the ICHD-2, there was no agreed-upon definition of medication overuse and related headache.[52,83] Thus, medication overuse and related headache are variably described in the literature included in this report.

2.2.3.1 Chronic Daily Headache Usual Care/Comparators

As mentioned previously, patients with CDH may present differently and with varying degrees of either CM or CTTH. Treatment of chronic combined migraine and tension headache varies depending on patient presentation and often includes the medications used to treat CM or CTTH.

2.3 Technologies & Interventions

2.3.1 Acupuncture

Acupuncture has been used for thousands of years and is part of a larger system of holistic medicine with roots in Eastern philosophy. This system considers the health of the whole body and focuses on activating or correcting qi. Qi is a difficult word to translate and is therefore often left untranslated. While many dictionaries support the definition that qi is the vital energy source in humans, "energy" is non-specific and has many interpretations. Research and patient response have led to expanded use of acupuncture in a Western medicine setting,[103] with the WHO reporting that acupuncture is effective in treating 28 conditions.[43]

Acupuncture uses solid, filiform needles that are thin and flexible and inserted into the body to directly or indirectly stimulate acupuncture points and other tissues to promote health, aiming to treat organic or functional disorders. Acupuncture can be performed using an individualized, semi-standardized, or standardized technique. Individualized acupuncture bases the points of insertion on the particular symptoms of the patient. The standardized treatment utilizes solely fixed insertion points that do not change between patients. The semi-standardized form is a combination of both techniques.

Acupuncture is commonly used in headache disorders. In 2006, a US survey found that 9.9% of patients that had used acupuncture used it to treat headache disorders.[36] The literature reports slightly different acupuncture techniques between migraine and TTH patients. Although there is variation, acupuncture for the treatment of migraine generally consists of 15 to 20 treatments; insertion points may be standardized or semi-standardized, and needles are left in place for between 20 and 30 minutes.[77] A Cochrane review of acupuncture for TTH prophylaxis found that studies consisted of 6 to 15 sessions, using primarily individualized or semi-standardized methods.[77] There is no U.S. FDA guidance for acupuncture as an intervention, but several different types of needles have received U.S. FDA approval for use in acupuncture.

Electro-acupuncture is another form of acupuncture where a pulsating electrical current is applied to traditional acupuncture needles. Electrodes attached to acupuncture needles send a continuous electrical pulse using an electro-acupuncture device. The added benefits of electro-acupuncture include better control of the stimulation intensity and a stronger stimulation without risk of tissue damage.

Auricular acupuncture is another specific type of acupuncture in which thin needles are inserted at specific points on the outer ear to control pain and other symptoms. It is believed that the outer ear contains a "map" of the whole body and that specific points on this map match up with certain parts of the body.[88]

2.3.1.1 **Proposed Benefits**

The mechanism of action for acupuncture for the treatment of headache disorders is unclear. With migraine, one proposed theory, called the neurovascular theory, is that acupuncture reduces the sensitivity of receptors on the wall of the temporal artery, an artery associated with the development of migraine.[122] The theory suggests that vasodilation caused by migraine activates receptors on the temporal artery, causing stimulation of trigeminal nerves, resulting in neurogenic inflammation.[122] The influence of acupuncture on cerebral hemodynamics is another possible mechanism. A systematic review found that acupuncture positively affected cerebrovascular dysfunction in migraine patients.[80] Acupuncture has also been shown to have effects on brain connectivity and the default mode network (a network of interacting brain regions that is active when a person is not focused on the outside world but rather on their internal mental-state processes) in patients with chronic migraine.[70,131] More recently, a randomized control trial of acupuncture for chronic migraine has suggested that the mechanism of acupuncture may be related to regulating serum levels of 5-hydroxytryptamine(HT) (i.e., serotonin), CGRP, and vascular endothelial growth factor.[74]

Although the mechanisms of acupuncture for the prophylaxis of both migraine and TTH remain somewhat unclear, studies generally agree that acupuncture causes physiological changes in an organism.[38] Some examples of these changes include stimulating the discharge of endorphins (substances that suppress the sensation of pain), increasing endomorphin-1, beta endorphin, enkephalin, and serotonin levels in plasma and brain tissue, and modulating the pain pathway between the peripheral nervous system and the central nervous system.[20,42,56,130] Another possible mechanism that has been suggested is that acupuncture influences the central nervous system. As a result, the intervention may reverse central sensitization and aid in the coping of stress.[53]

2.3.1.2 **Potential Harms and Adverse Events**

Complications associated with acupuncture include infection (e.g., Mycobacterium, Staphylococcus) and organ and tissue injuries.[127] A 2021 systematic review on the risks of acupuncture-related adverse events estimated the overall risk of at least one adverse event during a series of acupuncture treatments to be 9.31 (95% CI 5.10 to 14.62) per 100 patients treated. The estimated risk of an adverse event occurring during a single treatment was 7.57 (95% CI 1.43 to 17.95) per 100 treatments. All adverse events reported were considered minor and transitory; none were considered serious adverse events. Meta-analyses of the overall risk of a severe adverse event (SAE) resulted in 1.01 (95% CI 0.23 to 2.33) in 10,000 patients with an SAE across patients undergoing an acupuncture series and 7.98 (95% CI 1.39 to 20.00) SAEs in one million treatments.[21] The WHO does not recommend acupuncture for people with a disturbance of blood coagulation or unstable epilepsy, and states that acupunctured should not be administered to the lower abdomen or lumbosacral region in women who are pregnant (to avoid contraction of the uterus). Acupuncture treatment should not be administered where ulcers, sores, or scars are present and the depth of needle insertion should be strictly controlled for acupoints located close to vital blood vessels, nerve trunks, and vital organs.[94]

2.4 Published Clinical Guidelines

The ECRI Guideline Trust (based on the former National Guideline Clearing House), PubMed, Google, Google Scholar, professional societies, references in other publications, were searched for evidence-based clinical guidelines related to the use of acupuncture for preventing chronic migraine and chronic tension headache. A summary of the identified clinical guidelines and the strength of recommendations are provided in Table 3 below.

Table 3. Summary of guidelines and consensus statements

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
European Academy of Neurology (EFNS) 2010[24] (Included in prior report) *EFNS guideline on the treatment of tension-type headache – Report of an EFNS task force* Denmark	17 studies, type NR	Acupuncture may be a valuable option for patients with frequent TTH*, although there is no robust scientific evidence for efficacy.	NR
National Institute for Health and Care Excellence (NICE) 2012 (updated in May 2021)[13] (Included in prior report) *Headaches in over 12s: diagnosis and management* United Kingdom	Tension-type headache: 4 RCT Migraine: 4 RCTs†	Tension-type headache: Consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks for the prophylactic treatment of chronic tension-type headache. Migraine with or without aura: If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks according to the person's preference, comorbidities, and risk of adverse events	NR
Institute for Health Economics & Towards Optimized Practice 2016[116] *Primary care management of headache in adults: clinical practice guideline.* Canada	Chronic migraine: 2 guidelines, Institute of Health Economics Database Tension-type headache: 2 guidelines	Chronic Migraine: Acupuncture can be considered in the prophylactic treatment of patients with migraine. Treatment should consist of at least one to two sessions per week for several (two or more) months, with each treatment lasting approximately 30 minutes Tension-type headache: Acupuncture may be considered for	NR

		patients with frequent tension-type headaches.	
VA/DoD 2021[47] *VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache* USA	3 SRs, 1 RCT‡	There is insufficient evidence to recommend for or against acupuncture for the treatment of headaches.	Neither for nor against
Study Group for Chronic Headache Clinical Practice Guideline Development and The Japanese Headache Society 2019[18] *Clinical practice guideline for chronic headache 2013* Japan	NR	Non-pharmacotherapies for chronic tension-type headache include psycho-behavioral therapy, physical therapy, acupuncture, and Tiger Balm®, and those with proven usefulness warrant recommendation as treatment.	Grade A (Strongly recommend)
China Association of Chinese Medicine 2019[98] *Report of guidelines for diagnosis and treatment of common internal diseases in Chinese medicine: Headache* China	Migraine: 2 comparative studies (study design NR) Tension-type headache: 1 comparative study (study design NR)*	NR	Migraine: - Quality of Evidence (GRADE): C (Low) - Strength of recommendation: 1 (Strong) Tension-Type Headache: - Quality of Evidence (GRADE): B (Moderate) - Strength of recommendation: 1 (Strong)
National Clinical Guidelines for Qatar 2016[17] *Clinical Guidelines for the State of Qatar: Headaches in adults* Qatar	2 guidelines	Non-pharmacological treatment of chronic TTH and chronic Migraine should always be considered and should include acupuncture – consider a course of up to 10 sessions over 5-8 weeks	Chronic Tension-Type Headache: Recommendation Grade A2: Evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. Chronic Migraine: Recommendation Grade A1: demonstrates at least moderate

			certainty of at least moderate net benefit.

NR = not reported, RCT = randomized control trial, SR = systematic review, TTH = Tension-Type Headache
*Chronic or episodic was not specified
†Unclear if all trials met our inclusion criteria regarding "chronic" headache
‡Includes data on both chronic or episodic migraine and tension-type headache

2.5 Previous Systematic Reviews & Health Technology Assessments

Systematic reviews (SRs) and health technology assessments (HTAs) were found by searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from July 2017 to November 2021. All the identified SRs included studies of both episodic and chronic HA and/or migraine and none provided results or conclusions specific to chronic HA and/or Migraine only. Most SRs found that acupuncture was associated with fewer headache days. Reference lists of the identified SRs were screened for any potentially relevant studies not captured by the search. The 2017 report included three SRs of acupuncture for migraine and/or tension-type headache,[64,76,77] but none provided evidence specific to chronic headache and were included at the time for completeness only.

2.6 Medicare and Representative Private Insurer Coverage Policies

For this report, we obtained and summarized payer policies from two bellwether payers and any relevant information on National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) from the Centers for Medicare and Medicaid Services (CMS). Coverage decisions are summarized below (Table 4). No LCDs exist for acupuncture for chronic headache or migraine.

Table 4. Overview of CMS and payer policies

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
CMS NCD	N/A	Medicare doesn't cover acupuncture (including dry needling) for any condition other than chronic low back pain.	N/A
Aetna (2021)[14]	2 RCTs, 2 SRs	Aetna considers needle acupuncture (manual or electroacupuncture) medically necessary for chronic (minimum 12 weeks duration) headache. Aetna considers needle acupuncture (manual or electroacupuncture) experimental and investigational for tension headache (chronic/episodic not specified)	NR
Cigna (2021)[44]	3 SRs	If coverage for acupuncture services is available in the applicable benefit plan document, acupuncture may be provided as treatment for Tension-type Headache and Migraine Headache with or without Aura (chronic/episodic not specified) when ALL of the medical necessity factors and ALL of the treatment planning/outcomes listed below are met: <u>Medical Necessity Factors:</u> • Medically necessary services must be delivered toward defined reasonable and evidence-based goals;	NR

		• Medical necessity decisions must be based on patient presentation including diagnosis, severity, and documented clinical findings; • Continuation of treatment is contingent upon progression towards defined treatment goals and evidenced by specific significant objective functional improvements (e.g., outcome assessment scales, range of motion) • Certain conditions require that the patient is being co-managed by a medical physician in order to be considered medically necessary; • Medically necessary services including monitoring of outcomes and progress with a change in treatment or withdrawal of treatment if the patient is not improving or is regressing. <u>Treatment Planning/Outcome Factors:</u> • An individualized treatment plan (e.g., frequency and duration of service) is appropriately correlated with clinical findings and clinical evidence; • Treatment is expected to result in significant therapeutic improvement over a clearly defined period of time; • Therapeutic goals are functionally oriented, realistic, measurable, and evidence-based; • Proposed date of release/discharge from treatment is estimated; • Functional Outcome Measures (FOM)1, when used, demonstrates Minimal Clinically Important Difference (MCID)1 from baseline results through periodic re-assessments; • Documentation substantiates practitioner's diagnosis and treatment plan; • Demonstration of progression toward active home/self-care and discharge, and; • Maximum therapeutic benefit has not been reached.	

CMS = Centers for Medicare and Medicaid Services; N/A = not applicable; NCD = National Coverage Determination; NR = not reported; RCTs = randomized controlled trials; SR = systematic review.

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

This report aimed to evaluate and synthesize published evidence on the efficacy, safety, and cost-effectiveness of acupuncture compared with standard active treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults. This review updated the acupuncture section of 2017 Chronic Migraine and Chronic Tension-type Headache HTA and followed the same basic Key Questions, definitions, and scope as the prior report as they apply to acupuncture.

3.1.2 Key Questions

Specific key questions, as formulated by the HCA/Agency for the original report have been modified to reflect the focus of this update on the use of acupuncture for chronic migraine and chronic tension-type headache. For this update, public comments received following topic posting for a stand-alone review for acupuncture, and on draft key questions were reviewed and considered.

In adults with chronic migraine or chronic tension-type headache:

1. What is the evidence of the short- and long-term efficacy and effectiveness of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
2. What is the evidence regarding short- and long-term harms and complications of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
3. Is there evidence of differential efficacy, effectiveness, or safety of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?
4. What is the evidence of cost-effectiveness of acupuncture compared with standard active treatment options, placebo, sham, waitlist, or no treatment?

3.1.3 Inclusion/Exclusion Criteria

below provides a summary of the inclusion and exclusion criteria. At the request of the HTA program, the general scope of this re-review (e.g., headache definitions and population inclusion criteria) remained the same as the prior HTA with the exception that acupuncture is the sole intervention of interest. Briefly, included studies met the following requirements concerning participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with chronic migraine (with or without aura) or chronic tension-type headache. Chronic headache is defined as 15 or more days each month for at least 3 months or more than 180 days a year (International Classification of Headache Disorders, 3rd edition definition). 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 in the original report and chronic daily headache was defined as combined migraine and tension headache.

- **Intervention:** Acupuncture.
- **Comparators:** Standard/usual treatment(s) (e.g., pharmacological treatment, psychological/behavioral therapies, conventional physical therapy), placebo/sham, no treatment, waitlist.
- **Outcomes:** Primary clinical outcomes (studies must report at least one of the following for inclusion) are : 1) Proportion of responders (e.g., at least 50% reduction of headache frequency from baseline for 3–4 months following treatment); 2) Complete cessation/prevention of headache; reduction in the mean number of episodes and/or headache days; 3) Function/disability with a focus on validated measures (e.g., MIDAS, Migraine Disability Scale); 4) Harms, treatment-related adverse events, treatment discontinuation due to adverse events. Economic outcomes are incremental cost-effectiveness ratio (ICER) or similar outcomes.
- **Studies:** Studies must report at least one of the primary outcomes**.** The focus was on studies with the least potential for bias such as high-quality systematic reviews of randomized controlled trials (RCTs) which focus on the population of interest for this review and high-quality (low risk of bias) RCTs for Key Questions 1-2. For Key Question 3, RCTs that stratified on baseline patient characteristics and evaluated effect modification were included. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) were sought for Key Question 4.
- **Timing:** Focus was on intermediate (>8 weeks to <12 weeks) and long-term (≥12 weeks) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Table 5 below provides a summary of the inclusion and exclusion criteria. At the request of the HTA program, the general scope of this re-review (e.g., headache definitions and population inclusion criteria) remained the same as the prior HTA with the exception that acupuncture is the sole intervention of interest. Briefly, included studies met the following requirements concerning participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with chronic migraine (with or without aura) or chronic tension-type headache. Chronic headache is defined as 15 or more days each month for at least 3 months or more than 180 days a year (International Classification of Headache Disorders, 3rd edition definition). 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 in the original report and chronic daily headache was defined as combined migraine and tension headache.
- **Intervention:** Acupuncture.

- **Comparators:** Standard/usual treatment(s) (e.g., pharmacological treatment, psychological/behavioral therapies, conventional physical therapy), placebo/sham, no treatment, waitlist.
- **Outcomes:** Primary clinical outcomes (studies must report at least one of the following for inclusion) are : 1) Proportion of responders (e.g., at least 50% reduction of headache frequency from baseline for 3–4 months following treatment); 2) Complete cessation/prevention of headache; reduction in the mean number of episodes and/or headache days; 3) Function/disability with a focus on validated measures (e.g., MIDAS, Migraine Disability Scale); 4) Harms, treatment-related adverse events, treatment discontinuation due to adverse events. Economic outcomes are incremental cost-effectiveness ratio (ICER) or similar outcomes.
- **Studies:** Studies must report at least one of the primary outcomes**.** The focus was on studies with the least potential for bias such as high-quality systematic reviews of randomized controlled trials (RCTs) which focus on the population of interest for this review and high-quality (low risk of bias) RCTs for Key Questions 1-2. For Key Question 3, RCTs that stratified on baseline patient characteristics and evaluated effect modification were included. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) were sought for Key Question 4.
- **Timing:** Focus was on intermediate (>8 weeks to <12 weeks) and long-term (≥12 weeks) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Table 5. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Adults with chronic headache* of the following types: • Migraine (with or without aura) • Tension-type headache • Chronic daily headache, defined as coexistent chronic migraine and tension-type headache	• Persons <18 years old • Pregnant or breast-feeding women • Acute headache or acute migraine attacks • Episodic migraine, tension-type headache, or chronic daily headache (headaches occurring <15 days per month) • Menstrual migraine • New daily persistent headache • Hospitalized patients • Patients treated in the emergency department • Other primary headaches (e.g., trigeminal autonomic cephalgia including cluster headache) • Secondary headache types as defined in The International Classification of Headache Disorders, 3rd edition • Acute trauma-related headache

Study Component	Inclusion	Exclusion
		• Medication overuse headache/medication rebound headaches as the primary population/study focus • Headache due to malignancy; cancer-related headache • Operative or procedure-related headache • Cervical dystonia • Neuropathic pain • Neck pain not associated with headache
Interventions	• Acupuncture	• Treatments for acute headache; abortive treatments for acute episodes • Interventions that are not FDA approved and/or are not available in the U.S. • Dysport (abobotulinumtoxinA), incobotulinumtoxinA, RimabotulinumtoxinB) (not FDA approved for use in migraine/headache) • Evaluation of incremental value of combining interventions (e.g., chiropractic manipulation plus physical therapy) • Implantable devices (e.g., spinal cord stimulators, implantable occipital nerve stimulators, implantable catheters) • Treatments other than acupuncture included in the 2017 HTA: Botulinum toxin injection (Botox, OnabotulinumtoxinA, BoNTA), trigger point injection or dry needling, transcranial magnetic stimulation (TMS), manipulation/manual therapy (e.g., osteopathic, chiropractic), massage • Nerve block • Biofeedback • TENS • Peripheral nerve decompression surgery • Occipital nerve stimulation • Vagal nerve stimulation (implantable) • Hypothalamic deep brain stimulation • Intranasal sphenopalatine ganglion blocks • Psychological therapies or behavioral interventions (e.g. cognitive behavioral therapy, education, etc.) • Pharmacological treatment (including oral agents such as opioids, NSAIDS, beta blockers, antiepileptics, calcium channel blockers, calcium channel antagonists, antidepressants,

Study Component	Inclusion	Exclusion
		ACE inhibitors, Angiotensin II antagonists, etc.) • Intervention that is part of a multi-modal treatment • Dietary supplements • Exercise/physical activity • Yoga, Tai Chi • Physical therapy • Laser therapy • Ultrasound • Inferential therapy • Hyperbaric oxygen • Surgical treatment (e.g., suborbital nerve decompression, microvascular decompression of the trigeminal nerve) • Laser therapy • Transcranial direct current stimulation • Trager work/Trager approach
Comparator	• Usual treatment(s) (e.g., pharmacological treatment, psychological therapies or behavioral interventions including biofeedback, conventional physical therapy) • Placebo/Sham† • No treatment • Waitlist	• Comparisons of different forms of the same treatment • Comparisons of timing interventions • Combined pharmacological and procedural interventions • Combined interventions (e.g., chiropractic manipulation plus PT) • Medications that are not FDA approved for use in the United States • Excluded interventions from above except as noted for inclusion
Outcomes	**Primary** Studies must report at least one of the following for inclusion: • Proportion of responders (e.g., at least 50% reduction of headache frequency from baseline for 3-4 months following treatment) • Complete cessation/prevention of headache; reduction in mean number of episodes and/or headache days • Function/disability – focus on validated measures (e.g., BURMIG, burden of migraine; HADLI, Headache Activities of Daily Living Index; HDI, Headache Disability Index (Inventory); HDQ, Headache Disability	• Non-clinical outcomes • Intermediate outcomes • Imaging outcomes

Study Component	Inclusion	Exclusion
	Questionnaire; HIT-6, Headache Impact Test; MIDAS, Migraine Disability Scale) • Harms, treatment-related adverse events, treatment discontinuation due to adverse events **Secondary or intermediate** • Quality of life • Patient satisfaction • Emergency department visits • Loss of working days • Headache intensity • Frequency of analgesic use • Headache scores	
Study Design	Focus will be on studies with the least potential for bias. **Key Questions 1-2:** • High quality systematic reviews of RCTs will be considered if available. • Randomized controlled trials (RCTs) **Key Question 2:** • Randomized controlled trials (RCTs) • Data from non-randomized comparative studies at low risk of bias may be considered for safety if needed to supplement RCT safety data • Case series designed specifically to evaluate harms/adverse events may be considered only for rare events or short or long-term safety in the absence of information from high quality comparative studies **Key Question 3:** • RCTs which stratify on patient or other characteristics and formally evaluate statistical interaction (effect modification) **Key Question 4:** • Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Non-comparative studies (case series) (except as described to evaluate rare or long-term harms) • Incomplete economic evaluations such as costing studies • Studies with fewer than 10 patients per treatment group • Case reports • Studies in which <80% of patients have a condition or treatment of interest
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports	• Abstracts, editorials, letters

Study Component	Inclusion	Exclusion
		• Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions
Timing	• Focus will be on intermediate (>8 weeks to <12 weeks) and long term (≥12 weeks) for efficacy outcomes, particularly cessation/prevention; any time frame for harms	• Studies with less than 1 week follow-up past intervention

* While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more headache days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions and timeframes (e.g., 28-day period or 30-day period for a month). Given these variations, studies reporting populations with a mean of ≥12 headache days per month or ≥12 headache episodes or attacks per month or equivalent were considered to meet the criteria for chronic headache.

† Studies comparing treatments to sham treatments (even those which may be considered "active") as one type of comparator provides valuable information regarding treatment efficacy for pain conditions. Subjective improvement in patients may result from factors other than a given procedure, whether that treatment is an "active" sham or a specified intervention. Some of these factors include the natural course of the condition, the effects of placebo, and measurement error. A placebo effect does not require a physical placebo and reflects a change in a patient's condition attributable to the symbolic importance of a treatment versus specific physiologic or pharmacologic properties.

For this report, we have classified studies of patients presenting with the coexistence of migraine and tension-type headache that, in combination, occur > 15 days per month, as patients with chronic daily headache (CDH), which is generally consistent with the terminology used by authors. While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more headache days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions and timeframes (e.g., 28-day period or 30-day period for a month). Given these variations, for this report, trials reporting populations with a mean of ≥12 headache days per month or ≥12 headache episodes or attacks per month or equivalent were considered to meet the criteria for chronic headache.

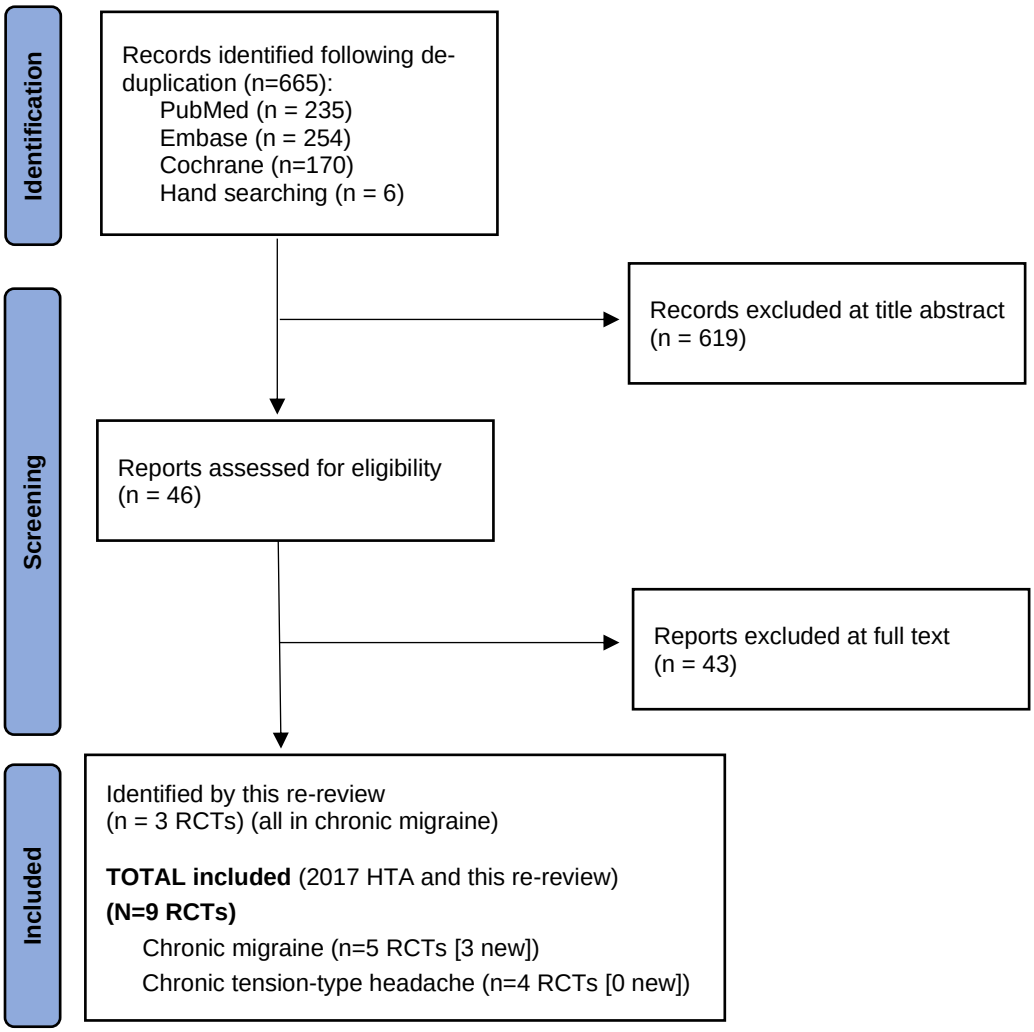
3.1.4 Data Sources and Search Strategy

We conducted an electronic literature search for the period July 1, 2016, to November 17, 2021, using identical search terms used for the original report for key questions 1 through 4. This search included 2 main databases: PubMed and Cochrane Library. We also searched Embase for this update; see Appendix B for search methodology and additional details. The searches were focused on the use of acupuncture in chronic migraine and chronic tension-type headache. In addition, a detailed evaluation of citations listed in a stakeholder petition to the HTAP was completed; citations were compared against the inclusion/exclusion criteria.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of the

comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of a priori retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full-text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report, Figure 2.

Figure 2. Flow of studies diagram



HTA = Health Technology Assessment; RCT = randomized controlled trial

3.1.5 Data Extraction

As in the previous report[105], reviewers extracted the following data from the clinical studies: study design, study period, setting, country, sample size, inclusion and exclusion criteria, study population characteristics, study interventions, follow-up time post-treatment, characteristics of the control intervention, study outcomes, and adverse events. Information on headache history (e.g., duration of headaches, frequency of episodes, number of headache days, etc.) was also abstracted. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. A second reviewer checked the data for accuracy. Detailed study and patient characteristics are available in Appendix F, Tables F1-F2, all results are available in the results section of this document and in Appendix F, Tables F3–F5.

3.1.6 Quality Assessment: Overall Strength of Evidence (SOE), Risk of Bias, and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) is based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations, and potential for bias based on study design as well as factors that may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[65] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Review*.[1] Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et. al. in conjunction with consideration of epidemiologic principles that may impact findings.[92] Based on these quality criteria, each study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating (Table 6 below); criteria are further detailed in Appendix D. Standardized, pre-defined abstraction guidelines were used to determine the RoB (or QHES) rating for each study included in this assessment. Discrepancies in ratings between reviewers were resolved through discussion and consensus.

Table 6. Definition of the risk of bias categories

Risk of Bias	Definition
Low risk of bias	Study adheres to commonly held tenets of high-quality design, execution and avoidance of bias
Moderately low risk of bias	Study has potential for some bias; does not meet all criteria for low risk of bias but deficiencies not likely to invalidate results or introduce significant bias
Moderately high risk of bias	Study has flaws in design and/or execution that increase potential for bias that may invalidate study results
High risk of bias	Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development, and Evaluation)[58,60,61] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1] The strength of evidence was based on the highest quality evidence available for the primary outcomes. Evidence on acupuncture from the prior report was combined with new evidence. Determination of SOE considered the whole body of available evidence.

In determining the strength of the body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range, and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of intervention comparisons are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is the concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had a large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias is difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[27,102] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High – Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect, or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7 Analysis

As in the previous report[105], evidence was summarized separately for chronic migraine, chronic tension-type headache, and chronic daily headache (defined as co-existent chronic migraine and tension headache). Outcomes were stratified by duration of follow-up post-intervention. For all trials, post-intervention follow-up times of short (≤ 8 weeks), intermediate (>8 weeks to 12 weeks), or longer-term (≥ 12 weeks) were reported. When more than one follow-up time was reported within a category, we used data from the longest duration available within that category.

Evidence was summarized qualitatively and quantitatively. Meta-analyses were considered when there were two or more studies with similar patient populations, indications, interventions, control groups, and outcomes. Initially, we grouped control treatments according to whether the control was a sham treatment or an active comparator (e.g., usual care, pharmacological agent, physical therapy). For all dichotomous outcomes, risk ratios (RR) or risk differences (RD) and their respective 95% confidence intervals (CI) were calculated to compare the rate of occurrence or relative risk between treatments. Studies were weighted and pooled together using the Mantel-Haenszel and DerSimonian-Laird methods.[48] For those dichotomous outcomes that could not be pooled, RRs and RDs (if applicable) were calculated using the Rothman Episheet.[7]

For all continuous outcomes on the same scale, mean differences (MD) and their respective 95% confidence intervals were calculated. We categorized the magnitude of effects for pain (i.e., headache intensity/severity) measures with a 0 to 10 scale as small (0.5 to 1 point), moderate (>1 to 2 points), or large/substantial (>2 points) using the same system as in the American College of Physicians/American Pain Society (ACP/APS) review on low back pain.[77] For outcomes that could be pooled, mean differences were weighted according to the inverse of their variance. A random-effects model was assumed to better account for inter-study variability. For some comparisons, the mean difference was calculated using the change between the follow-up and baseline scores. In studies with multiple intervention arms, care was taken to avoid including individual patients more than once in the meta-analysis. When necessary, the sample size of a treatment arm was adjusted (typically halved) so that the total pooled sample size always matched the number of patients. If standard errors (SE) or 95% confidence intervals were reported instead of standard deviations; these values were converted to standard deviations: SD = SE*√n), and SE = (95% CI upper bound – 95% CI lower bound) ÷ 3.92. If the follow-up SD had to be calculated from the baseline (B) and change (C) SD, the following equation was used: follow-up SD = [-1.6B ± √ [(-1.6B)^2 – 4(B^2-C^2)]] ÷ 2. If the standard deviation of the change score needed to be calculated the correlation between baseline and follow-up scores was assumed to be 0.8. In instances where SDs were missing and not possible to calculate from other accessible values, they were imputed using strategies suggested by the *Cochrane Handbook*.[65] These strategies included assuming follow-up values shared similar distributions as baseline values or if there were a sufficient number of other studies, then an average was assumed for the missing value. Lastly, if p-values were reported as only significant or non-significant (i.e., p<0.05 or NS) the upper limit was used. The SD was averaged across groups in this case. These methods are consistent with those outlined in the *Cochrane Handbook*.

We assessed the presence of statistical heterogeneity among the studies by using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I^2 statistic.[66] When statistical heterogeneity was present, we explored possible explanations based on patient populations, intervention delivery, and clinical factors and performed sensitivity analyses first by omitting obvious

outliers if sufficient data and trials were available. All meta-analysis results and figures were produced using Review Manager v5.4.1. Outcomes not represented in the meta-analyses are detailed in the evidence tables in the appendices and/or the body of the report.

4 Results

4.1 Number of Studies Retained & Overall Quality of Studies

The prior report identified and included six trials (across 9 publications)[39,72,107,108,114,117,118,128,129] of acupuncture for the treatment of chronic migraine or chronic tension-type headache. No trials evaluating acupuncture for chronic daily headache were included in the prior report. This update adds three trials[63,86,87] to the evidence base for a total of nine trials. All newly included trials assessed acupuncture for chronic migraine. No trials evaluating acupuncture for chronic tension-type headache or chronic daily headache and no formal economic studies that met inclusion criteria were identified for this update. Table 7 below provides a summary of the evidence base for this update.

Table 7. Number of studies for each comparison of efficacy for included conditions

Comparisons	2017 Report	2022 Update	Total
CHRONIC MIGRAINE			
Acupuncture vs. UC/Sham/WL	1 RCT[117,118]	2 RCTs[63,86]	3 RCTs (across 4 publications)[63,86,117,118]
Acupuncture vs. Pharmacological treatment*	1 RCT[128,129]	1 RCT[87]	2 RCTs (across 3 publications)[87,128,129]
Acupuncture vs. Botulinum toxin*	None identified.	1 RCT[87]	1 RCT[87]
TOTAL			5 RCTs (across 7 publications) [63,86,87,117,118,128,129]
CHRONIC TENSION-TYPE HEADACHE			
Acupuncture vs. Sham	2 RCT[72,114]	None identified.	2 RCTs[72,114]
Acupuncture vs. Physical Training†	1 RCT (2 publications)[107,108]	None identified.	1 RCT (across 2 publications) [107,108]
Acupuncture vs. Physiotherapy	1 RCT[39]	None identified.	1 RCT[39]
Acupuncture vs. Relaxation Training†	1 RCT (across 2 publications)[107,108]	None identified.	1 RCT(2 publications)[107,108]
TOTAL			4 RCTs (across 5 publications)[39,72,107,108,114]
CHRONIC DAILY HEADACHE			
	None identified.	None identified.	None identified.

RCT = randomized controlled trial; UC = usual care; WL = waitlist.

*One study (Naderinabi 2017)[87] had 3 arms: acupuncture, Botulinum toxin, and sodium valproate.

†One study (Soderberg 2006, 2011)[107,108] had 3 arms: acupuncture, physical training, and relaxation training.

Regarding the overall quality of included randomized controlled trials (RCTs), the majority (n=7) were rated at moderately high risk of bias (poor quality RCTs); two trials, both in chronic migraine, were rated at moderately low risk of bias (moderate-quality RCT).[86,129] No trial was rated at low risk of bias (good quality). Common methodological limitations across the trials included unclear randomization and allocation concealment methods, high (or unclear) loss to follow-up, and baseline differences between intervention groups. In trials with active controls (i.e., not sham), the inability to blind interventions was

a further limitation. One economic study (in chronic migraine) met inclusion criteria and was rated poor to moderate quality. Detailed descriptions of study quality are provided below for each headache type and comparator set and in Appendix E.

As was true for the previous report[105], while not directly related to study quality, aspects of study reporting described below should be considered for context.

The terminology and criteria related to headache classification have evolved over the last few decades and there is inconsistency in how headaches are described in the literature and clinically. As a consequence, the terminology used in clinical studies has also varied.

Across studies, headache types, and comparators, the majority of patients were female, with mean ages ranging from 33 to 49 years old (pooled mean age 44 years). The mean number of migraine days per month ranged from 12 to 27. In general, a large proportion of study participants reported previous use of prophylactic medications and a few trials permitted concurrent use of them. Almost all trials allowed the use of rescue medication. Overuse of medications was variably defined and variably reported across trials; some trials excluded patients with medication overuse, others reported a large proportion of participants with overuse. Given the evolution of criteria and recognition of medication overuse over the past two decades, the prevalence across studies is unclear as is the impact of it on findings. Where provided, we report data on medication overuse.

The majority of trials compared acupuncture with active alternate treatments that might be used to treat headache conditions. Three trials (1 chronic migraine and 2 chronic tension-type headache) employed sham as control groups. These types of controls provide valuable information regarding treatment efficacy for pain conditions by controlling for factors such as the natural course of the condition, the effects of placebo, and measurement error but do not provide comparative information regarding active treatments.

4.2 Key Question 1: Efficacy & Effectiveness

4.2.1 Chronic Migraine

Five trials (3 new to this report) of acupuncture for chronic migraine met inclusion criteria.[63,86,87,117,129] Comparators included sham plus usual pharmacologic therapy (1 new RCT)[63], waitlist (WL) plus usual care (UC) (1 new RCT)[63], UC alone (1 RCT)[117], pharmacologic treatment (2 RCTs [1 new])[87,129], and Botulinum toxin A (1 new RCT)[87]; one trial had three arms and compared acupuncture to both pharmacological therapy and Botulinum toxin A.[87] Two.[86,129] were rated at moderately low risk of bias (i.e., fair quality) and three.[63,87,117] were rated at moderately high risk of bias (i.e., poor quality). Brief overviews of each trial are provided below, and detailed information on patient and study characteristics is available in Appendix F, Table F1; for risk of bias ratings, see Appendix E, Tables E1–E2.

The addition of the three new trials[63,86,117] provided the opportunity to pool across outcomes that were not amenable to pooling previously. The results from the 2017 report were re-evaluated for accuracy and edits have been made for consistency with this updated review. Our primary analyses for chronic

migraine are presented below by outcome, across all comparator types, stratified by follow-up time frame (short or long term).

4.2.1.1 Summary of Results for Chronic Migraine

The bullet points below provide summary statements and strength of evidence only for the primary efficacy outcomes of interest to this report. Details on secondary outcomes can be found in the section that follows. In general, results indicated that acupuncture was beneficial for reducing the number and severity of acute headache episodes over the short and long term compared with sham and active treatments and in reducing disability over the short term compared with pharmacologic therapy; the strength of evidence was primarily low.

Treatment Responders

- In the short-term (1 week), more acupuncture patients experienced **≥50% reduction in *any* headache days** and **in *moderate to severe* headache days** from baseline compared with topiramate in one RCT[129] (low SOE for both outcomes).
- In the long-term (24–36 weeks), more acupuncture patients experienced **≥50% reduction in *any* headache days** from baseline compared with WL and/or UC across 2 RCTs[86,117] at 24 and 36 weeks post-treatment (moderate SOE) and in both ***moderate to severe* and *mild* headache days** compared with usual care in one RCT[117] at 36 weeks post-treatment (low SOE for both outcomes).
- In the long-term (36 weeks), more acupuncture patients had a **≥35% improvement in *headache score*** from baseline compared with UC in one RCT[117] (low SOE).

Reduction in Headache Frequency

Headache days per month

- In the short-term (1–8 weeks), acupuncture was associated with a greater **reduction in mean headache days per month** from baseline compared with sham/UC and active controls (topiramate, sodium valproate, and Botulinum toxin A) across 3 RCTs[63,87,129] and in ***moderate to severe* headache days per month** compared with topiramate in one RCT[129] (low SOE for both outcomes).
- In the long-term (12–36 weeks), acupuncture was associated with a greater **reduction in mean headache days per month** from baseline compared with sham/UC and active controls (WL and/or UC, sodium valproate, and Botulinum toxin A) across 3 RCTs[86,87,117] (moderate SOE) and in ***moderate to severe* and *mild* headache days per month** compared with UC in one RCT[117] (low SOE for both outcomes).

Headache episodes/attacks per month

- In the short-term (4 weeks), data from one RCT[63] comparing auricular acupuncture with sham plus UC were insufficient to draw conclusions regarding **reduction in headache episodes/attacks per month** from baseline.
- In the long-term (24 weeks), there was no difference between patients randomized to acupuncture versus WL/UC in a **reduction in headache episodes/attacks per month** from baseline in one RCT[86] (low SOE).

Migraine Disability Assessment (MIDAS)

- In the short-term (1 week), acupuncture was associated with a greater reduction in **MIDAS scores**, suggesting improved function, compared with topiramate in one RCT[129] (low SOE).
- In the long-term (24 weeks), there was no difference between patients randomized to acupuncture versus WL/UC in **MIDAS scores** in one RCT[86] (low SOE).

4.2.1.2 Description of Study Populations for Chronic Migraine

Acupuncture vs. Sham, Usual Care or Waitlist

Three trials (n=467)[63,86,117] compared acupuncture with sham (plus UC), WL (plus UC), or UC alone for the treatment of chronic migraine (Table 8). The frequency and duration of the acupuncture intervention varied greatly across the included trials. One trial[117] included up to 12 acupuncture treatments over 3 months, one trial[86] consisted of 14 acupuncture treatments over 3 months, and the third trial[63] consisted of two acupuncture treatments performed two weeks apart. Two of the trials employed Traditional Chinese Medicine Acupuncture[86,117] and one trial[63] used Auricular Acupuncture with semi-permanent needles. Manual manipulation to elicit De Qi was used in one trial[86] and the other two trials did not mention manipulation. Two trials reported on the number of acupuncture points or number of needles used. One trial[63] examined 20 acupuncture points and implanted a maximum of four needles in the most active points in each ear. The other trial[86] had four mandatory acupuncture points and 16 optional points with a limit of 9 to 12 needles used per session. In one trial[63], patients in the intervention group were also provided 20 mg of propranolol every 12 hours. Control groups included UC from a general practitioner (not otherwise specified)[117], sham acupuncture (a piece of adhesive tape placed on the inactive acupuncture points of the ears) plus usual treatment consisting of 20 mg of propranolol every 12 hours,[63] and WL plus standard pharmacological treatment (not otherwise specified)[86]. One trial[117] excluded patients with prior acupuncture within the last 12 months, one trial[63] excluded patients who previously received auricular acupuncture, and the third trial[86] excluded patients if they received acupuncture to the face, hands, legs, or front part of the body within the past 6 months. None of the trials reported whether patients had previously received preventative treatments other than acupuncture. The majority of patients were female (range 79%–89%). Mean age ranged from 37 to 46 years, mean frequency of headache ranged from 12.0 to 15.6 days per month, and mean duration of chronicity ranged from 11 to 25 years. Only one trial[117] reported excluded patients with medication over use headache, the other two made no mention of this. Of note, in the trial comparing acupuncture with UC alone, the authors report that some patients continued to receive acupuncture after the initial 12

week treatment period (25 patients [16%] after 12 weeks, 10 patients [6%] after 24 weeks, and 6 patients [4%] after 36 weeks); only three patients (2%) in the control group reported receiving acupuncture outside the study.[117] It is unclear how this continuation of treatment may have affected outcomes.

Two trials[63,117] were rated at moderately high risk of bias and one trial[86] was rated at moderately low risk of bias. Methodological limitations in the latter trial included a lack of blinded assessment (outcomes were patient-reported and patients could not be blinded) and baseline differences between groups (uncontrolled). In the two trials at moderately high risk of bias, primary limitations included unclear allocation concealment methods, violation of intention to treat principle, high (or unclear) loss to follow-up, and in the trial that included an active control, lack of blinded outcome assessment. Of note, in the trial comparing auricular acupuncture with sham[63], authors state that patients were excluded from the study if they developed redness or infection at the location of the needle implant, used other analgesics during the study, or were unwilling to continue their cooperation in the present study; none of these patients were accounted for, raising concerns about attrition/differential attrition that might impact the validity of the results.

Acupuncture vs. Pharmacological Treatment

Two trials (n=166)[87,129] compared acupuncture with pharmacological treatment for the treatment of chronic migraine (Table 9). One trial[129] compared 24 acupuncture treatments over 3 months with Topiramate (25 mg/day for the first month, then 100 mg/day for the final 2 months). The second trial[87] compared 30 acupuncture treatments over 2 months with 3 months of Sodium Valproate (500 mg/day). Both trials employed Traditional Chinese Medicine Acupuncture and used manual manipulation to elicit De Qi.[87,129] One trial[129] reported using seven needles total and the other trial[87] stated to provide acupuncture at 10 to 12 acupuncture points. Patients in both trials were excluded if they had recently received previous acupuncture or if they had taken prophylactic drugs within the past 3 months (including Botox for one trial[87]). The majority of patients were female (range 62%–90%). Mean age ranged from 37 to 48 years, mean duration of chronicity ranged from 10 to 13 years, and mean frequency of headache was 21 days per month in both trials. In one trial[129], 75% of patients were diagnosed with medication overuse headache, while the other trial[87] excluded patients with this diagnosis. The trials were rated at moderately low[129] (due to unclear allocation concealment methods and lack of blinded assessment) and moderately high[87] (due to unclear randomization and allocation concealment methods and lack of blinded assessment) risk of bias.

Acupuncture vs. Botulinum toxin A

One trial[87] (n=100) compared acupuncture with Botulinum toxin A for the treatment of chronic migraine (Table 9). Acupuncture treatment consisted of 30 acupuncture treatments over 2 months. This trial employed Traditional Chinese Medicine Acupuncture at 10 to 12 acupuncture points and used manual manipulation to elicit De Qi. For Botulinum toxin A treatment, investigators administered 31 fixed-site, fixed-dose, intramuscular injections across seven specific head/neck muscle areas every 12 weeks for 24 weeks (two cycles). Patients who had received prior preventative treatments (including acupuncture) were excluded. The majority of patients were female (56%) and the mean age was 37 years. No patient had a diagnosis of medication overuse headache. The frequency of headache was 22.5 headaches per month and the duration of chronicity was 9.8 years. The trial was rated at moderately high risk of bias due to unclear randomization and allocation concealment methods, lack of blinded assessment, and

differences at baseline between the acupuncture and Botulinum toxin groups on important clinical factors.

Table 8. Summary of patient, baseline and procedural characteristics from trials assessing acupuncture versus usual care, waitlist, or sham for the treatment of chronic migraine

Patient demographics	Study					
	Vickers 2004[††]		Habibabadi 2021		Musil 2018	
	N = 401		N = 80		N = 86	
	Acupuncture	Usual care[*]	Acupuncture	Sham[†]	Acupuncture	Waitlist[§]
Randomized	n=205	n=196	n=40	n=40	n=42	n=44
Treated	n=186	n=193	n=40	n=40	n=42	n=44
Mean Age, years	46.4	46.2	37.1	36.7	45.6	46.5
Female, %	83%	86%	80%	78%	88%	89%
Mean Chronicity of Headache (years)	21.3	21.9	10.7	10.5	26.9	23.0
Mean No. Migraine days/month	15.6	16.2	13.5	13.0	11.97	12.1
Mean No. Migraine attacks/month	NR	NR	14.9	16.0	6.4[**]	6.0[**]
Medication overuse, %	0%[‡‡]	0%[‡‡]	NR	NR	NR[§§]	NR[§§]
Prior acupuncture, %	0%[***]	0%[***]	0%[†††]	0%[†††]	0%[§§§]	0%[§§§]
Prior preventative treatments other than acupuncture, %	NR	NR	NR	NR	NR	NR
Procedural characteristics						
Acupuncture type	Traditional Chinese Medicine	NA	Auricular, semi-permanent	NA[†]	Traditional Chinese Medicine	NA
Number of acupuncture points, needles	NR	NA	20 examined; limit 4 needles in each ear	NA	4 mandatory, 16 optional; limit 9–12 needles each session	NA
Manipulation of needles	NR	NA	NR	NA	Manual, to elicit De Qi	NA
Number of treatment sessions	Maximum 12	NA	2	2	14	NA
Duration of treatment	12 weeks	12 weeks	2 weeks	2 weeks	12 weeks	12 weeks

Patient demographics	Study					
Followed, % (n/N)	78.5% (161/205)	71.4% (140/196)	100% (40/40)	100% (40/40)	95% (40/42)	93% (41/44)
Co-interventions	Standard care from GP (NOS)	NR – "avoid acupuncture"	propranolol 20 mg every 12 hours.; rescue medication as needed‡	propranolol 20 mg every 12 hours. rescue medication as needed‡	Prophylactic meds as needed****	Standard pharmacologic treatment††††
Country	United Kingdom		Iran		China	
Funding	NHS R&D National Coordinating Centre for HTA		NR		MH CZ-DRO (UHHK, 00179906)	

GP = general practitioner; NA = not applicable; NOS = not otherwise specified; NR = not reported; TCM = traditional Chinese medicine.
* Patients received usual care from their practitioner and were not referred to acupuncture
† A piece of adhesive tape was placed on the inactive points of the ears.
‡ If the patient had a VAS pain score of greater than 3, they were advised to take a Novafen capsule (acetaminophen 325 mg, caffeine 40 mg, and ibuprofen 200 mg) every 8 hours
§ Patients used standard pharmacological treatments following the appropriate guidelines.
** Distinct attacks were defined as attacks separated by an entire 24-hour period of freedom from headache as recommended by the guidelines for controlled trials of drugs in migraine.
†† 6% had CTTH
‡‡ Exclusion criteria
§§ Drug consumption, (ATC/DDD) 14.8 (14.3) vs. 11.5 (11.8); Anatomical Therapeutic Chemical Classification System/defined daily doses
*** Excluded if acupuncture w/in last 12 months
†††Excluded if had prior auricular acupuncture
§§§Exclude if acupuncture to the face, hands, legs or front part of body within 6 months
**** (e.g., beta blockers, tricyclic antidepressants, divalproex, topiramate, or in cases with insufficient effect monoamine oxidase inhibitors, flunarizine or gabapentin)
††††Following appropriate guidelines (Headache Classification Subcommittee of the International Headache Society, 2004)

Table 9. Summary of patient, baseline and procedural characteristics from trials assessing acupuncture versus pharmacological treatment for chronic migraine

Patient demographics	Study			
	Yang 2011		Naderinabi 2017	
	N = 66		N = 162*	
	Acupuncture	Topiramate	Acupuncture	Sodium valproate
Randomized	n=33	n=33	n=NR	n=NR
Treated	n=33	n=33	n=50	n=50
Mean Age, years	47.6	48.1	37.2	37.6
Female, %	91%	88%	58%	66%
Mean Chronicity of Headache (years)	13.2	13.5	10.3	9.2
Mean No. Migraine days/month	21.3	21.0	21.3	21.0
Mean No. Migraine attacks/month	NR	NR	NR	NR
Medication overuse, %	73%	76%	0%	0%
Prior acupuncture, %	0%‡	0%‡	0%	0%
Prior preventative treatments other than acupuncture, %	0%§	0%§	0%†	0%†
Procedural characteristics				
Acupuncture type	Traditional Chinese Medicine [fixed and classic acupuncture points]	NA	Traditional Chinese Medicine	NA
Manipulation of needles	Manual, to elicit De Qi	NA	Manual, to elicit De Qi	NA
Number of acupuncture points, needles / Medication dosage	7 needles	4-week titration, beginning with 25mg/day increased by 25mg/day weekly to maximum 100mg/day for 8 weeks	10-12 sites	500 mg/day
Number of treatment sessions	24		30	Taken once per day
Duration of treatment	12 weeks	12 weeks	8 weeks	8 weeks

Patient demographics	Study			
Followed, % (n/N)	NR	NR	92.6% (150/162)*	
Co-interventions	None**††	NR††	NR§§	NR§§
Country	Taiwan		Iran	
Funding	Taiwan Department of Health Clinical Trial and Research Center for Excellence, grant from Kuang Tien General Hospital		Research and Technology Vice-Chancellorship of Guilan University of Medical Sciences	

HA = headache; mg = milligrams; NA = not applicable; NR = not reported

* This study includes a third arm of patients who received botulinum toxin A (n=50)

† Patients with recent (past 3 months) use of prophylactic drugs were excluded as well as those who had history of receiving botulinum toxin A

‡ Patients with previous fearful experience of acupuncture or receiving acupuncture in the past 3 months were excluded

§ Patients with migraine prophylaxis agents had been used in the past 3 months, such as beta-blockers, anti-depressants, calcium channel blockers, anti-epileptic agents, cycle-modulating hormonal drugs, or vessel dilatation agents were excluded

** No herbs, moxibustion, cupping, rehabilitation, advice regarding dietary or lifestyle modifications allowed

†† Assumed that patients are allowed to take acute medications for headache since reduction in medication use was a reported outcome

§§ All patients were allowed to treat their acute migraine attacks with Novafen (Alhavi Pharmaceutical Company)

4.2.1.3 Efficacy Results for Chronic Migraine

4.2.1.3.1 Treatment Responders

≥50% Reduction in Number of Headache Days

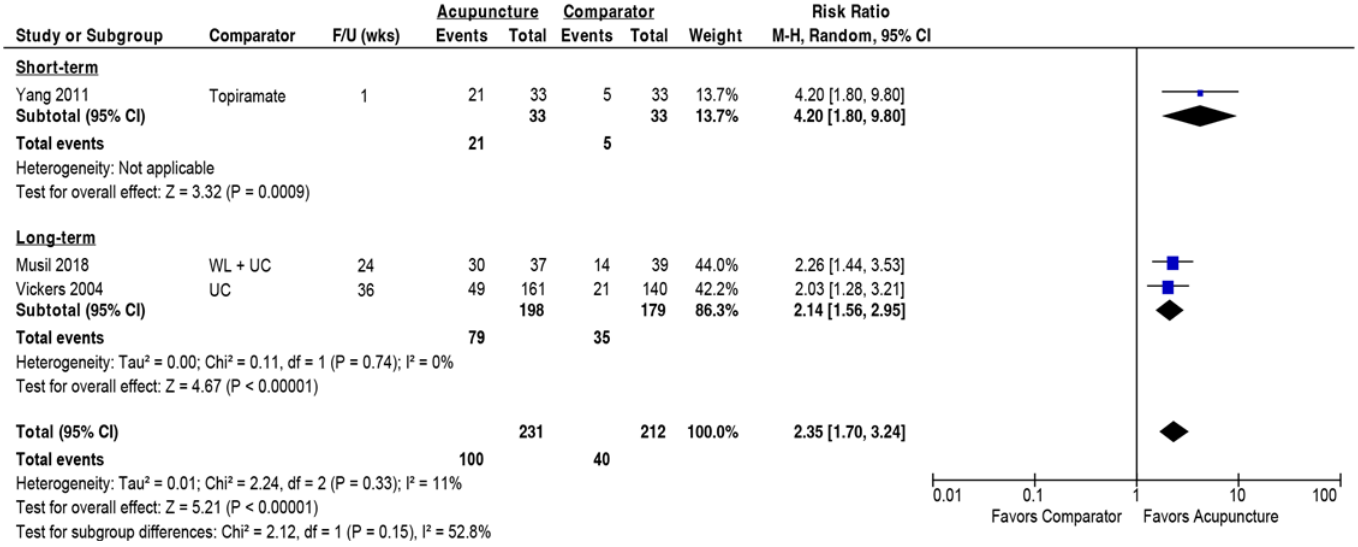
Short-term (1 week): Four times as many patients who received acupuncture compared with topiramate experienced a ≥50% reduction in the number of headache days per month from baseline recorded 1 week post-treatment (64% vs. 15%; risk ratio [RR] 4.2, 95% confidence interval [CI] 1.8 to 9.8; risk difference [RD] 48.5%, 95% CI 28.0% to 69.0%) in one small trial (N=66) at moderately low risk of bias, Figure 3.[129] Of note, 73% and 76% of acupuncture and topiramate patients, respectively, overused acute headache medication at baseline; it is unclear how this may have affected the outcome.

Longer-term (24–36 weeks): Across two trials (one moderately low and one moderately high risk of bias) comparing acupuncture with UC (plus WL in one trial),[86,117] acupuncture was associated with a higher proportion of patients with ≥50% reduction in the number of headache days per month from baseline (IHS definition) 24 to 36 weeks post-treatment (N=377; 40% vs. 20%; pooled RR 2.1, 95% CI 1.6 to 3.0, I^2=0%; pooled RD 29%, 95% CI 0% to 58%, I^2=86%), Figure 3. In one trial, days with headache was defined liberally as days on which a patient recorded headache severity of at least 1 out of 5 for at least one timepoint.[117]

Any timepoint (1–36 weeks) and comparator: Across all timepoints and comparators (UC, topiramate), acupuncture was consistently associated with a higher proportion of patients experiencing a ≥50% reduction in the number of headache days per month from baseline (3 RCTs, N=443; 43% vs. 19%; pooled RR 2.4, 95% CI 1.7 to 3.2, I^2=11%; pooled RD 35%, 95% CI 11% to 59%, I^2=86%), Figure 3.

Of note, in one of the trials comparing acupuncture with UC over long-term follow-up (36 weeks post-treatment), the authors report that some patients continued to receive acupuncture after the initial 12 week treatment period (25 patients [16%] after 12 weeks, 10 patients [6%] after 24 weeks, and 6 patients [4%] after 36 weeks); only three patients (2%) in the control group reported receiving acupuncture outside the study. [117] It is unclear how this continuation of treatment may have affected the outcome.

Figure 3. Treatment responders: ≥50% reduction in mean headache days/month



CI = confidence interval; F/U = follow-up; UC = usual care; WL = waitlist; wks = weeks.

≥50% Reduction in Number of <u>Moderate/Severe</u> Headache Days

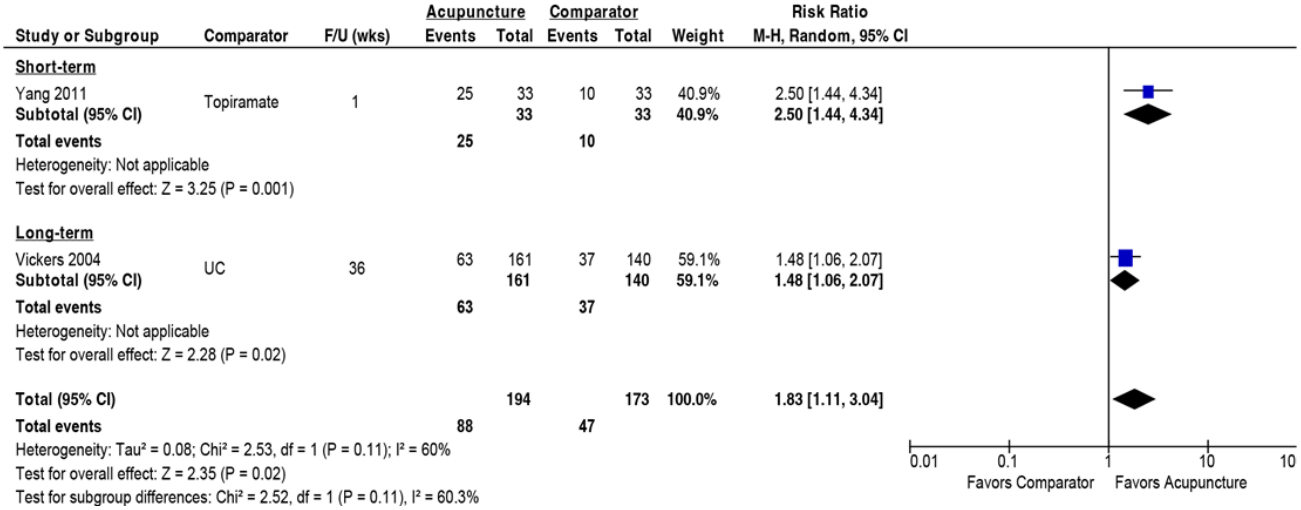
<u>Short-term (1 week)</u>: A higher proportion of patients who received acupuncture, as compared with topiramate, experienced a ≥50% reduction in the number of *moderate or severe* headache days per month from baseline at 1 week post-treatment (76% vs. 30%; RR 2.5, 95% CI 1.4 to 4.3; RD 46%, 95% CI 24% to 67%) in one small trial (N=66) at moderately low risk of bias, Figure 4.[129] Of note, 73% and 76% of acupuncture and topiramate patients, respectively, overused acute headache medication at baseline; it is unclear how this may have affected the outcome.

<u>Longer-term (36 weeks)</u>: A higher proportion of patients who received acupuncture, as compared with UC, experienced a ≥50% reduction in the number of *moderate or severe* headache days per month from baseline at 36 weeks post-treatment (39% vs. 26%; RR 1.5, 95% CI 1.1 to 2.1; RD 13%, 95% CI 2% to 23%) in one trial (N=301) at moderately high risk of bias, Figure 4.[117,118]

<u>*Any timepoint (1–36 weeks) and comparator*</u>: Across both timepoints and comparators (UC, topiramate), acupuncture was consistently associated with a higher proportion of patients experiencing a ≥50% reduction in the number of *moderate or severe* headache days per month from baseline (2 RCTs, N=367; 45% vs. 27%; pooled RR 1.8, 95% CI 1.1 to 3.0, I^2=60%; pooled RD 28%, 95% CI –4% to 60%, I^2=86%), Figure 4.[117,129]

Again, given that some patients continued to receive acupuncture after the initial 3-month treatment period in the trial comparing acupuncture with UC over the longer-term (36 weeks) it is unclear how this continuation of treatment may have affected the outcome.[117,118]

Figure 4. Treatment responders: ≥50% reduction in mean moderate or severe headache days/month



CI = confidence interval; F/U = follow-up; UC = usual care; wks = weeks.

≥35% Improvement in Headache Score

Longer-term (36 weeks): One trial at moderately high risk of bias reported the proportion of patients with ≥35% improvement from baseline in headache score, defined as the summed total of headache severity recorded 4 times per day on a 6-point Likert scale (study protocol definition of responder) over the long term.[117] Compared with UC, a higher proportion of patients who received acupuncture achieved this outcome at 36 post-treatment: 54.0% (87/161) versus 32.1% (45/140); RR 1.7 (95% CI 1.3 to 2.2) and RD 21.9% (95% CI 11.0% to 32.8%).

Again, given that some patients continued to receive acupuncture after the initial 3-month treatment period in this trial it is unclear how this continuation of treatment may have affected the outcome.

4.2.1.3.2 Frequency of Headache Days

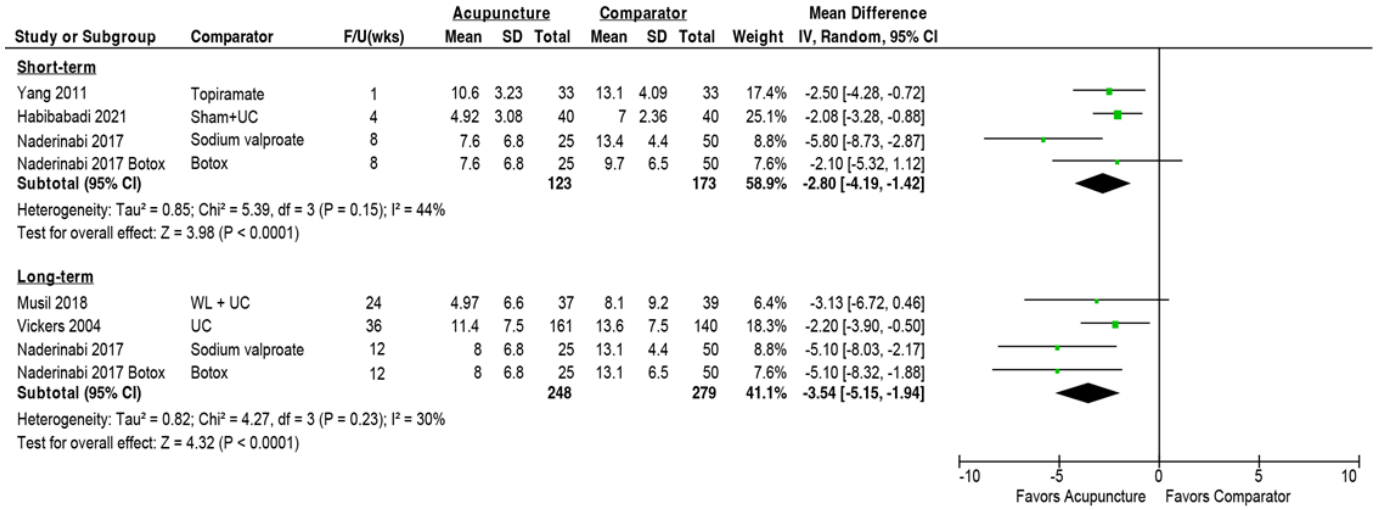
Reduction in Frequency of Headache Days

Short-term (1–8 weeks): Three trials (1 moderately low and 2 moderately high risk of bias) reported the frequency of headache days per month over the short term (up to 8 weeks); acupuncture was compared with sham plus UC (1 RCT), pharmacological therapy (topiramate, sodium valproate, in 1 RCT each), and Botulinum toxin A (1 RCT).[63,87,129] Acupuncture was associated with a greater reduction in the number of headache days per month in pooled estimates across comparators: N=296, 3 RCTs, pooled mean difference (MD) –2.8 (95% CI –4.2 to –1.4), I^2=44%, Figure 5. When considered individually, acupuncture was favored over comparators except for botulinum toxin at 8 weeks post-treatment (MD –2.1, 95% CI –5.3 to 1.1) in one trial at moderately high risk of bias.[87] Sensitivity analysis pooling only the two trials evaluating pharmacological therapy (1 moderately low and 1 moderately high risk of bias),[87,129] resulted in a larger effect favoring acupuncture (N=166, 2 RCTs, pooled MD –4.1, 95% CI –7.3 to –0.9, I^2=80%), (data not shown in the figure). Heterogeneity was high, possibly due to the different pharmacological

treatments used (topiramate, sodium valproate) and follow-up periods (1 week vs. 8 weeks post-treatment).

Longer-term (12–36 weeks): Three trials (1 moderately low and 2 moderately high risk of bias) reported the frequency of headache days per month over the long term (up to 36 weeks); acupuncture was compared with WL and/or UC (2 RCTs), pharmacological therapy (sodium valproate, 1 RCT), and Botulinum toxin A (1 RCT).[86,87,117] Acupuncture was associated with a greater reduction in the number of headache days per month in pooled estimates across comparators: N=527, 3 RCTs, pooled MD –3.5 (95% CI –5.2 to –1.9), I^2=30%, Figure 5. When considered individually, acupuncture was favored over comparators except for WL/UC at 24 weeks post-treatment (MD –3.1, 95% CI –6.7 to 0.5) in one trial (N=76) at moderately low risk of bias.[86] Sensitivity analysis pooling only the two trials evaluating WL and/or UC (1 moderately low and 1 moderately high risk of bias) resulted in a somewhat attenuated estimate in favor of acupuncture (N=377, 2 RCTs, pooled MD –2.80, 95% CI –4.19 to –1.42, I^2=44%; data not shown in figure).[86,117] Again, given that some patients continued to receive acupuncture after the initial 3 month treatment period in the larger of the two trials evaluating UC (N=301, moderately high risk of bias)[117]; it is unclear how this continuation of treatment may have affected the outcome.

Figure 5. Mean reduction in the frequency of headache days/month



Botox = Botulinum toxin A; CI = confidence interval; F/U = follow-up; SD = standard deviation; UC = usual care; WL = waitlist; wks = weeks.

Reduction in Frequency of Moderate or Severe Headache Days

Short-term (1 week): Acupuncture was associated with a greater reduction in the number of *moderate or severe* headache days per month from baseline compared with topiramate at 1 week post-treatment (MD –2.3, 95% CI –3.7 to –0.9) in one small trial (N=66) at moderately low risk of bias, Figure 6.[129] Of note, 73% and 76% of acupuncture and topiramate patients, respectively, overused acute headache medication at baseline; it is unclear how this may have affected the outcome.

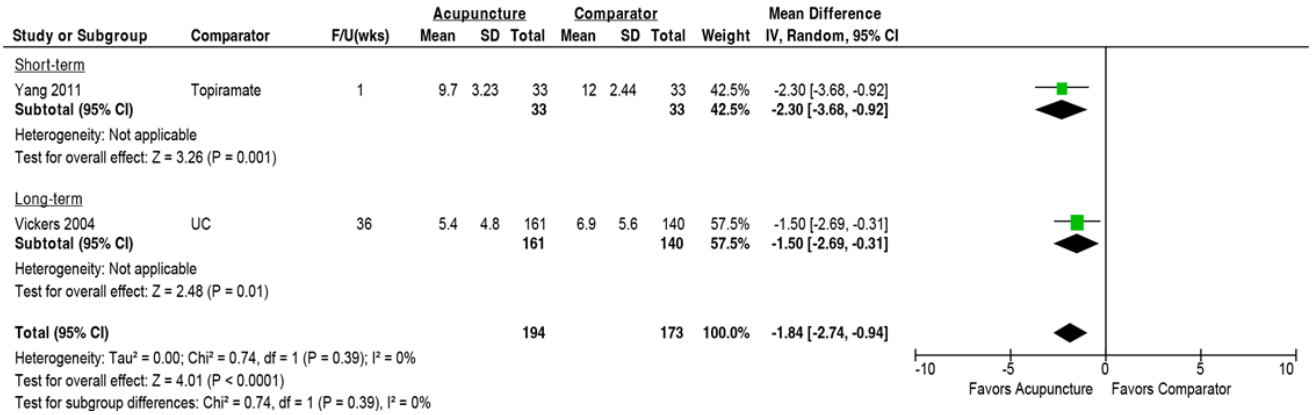
Longer-term (36 weeks): Acupuncture was associated with a greater reduction in the number of *moderate or severe* headache days per month from baseline compared with UC at 36 weeks post-

treatment (MD –1.5, 95% CI –2.7 to –0.3) in one trial (N=301) at moderately high risk of bias, Figure 6.[117,118]

Any timepoint (1–36 weeks): Across both timepoints and comparators (UC, topiramate), acupuncture was consistently associated with a greater reduction in the number of *moderate or severe* headache days per month from baseline (N=367, 2 RCTs, pooled MD –1.8, 95% CI –2.7 to –0.9, I^2=0%), Figure 6.[117,118,129]

Again, given that some patients continued to receive acupuncture after the initial 3-month treatment period in the trial comparing acupuncture with UC over the longer-term (36 weeks) it is unclear how this continuation of treatment may have affected the outcome.[117,118]

Figure 6. Mean reduction in the frequency of moderate/severe headache days/month



CI = confidence interval; F/U = follow-up; SD = standard deviation; UC = usual care; wks = weeks.

Reduction in Frequency of Mild Headache Days

Longer-term (36 weeks): In one RCT (N=301) at moderately high risk of bias, acupuncture was associated with a greater reduction in the number of *mild* headache days compared with UC at 36 weeks post-treatment (adjusted MD 1.6; 95% CI 0.5 to 2.6).[117,118] Again, given that some patients continued to receive acupuncture after the initial 3 month treatment period it is unclear how this continuation of treatment may have affected the outcome.

4.2.1.3.3 Frequency of Headache Episodes/Attacks

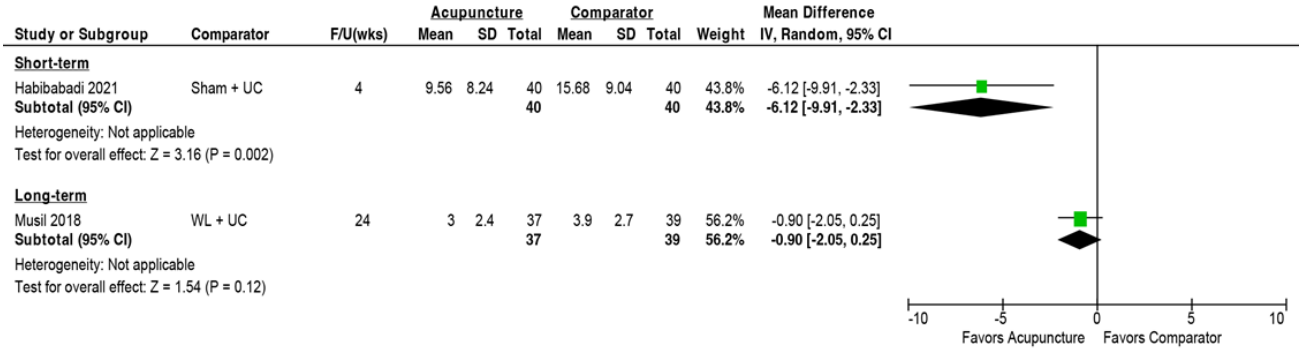
In addition to reporting the frequency of headache days per month, two trials reported the frequency of headache episodes or attacks per month.

Short-term (4 weeks): Auricular acupuncture was associated with a greater reduction in the number of headache episodes per month from baseline compared with sham plus UC at 4 weeks post-treatment (MD –6.1, 95% CI –9.9 to –2.3) in one trial (N=80) at moderately high risk of bias, Figure 7.[63] The authors did not define what constituted a headache episode.

Longer-term (24 weeks): In one trial (N=76) at moderately low risk of bias that compared acupuncture with WL plus UC, the difference in headache attacks per month between groups failed to reach statistical significance at 24 weeks post-treatment (MD –0.9, 95% CI –2.1 to 0.3), Figure 7.[86] Distinct

attacks were defined as attacks separated by an entire 24-hour period of freedom from headache as recommended by the guidelines for controlled trials of drugs in migraine. Given the statistical heterogeneity, data were not pooled across timepoints and comparators.

Figure 7. Mean reduction in the frequency of headache episodes or attacks/month



CI = confidence interval; F/U = follow-up; SD = standard deviation; UC = usual care; WL = waitlist; wks = weeks.

4.2.1.3.4 Function/Disability

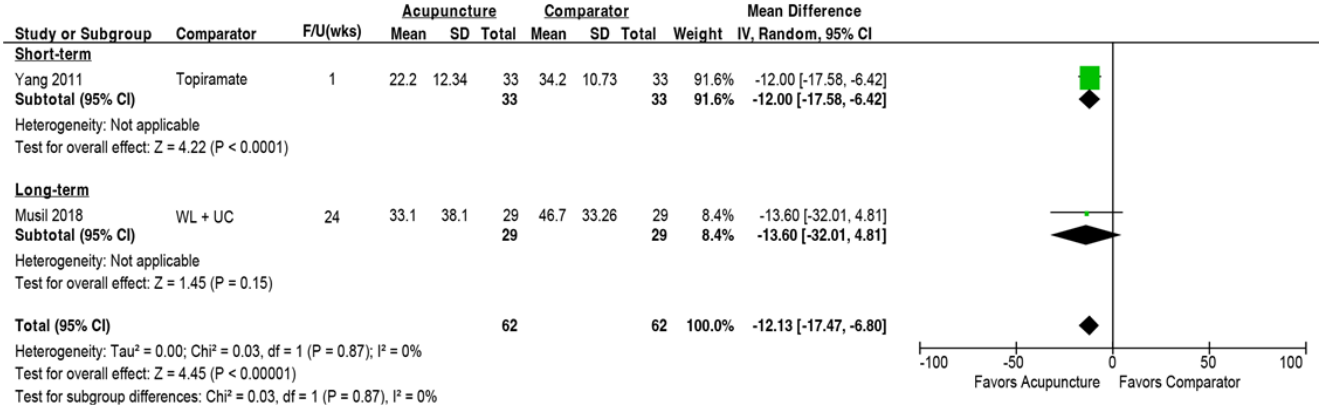
Disability was measured using the Migraine Disability Assessment (MIDAS). The MIDAS assesses how severely migraines affect a patient's life and includes questions about the frequency and duration of headaches, as well as how often these headaches limit patients' ability to participate in activities at work, at school, or at home. We were unable to find a minimally clinically important difference (MCID) for this outcome, so it is unclear if the differences below are clinically meaningful.

Short-term (4 weeks): Acupuncture was associated with greater improvement (i.e., lower score) on the MIDAS compared with topiramate at 1 week post-treatment in one small RCT (N=66) at moderately low risk of bias (MD –12.0, 95% CI –17.6 to –6.4), Figure 8.[129] It is unclear how medication overuse in this population (73% and 76%, respectively, met the criteria at baseline) may have affected the outcome.

Longer-term (24 weeks): There was no difference in MIDAS scores between acupuncture and WL plus UC at 24 weeks post-treatment in one small trial (N=58) at moderately low risk of bias (MD –13.6, 95% CI –32.0 to 4.8), Figure 8.[86]

Any timepoint (4–24 weeks): When results were pooled across both timepoints and comparators (WL/UC, topiramate), acupuncture was associated with a greater improvement in MIDAS scores (2 RCTs, N=124; pooled MD –12.1, 95% CI –17.5 to –6.6, I^2=0%), Figure 8.[86,129]

Figure 8. Function/disability: improvement in MIDAS scores



CI = confidence interval; F/U = follow-up; SD = standard deviation; UC = usual care; WL = waitlist; wks = weeks.

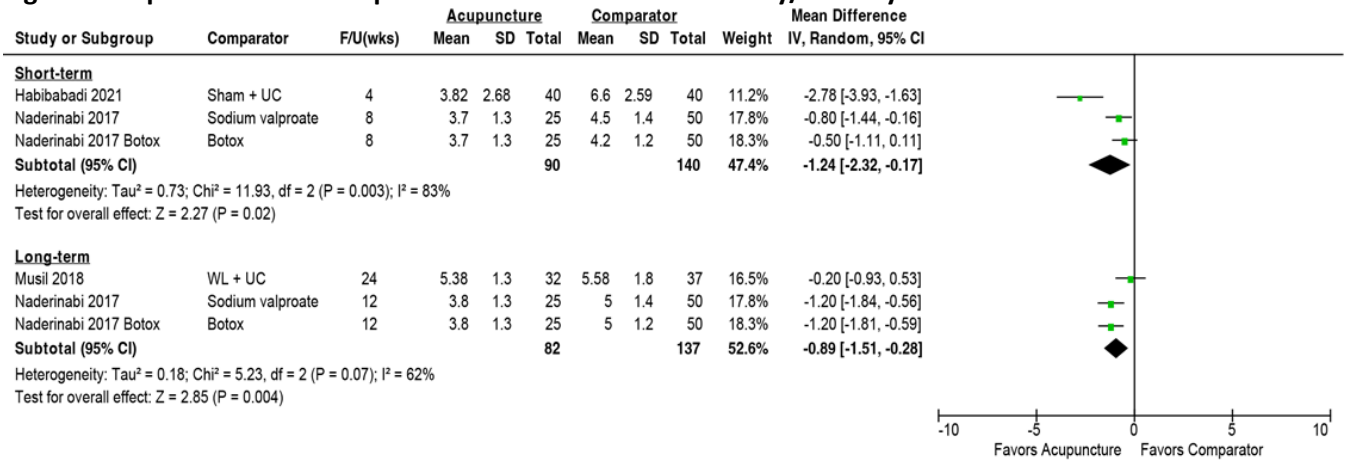
4.2.1.3.5 Secondary Outcomes

Reduction in visual analog pain scores

Short-term (4–8 weeks): Two trials (both moderately high risk of bias) reported visual analog pain scores (VAS) for headache intensity/severity over the short term (up to 8 weeks); acupuncture was compared with sham/UC in one RCT[63] and pharmacologic therapy (sodium valproate) and Botulinum toxin A in the other (3 arm trial).[87] Acupuncture was associated with a moderate improvement (i.e., reduction) in VAS pain scores in pooled estimates across comparators: N=230, 2 RCTs, pooled MD –1.2 (95% CI –2.3 to –0.2) on a 0–10 scale, I^2=83%, Figure 9. Heterogeneity was high, due to the much larger effect seen for the trial comparing acupuncture with sham/UC (MD –2.8, 95% CI –3.9 to –1.6) at the shortest follow-up interval (4 weeks post-treatment).[63] When considered individually, only the comparison with Botulinum toxin failed to reach statistical significance (barely) at 8 weeks post-treatment (MD –0.5, 95% CI –1.1 to 0.1) in one trial (N=100) at moderately high risk of bias.[87]

Longer-term (12–24 weeks): Two trials (1 moderately low and 1 moderately high risk of bias) reported VAS pain scores for headache intensity/severity over the long term (up to 24 weeks); acupuncture was compared with WL/ UC in one RCT[86] and with pharmacological therapy (sodium valproate) and Botulinum toxin A in the other (3 arm trial).[87] Compared with any alternative treatment, acupuncture was associated with a small improvement (i.e., reduction) in VAS pain scores: N=219, pooled MD –0.9 (95% CI –1.5 to –0.3) on a 0–10 scale, I^2=62%, Figure 9. When considered individually, acupuncture was favored over comparators except for WL/UC at 24 weeks post-treatment (MD –0.2, 95% CI –0.9 to 0.5), the longest follow-up available for this outcome, in one small trial (N=69) at moderately low risk of bias.[86]

Figure 9. Improvement in VAS pain scores for headache intensity/severity



Botox = Botulinum toxin A; CI = confidence interval; F/U = follow-up; SD = standard deviation; UC = usual care; WL = waitlist; wks = weeks.

Health-Related Quality of Life

Short-term (1 week): In one small RCT (N=66) at moderately low risk of bias, patients who received acupuncture reported greater improvement (i.e., increase in score) on all eight individual Short Form 36 (SF-36) questionnaire domains at 1 week post-treatment compared with those who received topiramate,[129] (Appendix F, Table F3).

Longer-term (36 weeks): In general, individual SF-36 domain scores favored the acupuncture group, compared with UC, at 36 weeks post-treatment in one RCT (N=301) at moderately high risk of bias; however, mean differences between the groups reached statistical significance in only three of the nine domains: physical role functioning (adjusted MD 8.8, 95% CI 0.6 to 17.0), energy/fatigue (adjusted MD 4.2, 95% CI 0.6 to 7.7), and change in health (adjusted MD 7.9, 95% CI 3.5 to 12.3); MDs were adjusted for baseline scores,[117] (Appendix F, Table F3).

Depression and Anxiety

Short-term (1 week): Compared with topiramate, acupuncture was associated with greater improvement from baseline (i.e., decrease in score) in both depression and anxiety as measured by the Beck Depression Inventory-II (MD 2.1, 95% CI 0.2 to 4.0) and the Hospital Anxiety and Depression Scale (MD 4.2, 95% CI 3.2 to 5.2) 1 week after the end of treatment in one small trial (N=66) at moderately low risk of bias,[129] (Appendix F, Table F3).

Proportion of Patients Requiring Rescue or Prophylactic Medication

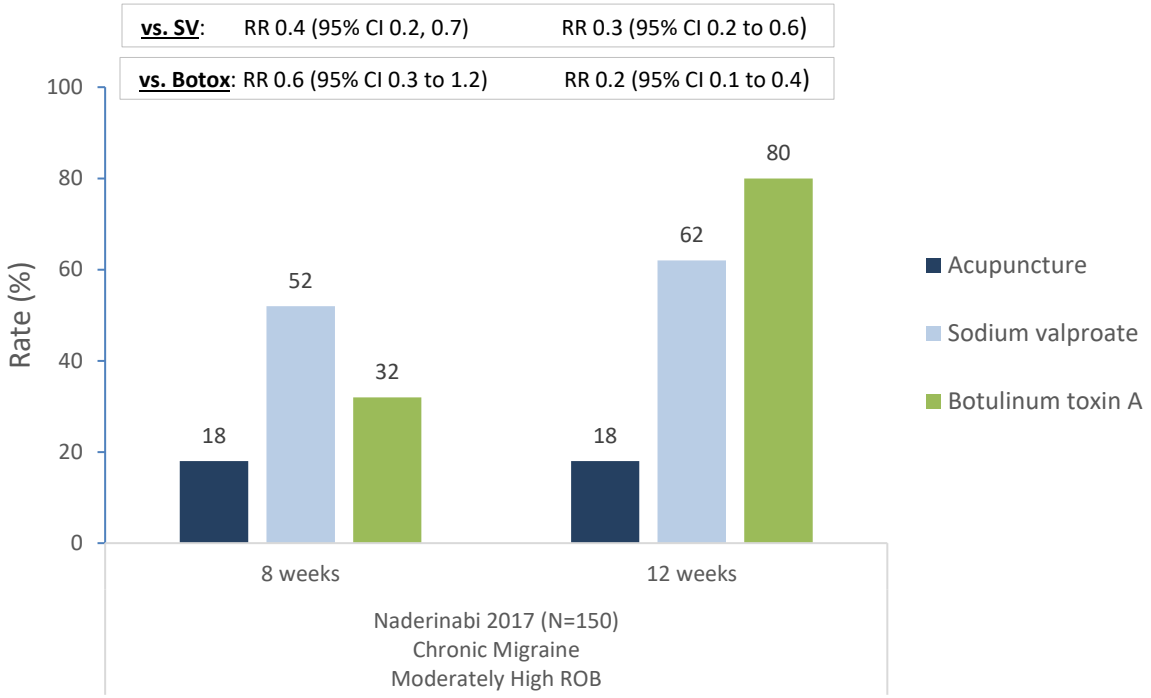
Short-term (8 weeks): One trial (N=150)[87] at moderately high risk of bias compared acupuncture with both sodium valproate and Botulinum toxin and reported that at 8 weeks post-treatment fewer patients who received acupuncture required the use of rescue medication (Novafen) compared with sodium valproate (RR 0.4, 95% CI 0.2 to 0.7); while almost half as many patients in the acupuncture group versus

the botulinum toxin A group required medication, the difference failed to reach statistical significance (RR 0.6, 95% CI 0.3 to 1.2), Figure 10.

Long-term (12 weeks): The same trial as above also reported outcomes at long-term and found that fewer patients in the acupuncture group required rescue mediation at 12 week post-treatment compared with both those in both the sodium valproate and Botulinum toxin A groups: RR 0.3 (95% CI 0.2 to 0.6) and RR 0.2 (95% CI, 0.1 to 0.4), Figure 10.[87]

A second trial (moderately high risk of bias) reported that over the long-term (36 weeks post-treatment), fewer patients who had received acupuncture reported using prophylactic medication in the month prior compared with UC: 14% (22/161) versus 26% (37/140); RR 0.5, 95% CI 0.3 to 0.8; the mean difference between groups adjusted for baseline scores was 13% (95% CI 4% to 22%).[117]

Figure 10. Proportion of patients requiring rescue medication over the short and long term



Botox = Botulinum toxin A; CI = confidence interval ROB = risk of bias; RR = risk ratio; SV = sodium valproate

Frequency of Analgesic Use

Short-term (1–8 week): Acupuncture was associated with a greater reduction in the mean number of days per month with acute headache medication intake compared with topiramate in one RCT at moderately low risk of bias: the MD in change from baseline between groups was –4.2 days (95% CI –6.2 to –2.2) as assessed 1 week post-treatment[129] (Table 10). A second trial (moderately high risk of bias)

compared acupuncture with both sodium valproate and Botulinum toxin A[87]; compared with both active treatments, acupuncture resulted in a greater reduction in the mean number of times patients needed medication per month measured at 8 weeks post-treatment (MD –5.3, 95% CI –7.1 to –3.5 and MD –2.8, 95% CI –4.3 to –1.3, respectively) (Table 10).

Long-term (36 weeks): One trial (moderately high risk of bias) compared acupuncture with both sodium valproate and Botulinum toxin A[87]; compared with both active treatments, acupuncture was associated with a greater reduction in the mean number of times patients needed medication per month measured at 12 weeks post-treatment (MD –3.7, 95% CI –5.4 to –2.1 and MD –3.0, 95% CI –4.5 to –1.5, respectively) (Table 10). A second trial (moderately low risk of bias) reported that patients who received acupuncture reduced their intake of relief medication to a greater extent compared with those in the WL/UC group[86]; the difference between groups in change from baseline to 24 weeks post-treatment was a median −3 (interquartile range [IQR] −5.8 to −0.7), (Table 10). In an unplanned analysis, a third trial (moderately high risk of bias) summed and scaled all medication taken by patients after randomization and compared the groups with adjustment for baseline intake.[117] Mean weekly intake of scaled prophylactic, but not scaled pain, medication was reduced in the acupuncture compared with the UC group at 36 weeks post-treatment (adjusted MD –3.9; 95% CI –7.4 to –0.5); mean weekly intake of total scaled medications was also reduced in the acupuncture group (Table 10).

Table 10. Frequency of analgesic use in chronic migraine trials

Author	Outcome	F/U post-treatment	Mean (SD)		MD (95% CI)
			Acupuncture (n=33)	**WL/UC (n=38)**	
Musil 2018	Δ from baseline, relief medication consumption (ATC/DDDs)	24 weeks	Median (IQR) −5.7 (−11, −3)	Median (IQR) −2.7 (−7, 0.02)	Difference −3 (−5.8, −0.7)
			Acupuncture (n=161)	**UC (n=140)**	
Vickers 2004*	Scaled prophylactic medication (weekly)	Baseline	9.0 (17.8)	13.3 (22.2)	
		36 weeks	5.0 (14.4)	11.1 (21.3)	Adj. –3.9 (–7.4, –0.5)*
	Scaled pain medication (weekly)	Baseline	16.5 (18.1)	14.3 (17.6)	
		36 weeks	8.5 (12.2)	18.7 (12.6)	Adj. –1.2 (–3.1, 0.6)*
	Total scaled medication (weekly)	Baseline	25.4 (25.1)	27.6 (28.8)	
		36 weeks	13.4 (18.2)	19.8 (24.4)	Adj. –5.2 (–9.2, –5.3)*
			Acupuncture (n=50)	**Sodium Valproate (n=50)**	
Naderinabi 2017†	Mean number of medication use/month	Baseline	14.6 (5.6)	14.1 (5.1)	
		8 weeks	3.1 (3.7)	8.4 (5.4)	–5.3 (–7.1, –3.5)
		12 weeks	3.3 (4.0)	7.0 (4.3)	–3.7 (–5.4, –2.1)
			Acupuncture (n=33)	**Topiramate (n=33)**	
Yang 2011	Δ from baseline, mean days with acute headache med intake/month	1 week	–9.6 (3.3)	–5.4 ± (4.7)	–4.2 (–6.2 to –2.2)
			Acupuncture	**Botulinum toxin**	

Author	Outcome	F/U post-treatment	Mean (SD)		MD (95% CI)
			(n=50)	(n=50)	
Naderinabi 2017†	Mean number of medication use/month	Baseline	14.6 (5.6)	17.8 (6.2)	–3.2 (–5.5, –0.9)
		8 weeks	3.1 (3.7)	5.9 (3.8)	–2.8 (–4.3, –1.3)
		12 weeks	3.3 (4.0)	6.3 (3.3)	–3.0 (–4.5, –1.5)

Δ = change score; ATC/DDDs: Anatomical Therapeutic Chemical Classification System/defined daily doses; CI = confidence interval; MD = mean difference; SD = standard deviation.
*Unplanned analysis; the authors summed and scaled all medication taken by patients after randomization and compared the groups with adjustment for baseline intake.
†This trial had 3 arms: acupuncture, sodium valproate, and botulinum toxin A.

Loss of Working Days or Social Activities

Short-term (8 weeks): Similar proportions of patients randomized to acupuncture (10%; 5/50), sodium valproate (14%; 7/50), and botulinum toxin (12%; 6/50) were absent from work or social activities over the short term (8 weeks post-treatment) in one RCT at moderately high risk of bias (Appendix F, Appendix Table F3).[87]

Long-term (12-36 weeks): The same trial as above also reported absenteeism over the long term (12 weeks post-treatment) with no statistical differences seen between acupuncture and either active treatment; though when compared with Botulinum toxin, the acupuncture group tended to have fewer days of missed work or social activities.[87] Similarly, there was no difference between the acupuncture and the UC group in the mean number of sick days reported at long-term follow-up (36 weeks after the end of treatment) in a second RCT at moderately high risk of bias: 12.6 versus 13.8 days, respectively; the adjusted incidence ratio was 0.84 (95% CI 0.64 to 1.09) indicating that the acupuncture group had 16% fewer days off sick.[117] (See Appendix F, Appendix Table F3 for details).

Patient Satisfaction with Improvement in Migraine Symptoms *(Short-term, 4 weeks)*

In one RCT (moderately high risk of bias), patients randomized to acupuncture were more satisfied with their symptom improvement compared with those in the sham/UC group; the MD between groups on a 0 to 10 scale (10 is extremely satisfied) was 4.0 (95% CI 2.8 to 5.2),[63] (Appendix F, Appendix Table F3).

Resource Use *(Long-term, 36 weeks)*

There were no differences between acupuncture and UC for the mean number of visits to a general practitioner (1.7 vs. 2.3), complementary therapist (2.0 vs. 2.3), or specialist (0.22 vs. 0.14) over the study period (36 weeks post-treatment) in one RCT at moderately high risk of bias[117]; the corresponding incidence ratios indicate that the acupuncture group had fewer visits to a general practitioner and a complementary therapist (23% and 44% fewer, respectively) but 13% more visits to a specialist, (Appendix F, Appendix Table F3).

Headache Scores *(Long-term, 36 weeks)*

In one RCT (moderately high risk of bias),[117] greater improvements were seen in the acupuncture group in the mean weekly headache score (i.e., the summed total of headache severity recorded 4 times per day on a 6-point Likert scale) compared with the UC group at long-term follow-up (34% vs. 16%

reduction from baseline at 36 weeks, respectively): MD adjusted for baseline scores, 4.6 (95% CI 2.2 to 7.0) (Appendix F, Appendix Table F3). Authors report that the result was robust to sensitivity analysis incorporating imputation for missing data. Again, the authors report that some patients continued to receive acupuncture after the initial 3-month treatment period (25 patients [16%] after 12 weeks, 10 patients [6%] after 24 weeks, and 6 patients [4%] after 36 weeks); only three patients (2%) in the control group reported receiving acupuncture outside the study.

4.2.2 Chronic Tension-type Headache

Our updated search did not identify new RCTs of acupuncture for the treatment of chronic tension-type headache (CTTH) that met the inclusion criteria. The results from the 2017 report were re-evaluated for accuracy and edits have been made for consistency with this updated review. The following results are excerpted from the 2017 report.[105] Differences in reported outcomes and length of follow-up across trials precluded pooling of data across studies of acupuncture for CTTH. All trials were at a moderately high risk of bias (i.e., poor quality).

4.2.2.1 Summary of Results for Chronic Tension-Type Headache

The bullet points below provide summary statements and strength of evidence only for the primary efficacy outcomes of interest to this report. Details on secondary outcomes can be found in the section that follows.

Treatment Responders

- Only one trial reported this outcome. There was no difference between acupuncture and sham acupuncture either short-term (4-6 weeks) or long-term (52 weeks) in the proportion of patients **achieving >33% or >50% improvement** from baseline on the Headache Index (HI) in one small trial (insufficient SOE for both times).[114]

Reduction in Headache Frequency

- There were no differences between acupuncture and sham based on the pooled mean **reduction in headache episodes per month** across two small trials at short-term (4-6 weeks) follow-up[72,114] or in one of the trials longer-term (26-52 weeks)[72,114] (insufficient SOE for all outcomes).
- In one trial,[107,108] at longer-term (12 and 26 weeks), no differences were seen between the acupuncture and physical training/exercise or between acupuncture and relaxation training in **the number of headache-free periods or headache-free days per week** (insufficient SOE for all outcomes and comparisons).

Function

- Short-term (4 to 9 weeks), one trial reported that the acupuncture group improved significantly more than the physiotherapy group on **Sickness Impact Profile (SIP) score** category for Sleep and Rest but not for the psychosocial categories (insufficient SOE).[39]

4.2.2.2 Description of Study Populations for Chronic Tension-Type Headache

A total of four RCTs comparing acupuncture with either sham acupuncture or active comparators were met the inclusion criteria.[39,72,107,108,114] Two small RCTs (samples sizes 30 and 39) comparing acupuncture with a sham procedure[72,114] and two RCTs comparing acupuncture with an active control group[39,107] were identified. Active comparisons included physical training/exercise or relaxation therapy in one trial (N=90) (outcomes reported across two publications)[107,108] and physiotherapy in the other (N=62)[39]. Detailed patient and study information are available in Appendix F, Table F2.

4.2.2.2.1 Acupuncture versus Sham Acupuncture

The two trials[72,114] of acupunctures versus sham acupuncture differed in mean age (32.9 vs. 48.9 years) and proportion of females (86.7% vs. 48.7%) and headache mean frequency per month (17.5 vs. 27.0) (Table 11). One trial reported a condition duration of 7.8 (range 1–31) years[114]; the other trial only reported that it was "chronic" in nature.[72] Post-treatment follow-up also differed between trials (6 weeks vs. up to 52 weeks).

Both sham-controlled trials employed traditional Chinese acupuncture but treatment regimens differed slightly; in one trial, patients underwent one 20-minute session per week for 8 weeks (total of 8 sessions)[114] while in the second trial, patients received two 30-minute sessions per week over 5 weeks (total of 10 sessions).[72] The needles were left in place without the use of any manual or electrical stimulation as specified by one trial[114]; the second trial did not mention using a form of stimulation. The sham procedure in one trial consisted of insertion of the same number of needles, but more superficially, in the same region used in the verum acupuncture but in areas without acupuncture points.[114] In the second trial, for the sham procedure, a blunt placebo needle was used to create a pricking sensation on the skin to simulate puncturing the skin; it was placed using a cube-shaped elastic foam which was fixed upon the acupoint, masking the fact that the placebo needle is not inserted into deeper tissue layers.[72] The use or prior use of prophylactic headache treatment was not detailed by either trial. One required patients to abstain from all other therapies previously undertaken (except rescue analgesics) for the duration of the trial[114]; the second trial stated that concomitant medication was permitted.[72] Analgesic consumption per month was similar between the studies, mean 11.5 and 9.2 pills. Both trials allowed patients to continue taking non-narcotic analgesics as needed but required careful documentation in home diaries. One trial specifically excluded patients with rebound analgesic headache syndrome as well as other concomitant headaches; in particular, patients with any history of migraine were excluded.[72] The other trial did not mention specific exclusion criteria or note that any of the patients had concomitant headaches.

Both RCTs were considered to be at a moderately high risk of bias.[72,114] Common concerns across them were unclear random sequence generation, concealment of allocation, and intention-to-treat. In one RCT, there was no accounting for loss to follow-up and no control for unevenly distributed baseline characteristics between treatment groups (the acupuncture group had fewer females compared with the sham group: 38% vs. 61%).[72] Detailed risk of bias ratings is available in Appendix Table E3.

4.2.2.2.2 Acupuncture versus Active Controls

Two trials comparing acupuncture versus active controls were identified (Table 12).[72,114] One trial (with outcomes reported across two publications) included a total of 90 patients and randomized 30 each to receive acupuncture, relaxation therapy, or physical training for the treatment of CTTH[107,108] and the other randomized 62 female subjects to receive either acupuncture or physiotherapy.[39]

In the trial comparing acupuncture with physical training and relaxation therapy, patients were followed for 26 weeks post-treatment.[107,108] The acupuncture and physical training groups were well matched at baseline on age (median 35.0 years in both groups), sex distribution (77% female in both groups), and education/work (80% were "higher level" in both groups), however, the median duration of headache was longer in patients who received acupuncture: 10.0 (range, 2.0–35.0) years compared with 5.0 (range, 2.0–30.0) years in the physical training group and the mean number of headache-free periods per week (0–28 periods/week) was 4.13 and 5.74, respectively, and the mean number of headache-free days differed (0–7 days/weeks), 0.73 and 0.97. There were also differences in baseline characteristics between the acupuncture and the relaxation training groups; the acupuncture group had fewer females (77% vs. 90%), was younger (median 35.0 vs. 43.5 years), and had a greater proportion of patients with a higher level education and work (80% vs. 27%) than those allocated to relaxation. Headache duration was the same between the groups: median 10.0 years (range, 2.0–37.0) as was the mean number of headache-free periods per week (4.13 and 3.32); the mean number of headache-free days (0-7 days/weeks), 0.73 and 0.38 differed. Current or prior prophylactic treatments were reported. Patients were excluded if they used analgesics and/or triptans >10 days per month or if they had experienced migraine more than once a month during the year before enrollment (the proportion of patients who had coexisting migraine and tension-type headache was not reported). Patients who received acupuncture underwent 10 to 12, 30 minutes sessions; the needles were twilled by hand three times during each session. Patients randomized to physical training performed 10 training sessions (based on principles of Medical Training Therapy) and an additional home training program, for a total of 25 training sessions; both the performance and the amount of exercise were the same for all patients (weights which were individually adjusted). All exercises focused on the neck and shoulder muscles. Patients randomized to relaxation received 8 to 10 individual, supervised relaxation training sessions once a week (Larsson-Daleflod) relaxation training program and an audiotape for home practice.

The RCT[39] comparing acupuncture with physical therapy did not present baseline demographic data stratified by treatment group stating only that "the social and demographic characteristics and the values for pain, function, and mood were evenly distributed". The population mean age was 34 years; the majority of patients had completed higher-level education (80%) and were gainfully employed (70%) and had a mean headache duration of 9 years and a mean headache intensity of 47 on VAS (0-100, worst) at baseline. Diagnostic criteria for tension headache in this trial was based on the criteria established for muscle contraction headache by the National Institute of Health in 1962, described as follows: "occurs almost daily as a constant tight pressing or band-like sensation in the occipital, temporal and/or frontal areas. The pain is bilateral but not necessarily symmetrical". (The new operational criteria of the International Headache Society used in the majority of the studies in this report was not published at the time this trial was initiated). Of note, 23 (37%) patients had a combination of CTTH and migraine with a clear predominance of the tension headache. The migraine component was reported as mild, ranging from three attacks a year up to one attack a month. Baseline analgesic consumption was

unclear, however, 97% had previously tried some form of prophylactic therapy which included analgesics, either exclusively or in combination with other therapies (such as relaxation, TENS, ultrasound, or acupuncture); in all cases, these therapies reportedly had no or little effect on the patients' symptoms. Patients were asked to reduce or stop their intake of analgesics. Medication overuse was not reported/unclear.

In the acupuncture group, classic Chinese acupuncture was performed; needles were twiddled by hand and electrical stimulation via the needles was sometimes used. Patients underwent a trial period of two to four weeks, during which four to five, 20-minute treatments were given, with additional four to five treatments performed if the patient reported clear pain relief following the trial. Physical therapy was tailored to each patient to teach them to handle situations with as little physical tension as possible and to show them they can get pain relief without analgesics. Information on body awareness and possible headache triggers was provided and relaxation techniques, auto-massage, cryotherapy, and transcutaneous electrical nerve stimulation were used; smooth stretching of the shortened contracted muscles was performed. Patients completed a total of 10 to 12 sessions (1–2 sessions/week) over 2 to 3 months, each with 30 to 45 minutes of individualized instruction. Patients were followed for 4 to 9 weeks post-treatment. The authors state that patients who were lost to follow-up did not differ from the trial patients with respect to headache intensity but differed with respect to certain social and demographic characteristics. Data for patients completing the study are reported as that was what was provided by the authors

Both RCTs comparing acupuncture with active controls were considered to be at moderately high risk of bias. Common methodological flaws across them included: unclear random sequence generation, allocation concealment, and intention to treat; lack of blinded assessment (outcomes were self-reported and patients could not be blinded). Additional concerns in one RCT were differential loss-to-follow-up (26% in the acupuncture vs. 6% in the physiotherapy group) and lack of reporting on baseline characteristics leading to uncertainty regarding the need to control for possible confounding.[39] Additional concerns in the other RCT included unclear reporting of co-interventions, >80% loss to follow-up (61%) at 26 weeks, and lack of control for the difference in headache duration between groups.[107,108] In this trial, Data were analyzed based on imputed values using the last-value-carried-forward method, assuming no change for non-completers. Detailed risk of bias ratings is available in Appendix Table E3.

Table 11. Summary of patient, baseline and procedural characteristics from trials assessing acupuncture versus sham for the treatment of chronic tension-type headache

Patient demographics	Randomized Controlled Trial			
	Karst 2000		Tavola 1992	
	N = 39		N = 30	
	Acupuncture	Sham*	Acupuncture	Sham†
Randomized	n=21	n=18	n=15	n=15
Treated	n=21	n=18	n=15	n=15
Mean Age, years	50.4	47.3	32.5	33.3
% Female	38%	61%	87%	87%
Mean Chronicity of Headache (years)	NR	NR	7.5	8.1
Mean # HA days/month	26.9	27.2	NR	NR
Mean # HA attacks/month	NR	NR	18.3 crises	16.8 crises
Percent with medication overuse	NR	NR	NR	NR
Prior acupuncture, %	NR	NR	NR	NR
Prior preventative treatments other than acupuncture, %	NR	NR	NR	NR
Procedural characteristics				
Acupuncture type	NR	NA	Traditional Chinese Acupuncture	NA
Number of acupuncture points, needles	10 points (max 15 needles)	NA	6-10 needles	6-10 needles
Manipulation of needles	NR	NR	No use of any manual or electrical stimulation	NA
Number of treatment sessions	10	NR	8	8
Duration of treatment	5 weeks	5 weeks	8 weeks	8 weeks
% Followed	100% (21/21)	100% (18/18)	100% (15/15)	100% (15/15)
Co-interventions	Yes‡	Yes‡	Yes§	Yes§
Country	Germany		Italy	

Patient demographics	Randomized Controlled Trial	
Funding	NR	NR

HA = Headache; NA = not applicable; NR = not reported

* Blunt placebo needle simulated puncturing sensation without being inserted. Elastic foam was used to shield needle type

† Patients administered the same treatment, but needles were inserted into non-acupoints

‡ Concomitant medication was allowed (including analgesics and rescue medications) but patients were required to document carefully any pharmacotherapeutics in their home diary.

§ Patients were required to abstain from all other therapies previously undertaken from the beginning to the end of follow-up except for non-narcotic analgesics taken for a headache episode.

Table 12. Summary of patient, baseline and procedural characteristics from trials assessing acupuncture versus active controls for the treatment of chronic tension-type headache

Patient demographics	Randomized Controlled Trial				
	Carlsson, 1990		Söderberg, 2006 & 2011		
	N = 62		N = 90		
	Acupuncture	Physiotherapy‡	Acupuncture	Physical Training§	Relaxation Training**
Randomized	n=31	n=31	n=30	n=30	n=30
Treated	n=23	n=29	n=30	n=30	n=30
Mean Age, years	34 years		38 years		
% Female	100%		81%		
Mean Chronicity of Headache (years)	9 years		NR		
Mean # HA days/month	NR		Minimum 15 days/month		
Mean # HA attacks/month	NR		NR		
Percent with medication overuse	NR		NR		
Prior acupuncture, %	NR		NR		
Prior preventative treatments other than acupuncture, %	96%		NR		
Procedural characteristics					
Acupuncture type	Classical Chinese Acupuncture	NA	NR	NA	NA
Number of acupuncture points, needles	3 points, 3 needles	NA	10-12 needles	NA	NA
Manipulation of needles	Electrical stimulation via the needles	NA	Manual, to elicit De Qi	NA	NA
Number of treatment sessions	Variable*	1-2 sessions per week, 10-12 sessions over 2-3 months	10-12	10	8-10
Duration of treatment			10-12 weeks	2.5 to 3 months	2 to 2.5 months

Patient demographics	Randomized Controlled Trial				
% Followed	74%	93%	57%	63%	63%
Co-interventions	NR†	NR†	None	None	None
Country	Sweden		Sweden		
Funding	Swedish Fund for Scientific Research without Animal Experiments		Vardalsstiftelsen Kommunala Landstingsforbundet for Landstinsangelagenheter, te Renee Eanders Fond, and GlaxoSmith Kline		

HA = Headache; NA = not applicable; NR = not reported

* A standard trial period of 2-4 weeks was used. During this period, 4-5 single treatments were performed. If the patients hereafter reported clear pain relief, a further 4-5 treatments were given.

† The patients were asked to reduce their intake of analgesics as much as they considered possible.

‡ Specific for each patient, including: relaxation techniques, auto-massage, cryotherapy and transcutaneous electrical nerve stimulation.

§ Sessions were a combination of in-clinic and home-training but all focused on neck and shoulder muscles.

** Combination of neuromuscular and self-hypnotic techniques, as well as breathing techniques, stress coping mechanisms, and how to relax during the day and during activity.

4.2.2.3 Efficacy Results for Chronic Tension-Type Headache

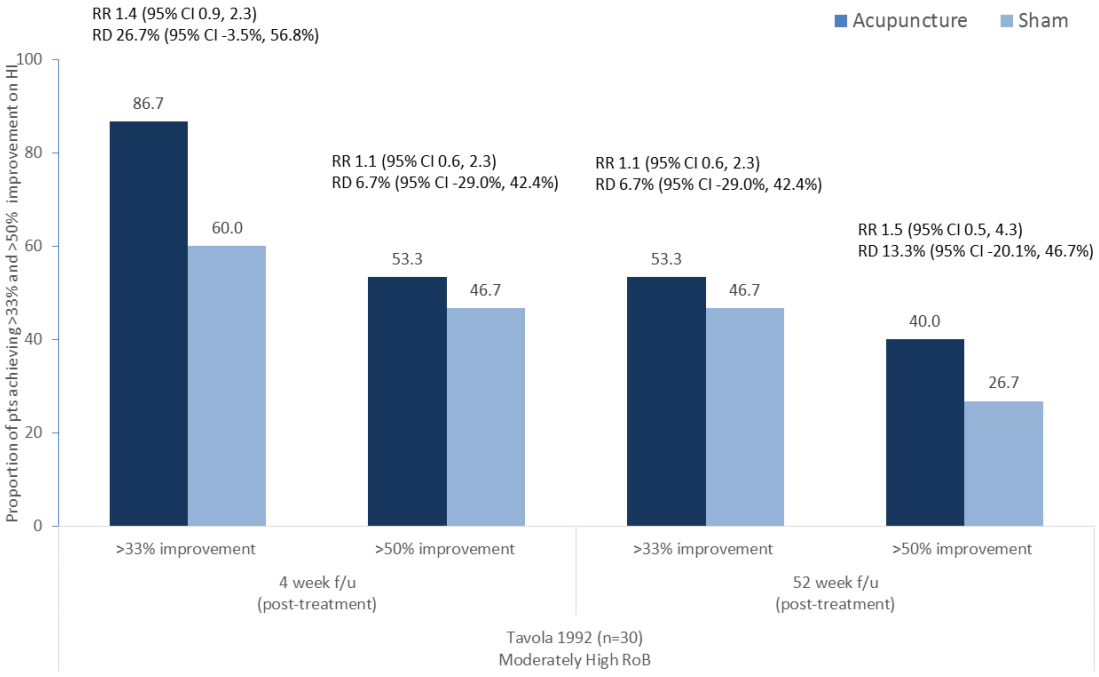
4.2.2.3.1 Treatment Responders

Only one RCT[114], which compared acupuncture with sham acupuncture reported on this outcome. Trials comparing acupuncture with active controls did not report on it.

Short-term (4 weeks): In one RCT,[114] comparing ***acupuncture versus sham acupuncture***, treatment responders were defined as the proportion of patients achieving improvement on the Headache Index (HI) using two different cut-offs: >33% and >50% improvement over baseline. At 4 weeks after the end of treatment, although the proportion of patients that experienced improvement on the HI using both criteria was greater in the acupuncture group compared with the sham group, the differences did not reach statistical significance (Figure 11). The small sample size may have been a factor; there were only 15 patients randomized to each group.

Long-term (52 weeks): Likewise, although the proportion of patients that experienced both a >33% and a >50% improvement on the HI was somewhat greater in the acupuncture group compared with the sham group 52 weeks after the end of treatment, the differences did not reach statistical significance,[114] (Figure 11). Again, the small sample size is likely a factor in this finding.

Figure 11. Proportion of patients achieving >33% and >50% improvement from baseline on the Headache Index over the short (≤8 weeks) and long term (≥12 weeks), acupuncture versus sham for CTTH



CTTH: chronic tension-type headache; f/u: follow-up; HI: headache index; RD: risk difference; RoB: risk of bias; RR: risk ratio.

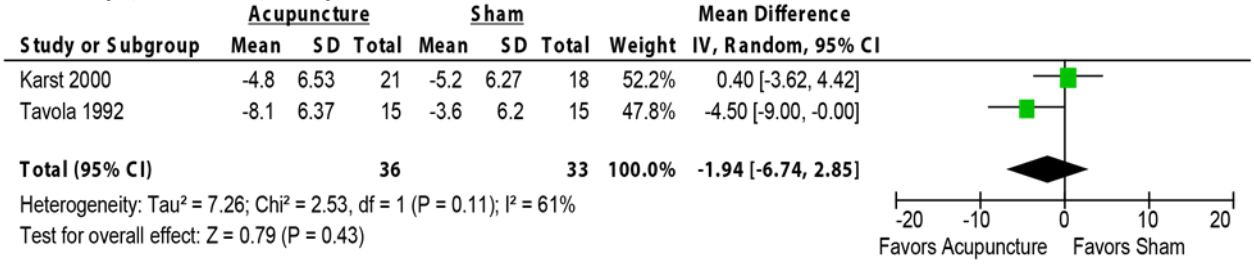
4.2.2.3.2 Reduction in Frequency of Headache Attacks

Both RCTs[72,114], comparing acupuncture with sham acupuncture and both RCTs[39,107] comparing acupuncture with active controls reported limited information on this outcome. There were no differences across the two trials of acupuncture versus sham acupuncture at either short-term or in the one trial longer-term.[114] Compared with active controls, no data comparing acupuncture with physiotherapy were provided in one trial short-term[39], and no differences between acupuncture and physical training/exercise or acupuncture and relaxation training were reported at longer-term in the other trial.[107] Details are provided below.

Acupuncture versus sham

Short-term (6 weeks): No difference was seen between **acupuncture and sham** in mean change from baseline in the number of headache episodes per month as reported by two trials[72,114]; the pooled MD was –1.9 (95% CI –6.7 to 2.9), I^2= 61% measured at 4 to 6 weeks post-treatment, Figure 12 (Appendix Table F4). This analysis resulted in a large amount of heterogeneity. Both trials rated at a moderately high risk of bias. There are differences in study populations that may account for some of the heterogeneity (females comprised 87% of one population vs. 49% of the other; patients in one trial were a mean 16 years younger than those in the other, 33 vs. 49 years; and mean headache frequency at baseline was 17.5 attacks in one trial vs. 27.0 attack in the other).

Figure 12. Mean change from baseline in the number of headache episodes per month at short-term follow-up (4-6 weeks), acupuncture versus sham for CTTH.



CI = confidence interval; CTTH = chronic tension-type-headache; SD = standard deviation.

Longer-term (26-52 weeks): In one small trial, authors state that the frequency of headache episodes per month continued to decrease significantly over time (through 26 and 52 weeks post-treatment) with no statistical difference between groups, however, no data are presented.[114]

Acupuncture versus physiotherapy, physical training, or relaxation training

Short- to Intermediate-Term (4 to 9 weeks): For the comparison of **acupuncture versus physiotherapy**, headache frequency (measured on a 1 to 5 scale, respectively: almost never, once or twice a month, once a week, several times a week, and daily) was significantly (<0.001) reduced in both groups 4 to 9 weeks after treatment; however, no data or information regarding the between-group difference was provided.[39]

Longer-term (26 weeks): No difference was seen between ***acupuncture and physical training*** in the number of headache-free periods per week (0–28 periods/week) over the course of follow-up,

respectively (Appendix Table F4): mean 6.25 and median 0.25 (range, 0.00–28.00) versus mean 7.46 and median 5.00 (range, 0.00–28.00) at 12 weeks post-treatment; and mean 7.58 and median 0 (range, 0.00–28.00) versus mean 9.37 and median 9.38 (range, 0.00–28.00) at 26 weeks post-treatment.[107] The authors report that the physical therapy group, but not the acupuncture group, showed statistically significant improvement at 26 weeks compared with baseline.

Longer-term (26 weeks): No statistical differences were seen between ***acupuncture and relaxation training*** in the number of headache-free periods per week (0–28 periods/week) over the course of follow-up, respectively (Appendix Table F4): mean 6.25 and median 0.25 (range, 0.00–28.00) versus mean 7.67 and median 2.0 (range, 0.00–29.00), respectively, at 12 weeks post-treatment; and mean 7.58 and median 0 (range, 0.00–28.00) versus mean 8.29 and median 2.0 (range, 0.00–29.00) at 26 weeks post-treatment.[107] The authors report that the relaxation training group, but not the acupuncture group, showed statistically significant improvement at both timepoints compared with baseline.

4.2.2.3.3 Reduction in Number of Headache Days

Neither study of acupuncture versus sham reported on this outcome. Only the trial[107] comparing acupuncture with physical training/exercise or relaxation training reported on this outcome. No differences in the number of headache-free days were seen between acupuncture or either comparator at longer-term.

Longer-term (26 weeks): No differences were seen between **acupuncture and physical training** in the number of headache-free days per week (0-7 days/week) both at 12 weeks post-treatment, respectively, mean 1.18 and median 0 (range, 0.00–7.00) versus mean 1.23 and median 0.50 (range, 0.00–7.00) and at 26 weeks post-treatment, respectively, mean 1.56 and median 0 (range, 0.00–7.00) versus mean 1.66 and median 1.00 (range, 0.00–7.00),[107] (Appendix Table G5) Authors report that the physical therapy group, but not the acupuncture group, showed statistically significant improvement at 26 weeks compared with baseline.

Longer-term (26 weeks): No differences were seen between **acupuncture and relaxation training** in the number of headache-free days per week (0–7 days/week) both at 12 weeks post-treatment, respectively, mean 1.18 and median 0 (range, 0.00–7.00) versus mean 1.58 and median 0.13 (range, 0.00–7.25) and at 26 weeks post-treatment, respectively, mean 1.56 and median 0 (range, 0.00–7.00) versus mean 1.73 and median 0.13 (range, 0.00–7.25),[107] (Appendix Table G5). Authors report that the relaxation training group, but not the acupuncture group, showed statistically significant improvement at both timepoints compared with baseline.

4.2.2.3.4 Functional disability

One trial comparing acupuncture with physiotherapy reported a functional disability outcome.

Short- to Intermediate-Term (4 to 9 weeks): At 4 to 9 weeks post-treatment, **acupuncture and physiotherapy** one trial reported mean overall Sickness Impact Profile (SIP) (0–100, poorer health) scores of 9 (change score, –3.5) versus of 4.5 (change score, –5.0), respectively; it is unclear whether this represents a clinically important difference between the treatment groups.[39] The acupuncture group improved significantly more than the physiotherapy group in the SIP category Sleep and Rest ($p<0.05$) but significantly less ($p<0.05$) with respect to the psychosocial categories Emotional Behavior, Work,

Eating, and Recreation and Pastimes. Psychosocial functioning (SIP Psychosocial dimension) was improved in both groups, though somewhat less in the acupuncture group (statistical significance not reported). Data was provided in graphs only; see Appendix Table F4 for more detail.

4.2.2.3.5 Secondary Outcomes

Included trials reported on a variety of secondary outcomes.

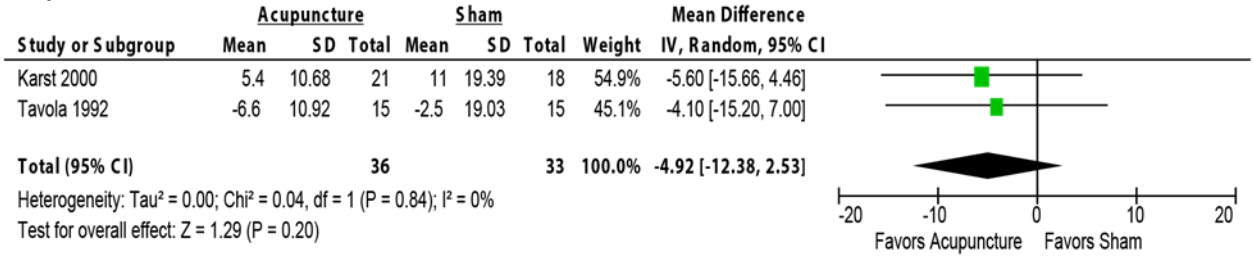
Acupuncture versus sham

Quality of life: In one trial, the authors state that quality of life parameters (Nottingham Health Profile, Everyday-Life-Questionnaire, Freiburg Questionnaire of Coping with Illness and von Zerssen Depression Scale) did not differ between the **acupuncture and the sham** group at any follow-up, however, no data are presented.[72]

Patient perception of improvement: In one RCT,[72] patients were asked to give their impression of improvement on a clinical global impressions (CGI) scale (range –4 to 4, best) with no difference seen between the two groups at short-term follow-up (6 weeks post-treatment): acupuncture 1.3 ± (standard deviation) 1.4 versus sham 1.1 ± 1.7 (Appendix Table F4).

Analgesic consumption: No difference was seen between acupuncture and sham in the mean change from baseline in analgesic consumption per month; the pooled MD was –4.9 (95% CI –12.4 to –2.5, I^2=0%) as measured over the short-term (4–6 weeks post-treatment),[72,114] Figure 13. One small RCT[114] also reported analgesic consumption over the longer term (26 and 52 weeks post-treatment) with no statistical difference see between the acupuncture and the sham group, respectively: baseline, 11.6 ± 10.2 versus 11.5 ± 12.7; 26 weeks, 5.0 versus 8.5; and 52 weeks, 6.5 versus 9.5 (all scores expect baseline were estimated from graphs in the article) (Appendix Table F4).

Figure 13. Mean change from baseline in analgesic consumption at short-term follow-up (4-6 weeks), acupuncture versus sham for CTTH



CI = confidence interval; CTTH = chronic tension-type-headache; SD = standard deviation.

Headache intensity: In one RCT,[72] no statistical difference was seen in headache intensity, rated on a 0 to 10 (worst) VAS, between the acupuncture group and the sham group at 6 weeks after the end of treatment (short term): mean 4.0 ± 2.5 versus 3.9 ± 2.7, respectively Appendix Table F4.

Headache Index scores: In one small RCT,[114] both the acupuncture and the sham group showed improvement (i.e., reduction) in mean Headache Index scores (measured as the intensity X duration X frequency of headache/30) at short- and long-term follow-up, but with no difference seen between groups, respectively: baseline (4.3 ± 3.9 vs. 4.5 ± 3.4), 4 weeks (2.4 vs. 3.0), 26 weeks (2.2 vs. 3.1) and 52 weeks (3.2 vs. 3.7) (all scores except baseline were estimated from graphs in the article) Appendix Table F4.

Pressure Point Threshold (PPT): In one RCT,[72] PPT (i.e., the minimum force applied which induces pain) was determined according to the method of Jensen et al. An algometer was held perpendicular to the skin against the temporal region where palpation had shown the anterior part of the temporal muscle to be most prominent; subjects were instructed to push a button as soon as the pressure became painful and the pressure was immediately released. PPTs increased significantly in the acupuncture group from baseline to 52 weeks after the end of treatment (long term): left side, from 329.1 ± 70.5 to 360.0 ± 41.3 kilopascal (kPa) and right side, from 312.9 ± 78.8 to 368.2 ± 439.4 kPa. PPTs in the sham group were essentially unchanged over time (Appendix Table F4). The clinical significance of this finding is unclear.

Acupuncture versus active comparators

Both trials comparing acupuncture with active comparators reported quality of life measures and headache intensity.[39,107,108]

Quality of Life:

Across studies and comparators, results are mixed regarding acupuncture's impact on quality of life compared with various active comparators. Differences in measures used and small sample sizes may contribute to this.

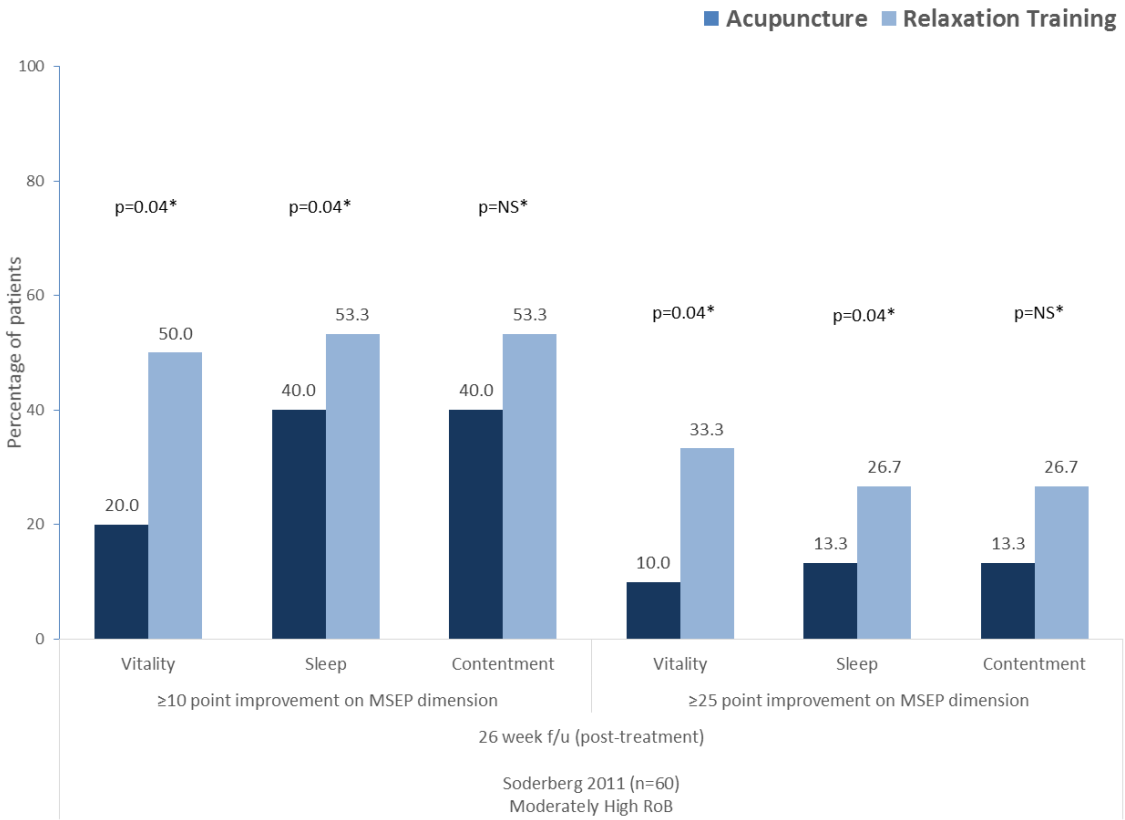
In one trial **comparing acupuncture with physiotherapy[39]**, acupuncture was associated with improved mood/mental well-being based on The Mood Adjective Check List (MACL) (scale 1–4, more positive emotional state). Overall MACL scores improved significantly less ($p<0.05$) in the acupuncture (baseline, 2.79 ± 0.37 vs. follow-up, 2.77 ± 0.43) compared with the **physiotherapy group** (baseline 2.77 ± 0.48 vs. follow-up, 2.97 ± 0.48) at the 4 to 9 week assessment,[39] Appendix Table F4.

In the trial comparing **acupuncture with physical training/exercise and acupuncture with relaxation training[107,108]**, patients' subjective well-being and quality of life (QOL) were assessed with the Minor Symptom Evaluation Profile (MSEP) over the longer-term (≥12 weeks). The MSEP is designed to detect changes in subjective symptoms considered to be CNS-related. Standardized items, categorized in three primary dimensions (contentment, vitality, and sleep), are measured on a VAS scale with low scores reflecting positive feelings and high scores reflecting negative feelings. Overall MSEP scores (lower score = better) were compared. The proportion of patients with an improved total score (i.e., change score <0 on VAS) was similar between the **acupuncture and the relaxation training** group both at 12 weeks (56.7% (17/30) vs. 66.7% (20/30), respectively) and 26 weeks (56.7% (17/30) vs. 73.3% (22/30), respectively) post-treatment.[108] However, the proportion was significantly lower in the **acupuncture group compared with the physical training group at** 12 weeks post-treatment (56.7% (17/30) vs. 86.7% (26/30), respectively, p=0.036; RR 0.65 (95% CI 0.46 to 0.92); RD 30.0% (95% CI 8.5% to 51.5%))[108]; though fewer patients in the acupuncture group continued to show improvement on the MSEP at the 26 weeks follow-up, the difference was no longer statistically significant: 56.7% (17/30) vs. 80.0% (24/30),

respectively; RR 0.71 (95% CI 0.49 to 1.0). The small sample size may have played a factor in some results.

Comparing improvement of ≥10 or ≥25 points on VAS for the three MSEP dimensions, a significantly lower proportion of patients in the acupuncture group met these criteria for two of the dimensions, Vitality and Sleep QOL, at 26 weeks post-treatment **compared with the relaxation** group[108] (Figure 14); there was no statistical difference between groups in the Contentment dimension at 26 weeks or for any of the three MESP dimensions at 12 weeks post-treatment. For the comparison of **acupuncture with physical training/exercise**[108], no difference between the groups was seen when comparing improvement for thresholds of ≥10 or ≥25 points on VAS for the three MSEP dimensions (vitality, sleep QOL, and contentment) at 12 and 26 weeks after the end of treatment (see Appendix Table F4 for details).

Figure 14. Proportion of patients with ≥10 or ≥25 improvement on the three dimensions of the MSEP over the long term, acupuncture versus relaxation for CTTH



CTTH: chronic tension-type headache; f/u: follow-up; MSEP: Minor Symptom Evaluation Profile; RD: risk difference; RoB: risk of bias; RR: risk ratio.
*p-values as reported by the authors.

Headache intensity:

Headache intensity was reported across both trials comparing acupuncture with an active comparator.[39,107,108] Results across comparators were somewhat mixed. One trial reported less improvement in VAS

pain with acupuncture versus physiotherapy short-term[39], however no differences between acupuncture and relaxation training or physical training/exercise were seen longer term in the second trial.[107,108]

In one trial[39], the acupuncture group had significantly less improvement with respect to headache intensity (average pain level during the last weeks) rated on the VAS (0-100, worst) ($p<0.01$) and a 5-point scale (no or negligible, mild, moderate, severe, and incapacitating ($p<0.05$) compared with **the physiotherapy group**, [39] (Appendix Table F4). The mean group scores for headache intensity on VAS were 40 versus 28 at 4 to 9 weeks post-treatment and 52 versus 29, respectively, at 28-52 weeks (estimated from graphs provided in the article); no data were provided for the 5-point pain scale.

In the other trial[107], no differences were seen between the **acupuncture group and relaxation training** in headache intensity rated on a 0-100 (worst) VAS (recorded 4x/day in the patients' diaries) at 12 weeks post-treatment (mean 18.93 (range, 0.00–53.38) versus 16.14 (range, 0.00–66.64), respectively) or at 26 weeks post-treatment (mean 17.72 (range, 0.00–50.27) versus 15.08 (range, 0.00–70.48), respectively)[107]. According to the authors, both the acupuncture and the relaxation group reported a significant decrease in headache intensity from baseline at both long-term timepoints. Similarly, there were no differences between the **acupuncture group and physical training** for headache intensity rated on the VAS at 12 weeks post-treatment (mean 18.93 (range, 0.00–53.38) versus 16.88 (range, 0.00 to 61.67), respectively) or at 26 weeks post-treatment (mean 17.72 (range, 0.00–50.27) versus 14.66 (range, 0.00–56.75), respectively). Authors report that in the acupuncture group, the change from baseline was significant at both long-term timepoints; for the physical training group, only the change at 12 weeks showed significant improvement from baseline. (Appendix Table F4).

4.2.3 Chronic Daily Headache

No trials evaluating acupuncture for the treatment of chronic daily headache that met the inclusion criteria were identified for the prior report. Similarly, our updated search did not identify new RCTs of acupuncture in this population that met inclusion criteria.

4.3 Key Question 2: Harms & Complications (Safety)

4.3.1 Number of studies retained

All included RCTs identified were evaluated for harms and complications. The overall strength of evidence for most safety outcomes was considered low or insufficient across interventions and comparators. Section 5 of the report provides additional detail of the strength of evidence determination for each outcome.

4.3.1.1 Summary of Results for all Headache Types

Chronic Migraine

Serious adverse events

- There is insufficient evidence to draw conclusions regarding the risk of **any serious adverse events (to include death)** for acupuncture compared with active control treatments. No serious adverse events occurred in any group (acupuncture, topiramate, UC) as reported by two RCTs with follow-up ranging from short to long term (1 to 36 weeks post-treatment)[117,129]; no data and no further information was provided. No deaths occurred in either the acupuncture or topiramate group as reported by one of these (small) trials at 1 week post-treatment.[129]
- There was no statistical difference between groups across the short and long term in the risk of **adverse events leading to study withdrawal** across two RCTs, one comparing acupuncture with UC (1 case in the acupuncture group at 36 weeks post-treatment)[117] and the other with topiramate (3 cases in the topiramate group at 1 week post-treatment)[129] (low SOE). It is unclear, however, whether there was a sufficient sample size to detect a difference.

Any minor adverse events/side effect

- Fewer minor adverse events or side-effects occurred following acupuncture versus topiramate and versus Botulinum toxin A across two RCTs with 1- and 12-week follow-up periods post-treatment.[87,129] All events were mild and self-limiting. One of these RCTs also compared acupuncture with sodium valproate,[87] and though a direct comparison was not made for this outcome, it can be inferred from the data provided that acupuncture had fewer side effects overall over 12 weeks (low SOE).

Headache

- There was no difference between groups in the frequency of headache post-treatment in one RCT[117]: there were five cases in four patients following acupuncture and no cases in the UC group (low SOE). It is unclear whether sample size played a role in these findings.

Other adverse events

Evidence was considered insufficient to draw a conclusion for the following adverse events/side effects:

- **Hematoma, facial hematoma**: auricular acupuncture versus sham/UC (1 RCT)[63] and traditional acupuncture versus WL/UC (1 RCT)[86]
- **Ear swelling, ear pain, erythema, and ear infection:** auricular acupuncture versus sham/UC (1 RCT)[63]

Chronic Tension-Type Headache

- Over the short- (4 weeks) and intermediate-term (9 weeks), one trial that compared acupuncture with physiotherapy reported that a few patients in the acupuncture group had a **slight vasovagal reaction**[39]; no other complications were noted, and no data was provided (insufficient SOE).

- Adverse events were not reported for the following comparisons included for efficacy: acupuncture versus sham (2 RCTs)[72,114]and acupuncture versus physical training and versus relaxation (1 RCT).[107,108]

Chronic Daily Headache

- No trials were identified that met the inclusion criteria.

4.3.2 Chronic Migraine

A summary of safety outcomes for all interventions and comparators is provided below and is organized by serious and non-serious adverse events (AEs). The focus of the summary below is on rates of adverse events that can be compared across the acupuncture and comparator groups as well as any AEs specific to acupuncture. A variety of AEs specific to the various pharmacologic treatments employed were reported and can be found in Table 13 but are not summarized in the text below.

4.3.2.1 Serious Adverse Events

Two RCTs (moderately low and moderately high risk of bias), one comparing acupuncture with UC over the long term (36 weeks post-treatment)[117] and the other comparing acupuncture with topiramate over the short term (1 week post-treatment),[129] reported that no serious AEs (not further defined), to include death, were reported in any treatment group. AEs leading to withdrawal from the study occurred in one patient randomized to acupuncture (0.6%; 1/161) versus no patient in the UC group in one trial[117]; in the second trial, no acupuncture patients withdrew due to AEs compared with three patients in the topiramate group (9.1%; 3/33), p=0.08,[129] Table 12.

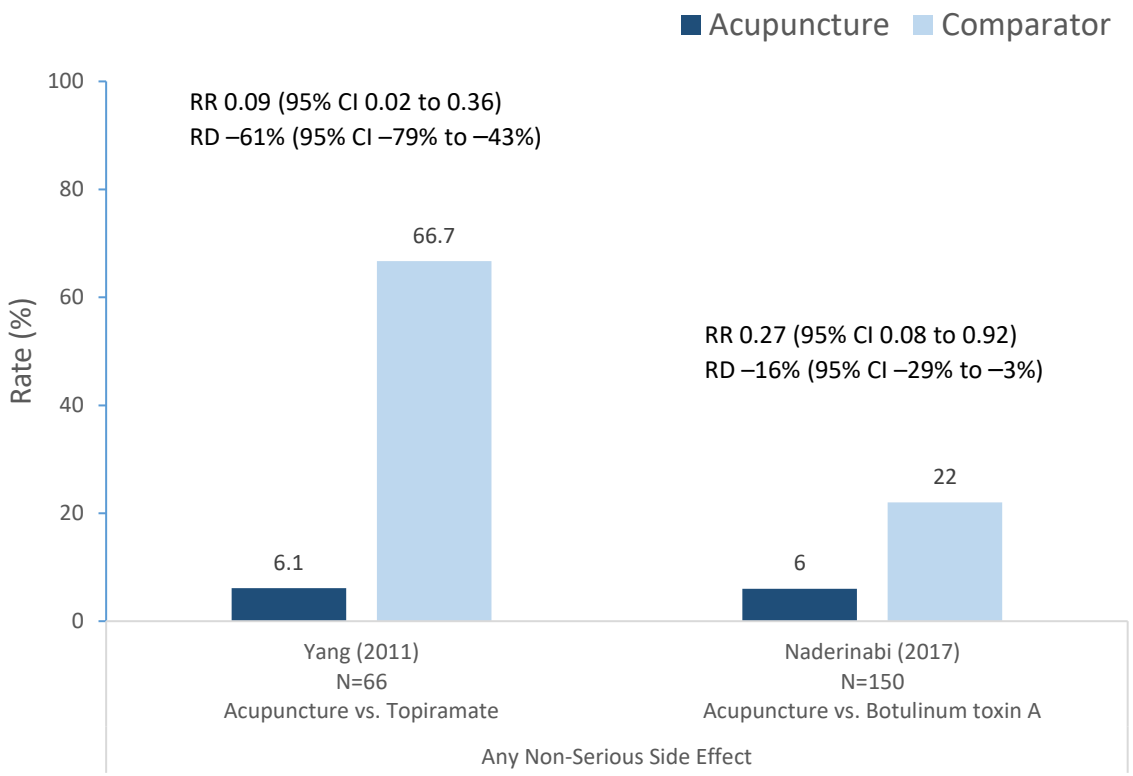
4.3.2.2 Non-Serious Adverse Events

4.3.2.2.1 Any Non-Serious Adverse Event

Acupuncture was associated with a reduced risk of any non-serious AEs compared with other treatments across both the short and long term as reported by two RCTs; most of the AEs were mild and self-limiting. In one small RCT (N=33) at moderately low risk of bias, acupuncture had more than 10-times fewer non-serious adverse events compared with topiramate 1 week post-treatment (6% vs. 66%; RR 0.1, 95% CI 0.02 to 0.4),[129] Figure 15, Table 13. AEs in the acupuncture group primarily related to local insertion of needles, i.e., local pain after treatment, ecchymosis, and local paresthesia during treatment; in the topiramate group, the most common AEs included paresthesia (48%), difficulty with memory (36%), dyspepsia (36%), fatigue (24%), dizziness (21%), somnolence (18%), and nausea (12%). Similarly, in the second RCT (moderately high risk of bias),[87] acupuncture patients had almost 4-times fewer non-serious AEs compared with Botulinum toxin A at 12 weeks post treatment (6% vs. 22%; RR 0.3, 95% CI 0.1 to 0.9); AEs in the acupuncture group including bleeding or subcutaneous hematoma and in the Botulinum toxin group, ptosis, facial masking or asymmetry (Figure 15, Table 13). This trial also

compared acupuncture with sodium valproate and although the authors did not provide the number of patients in this group with any non-serious AE, given the rates of reported side-effects (asthenia [10%], anorexia [4%], weight gain [4%], tremor [18%], somnolence [18%], insomnia [8%], alopecia [14%]), acupuncture appeared to be a safer treatment in this population.

Figure 15. Risk of any non-serious adverse event across two RCTs evaluating acupuncture for chronic migraine.



CI = confidence interval; RD = risk difference; RR = risk ratio.

4.3.2.2.2 Hematoma, Erythema, and Infection

One small trial at moderately low risk of bias reported one mild case (2.5%; 1/40) of facial hematoma over the 3-months of acupuncture treatment which resolved within 2 days without medical intervention.[86] This trial compared acupuncture with WL/UC and did not report adverse events for the comparator group. A second trial (moderately high risk of bias), which compared auricular acupuncture with sham plus UC, reported no cases of hematoma, erythema, or ear infection in either group,[63] however, authors state that patients were excluded from the study if they developed redness or infection at the location of the needle implant, so these results should be interpreted with extreme caution (Table 13).

4.3.2.2.3 Ear Swelling, Ear Pain

In the trial evaluating auricular acupuncture versus sham plus UC,[63] the proportion of patients who experienced ear swelling in the acupuncture group (n=40) ranged from 3% to 10% over 4 weeks of follow-up and for ear pain, the range was 5% to 18%; no cases were reported in the sham/UC group (Table 13).

4.3.2.2.4 Treatment-related Headache

One trial reported five cases of headache in four acupuncture patients (2.2%; 4/186); the timing of reporting was unclear.[117] Adverse events were not reported for the UC group.

Table 13. Safety Outcomes from RCTs Evaluating Acupuncture for Chronic Migraine

				Results, % (n/N)		Effect Estimate (95% CI)*	p-value*
Outcome	**Author**	**Comparator**	**F/U post-tx**	**Acupuncture**	**Comparator**		
Serious AEs							
Serious AEs (NOS)	Yang 2011	Topiramate	1 week	0% (0/33)	0% (0/33)	-----	-----
	Vickers 2004	UC	36 weeks	0% (1/161)	0% (0/140)	-----	-----
Death	Yang 2011	Topiramate	1 week	0% (0/33)	0% (0/33)	-----	-----
AEs leading to treatment withdrawal	Yang 2011	Topiramate	1 week	0% (0/33)	9.1% (3/33)	NR	0.079
	Vickers 2004	UC	12 weeks	0.6% (1/161)	0% (0/140)	NR	0.351
Non-serious AEs							
Any non-serious AE (mild, self-limiting)	Yang 2011	Topiramate	1 week	6% (2/33)†	66% (22/33)‡	RR 0.09 (0.02 to 0.36)	NR
	Naderinabi 2017	Sodium valproate	12 weeks	6% (3/50)§	NR	-----	NR
		Botulinum toxin A	12 weeks	6% (3/50)§	22% (11/50)§	RR 0.27 (0.08 to 0.92)	0.021
Fatigue/asthenia	Yang 2011	Topiramate	1 week	NR	24.2% (8/33)	-----	-----
	Naderinabi 2017	Sodium valproate	12 weeks	NR	10% (5/50)	-----	-----
Somnolence	Yang 2011	Topiramate	1 week	NR	18.1% (6/33)	-----	-----
	Naderinabi 2017	Sodium valproate	12 weeks	NR	18% (9/50)	-----	-----
Nausea, vomiting	Yang 2011	Topiramate	1 week	NR	12.1% (5/33)	-----	-----
	Naderinabi 2017	Botulinum toxin A	12 weeks	NR	NR – "higher"	-----	0.027
Hematoma**, Facial hematoma††	Habibabadi 2021	Sham + UC	4 weeks	0% (0/40)	0% (0/40)	-----	-----
	Musil 2018	WL + UC	12 weeks	2.5% (1/40)	NR	-----	-----
Paresthesia	Yang 2011	Topiramate	1 week	NR	48.4% (16/33)	-----	-----
Difficulty with memory				NR	36.3% (12/33)	-----	-----
Dyspepsia				NR	36.3% (12/33)	-----	-----
Dizziness				NR	21.2% (7/33)	-----	-----
Anorexia	Naderinabi 2017	Sodium valproate	12 weeks	NR	4% (2/50)	-----	-----
Weight gain				NR	4% (2/50)	-----	-----
Tremor				NR	18% (9/50)	-----	-----
Insomnia				NR	8% (4/50)	-----	-----
Alopecia				NR	15% (7/50)	-----	-----
Headache	Vickers 2004	UC	Unclear	2.2% (4/186) (5 cases)	NR	-----	-----
Ear swelling	Habibabadi 2021	Sham + UC	1 week	10% (4/40)	0% (0/40)	-----	0.116
			2 weeks	2.5% (1/40)	0% (0/40)	-----	0.999
			3 weeks	10% (4/40)	0% (0/40)	-----	0.116

				Results, % (n/N)		Effect Estimate (95% CI)*	p-value*
Outcome	Author	Comparator	F/U post-tx	Acupuncture	Comparator		
			4 weeks	5% (2/40)	0% (0/40)	-----	0.494
Ear pain			1 week	7.5% (3/40)	0% (0/40)	-----	0.210
			2 weeks	17.5% (7/40)	0% (0/40)	-----	0.022
			3 weeks	15% (6/40)	0% (0/40)	-----	0.039
			4 weeks	5% (2/40)	0% (0/40)	-----	0.494
Erythema**			4 weeks	0% (0/40)	0% (0/40)	-----	-----
Ear infection**			4 weeks	0% (0/40)	0% (0/40)	-----	-----

Cells shaded gray indicate comparison with Sham, UC or WL.

AE = adverse event; CI = confidence interval; F/U = follow-up; NOS = not otherwise specified; NR = not reported; SD = standard deviation; tx = treatment; UC = usual care; WL = waitlist.

*Effect calculated by AAI; p-values as reported by authors except for "AEs leading to treatment withdrawal" which were calculated by AAI.

†Non-serious adverse events/side effects, primarily related to local insertion of needles, i.e., local pain after treatment, ecchymosis, local paresthesia during treatment

‡The most common nonserious adverse events are listed individually below.

§For Acupuncture group, includes only bleeding or subcutaneous hematoma; for Botulinum toxin A group, includes ptosis, facial masking or asymmetry.

**The authors state that patients were excluded from the study if they developed redness or infection at the location of the needle implant, so these results should be interpreted with extreme caution.

††Mild and common adverse event, resolved within 2 days without medication or medical help.

4.3.3 Chronic Tension-Type Headache

Adverse events were not reported by either trial that evaluated the efficacy of acupuncture versus sham for the treatment of chronic tension-type headache.[72,114] No safety data were reported by the trial comparing acupuncture with physical training and relaxation.[107,108]

Only one of the RCTs identified that evaluated the efficacy of acupuncture versus an active control (physiotherapy) for treatment of chronic tension-type headache provided data on adverse events.[39] Study and patient characteristics have been described with Key Question 1 (and can be found in Appendix Table F2); detailed information on individual adverse events can be found in Appendix Table F5. In this trial, comparing **acupuncture with physiotherapy**,[39] the following statement was made related to safety: "In a few patients, a slight vasovagal reaction was seen at the first treatment [in the acupuncture group]. Otherwise, no complications were noted." No other information was provided. The follow-up period was 4 to 9 weeks (short to intermediate-term).

4.3.4 Chronic Daily Headache

No trials evaluating acupuncture for the treatment of chronic daily headache that met the inclusion criteria were identified for the prior report or this update report.

4.4 Key Question 3: Differential Efficacy/Effectiveness & Harms in Subpopulations

To evaluate differential efficacy and safety (heterogeneity of effect, interaction) RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. When assessing the quality of evidence for studies performing subgroup analysis, we also considered sample size, whether the subgroup analysis was preplanned (a priori) with a relevant hypothesis provided, whether a test for interaction was done, and performance of multiple analyses. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis-generating, and additional confirmatory evidence should be sought.[95,113,121] Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. If a comparison is not listed below there was either no evidence identified that met the inclusion criteria or the included trials did not provide information on differential efficacy or harms.

4.4.1 Summary of results

Acupuncture versus Active Control for Chronic Migraine

- Acupuncture vs. Usual Care (1 RCT)[117]:
    - Baseline headache score modified the treatment effect such that those with more severe symptoms at baseline showed greater improvement with acupuncture vs. usual care (UC); all other variables (headache diagnosis, age, sex, chronicity) did not modify the treatment effect (insufficient SOE).

- Acupuncture vs. Topiramate (1 RCT, 2 publications)[128,129]:
    - Baseline headache days (overall and in patients with moderate/severe at baseline) may modify treatment effect such that patients with higher (≥20 days/month) compared with lower (<20 days/month) frequency showed greater improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect (insufficient SOE).

4.4.2 Chronic Migraine

4.4.2.1 Acupuncture vs. Usual Care for Chronic Migraine

One RCT at moderately high risk of bias included for efficacy (N=301) reported formal tests for interaction for several factors (i.e., age, sex, chronicity, baseline headache score, headache diagnosis). No data were provided for evaluation.[117] Likewise authors do not specify these analyses *a priori* or consider such analyses in sample size calculations. Details regarding this study population are available in the section on efficacy and Appendix Table F2. The authors state that baseline headache score modified the treatment effect such that a statistically greater improvement in headache score at follow-up was seen in those with more severe symptoms initially, compared with less severe symptoms, following acupuncture but not UC (interaction p=0.004). This effect was significant even after controlling for regression to the mean. Headache diagnosis (chronic migraine vs. tension-type headache) did not modify treatment effect in this population, though improvements in mean headache score following acupuncture compared with UC were larger for migraine patients (4.9; 95% CI 2.4 to 7.5; n=284) than those with tension-type headache (1.1, 95% CI –2.4 to 4.5, n=17); the small numbers of patients with tension-type headache likely precluded detection of effect modification of acupuncture in this analysis. Age, sex, and chronicity did not modify the treatment effect.

4.4.2.2 Acupuncture vs. Topiramate for Chronic Migraine

One small RCT (N= 66) at moderately low risk of bias included for efficacy that compared acupuncture with topiramate for the treatment of chronic migraine stratified on multiple factors and performed formal tests for interaction in a subsequent publication.[128,129] These analyses do not appear to have been pre-planned or included in sample size calculations. Details regarding this study population can be found in the section on efficacy and Appendix Table F2. The baseline number of headache days was the only patient characteristic found to differentially affect treatment in this trial for the outcome of ≥50% reduction from baseline in moderate/severe headache days: patients with higher (≥20 days/month), as opposed to lower (<20 days/month), baseline headache days (interaction p= 0.002) and moderate/severe headache days at baseline (interaction p = 0.007) showed a significantly greater reduction in the mean number of moderate/severe headache days per month following treatment with acupuncture but not with topiramate (Table 14).

Table 14. Changes in Mean Number of Moderate/Severe Headache Days Per 4 Weeks* by Baseline Headache Frequency

	Acupuncture			Topiramate			Interaction
	n	Median	IQR	n	Median	IQR	P†
Headache days							0.002
≤20	13	-10	1	13	-9	5	
>20	20	-12	2	20	-8	3.5	
Moderate/severe headache days							0.007
≤20	20	-10	2	19	-9	6	
>20	13	-12	1	14	-8	3	

*Change in mean number of moderate/severe headache days per 4 weeks = number of moderate/severe headache days within 12 weeks/3, minus number of moderate/severe headache days at baseline within 4 weeks; medians of the continuous baseline variables were used as cut-off values to categorize the patients into 2 groups.
†Interaction was examined by logistic regression with a dichotomized outcome as the dependent variable (whether or not the reduced moderate/severe headache days was ≥50% of the baseline level).

The following characteristics were also evaluated but none were found to modify the treatment effect of acupuncture versus topiramate in chronic migraine patients:

***Demographic characteristics*:**
- Sex
- Age (≤46 vs. >46 years)
- Duration (≤13 vs. >13 years
- Education (≤12 vs. >12 years)
- Acute medication intake (≤14.5 vs. >14.5 days)
- MIDAS (≤61.5 vs. >61.5)
- HADS (≤11 vs. >11)
- BDU-II (≤16.5 vs. >16.5)
- SF-36 PCS (≤41 vs. >41)
- SF-36 MCS (≤39 vs. >39)

***Headache characteristics*:**
- Unilateral predominant (No/Yes)
- Throbbing (No/Yes)
- Nausea/Vomiting (No/Yes)
- Photophobia (No/Yes)
- Phonophobia (No/Yes)
- Cutaneous allodynia (No/Yes)

***Treatment Expectation (0-10, best)*:**
- General expectation (≤5 vs. >5)
- Expectation for acupuncture (≤5 vs. >5)
- Expectation for topiramate (≤5 vs. >5)

This trial also conducted a subgroup analysis of all patients overusing acute headache medications at baseline (defined as intake of simple analgesics on more than 15 days per month or the intake of a combination of analgesics, opioids, ergots, or triptans on more than 10 days per month); this included 24 (out of 33) in the acupuncture group and 25 (out of 33) in the topiramate group.[129] The results were similar to those seen for the population as a whole with significant improvements seen following treatment with acupuncture compared with topiramate for all outcomes measured: ≥50% reduction in the number of headache days (any or moderate/severe) from baseline, mean reduction in the number of headache (any or moderate/sever) days from baseline, the Migraine Disability Index, the Beck Depression Inventory II, the Hospital Anxiety and Depression Scale, all eight individual domains of the Short-Form-36 questionnaire, and reduction in analgesic consumption (Appendix Table F3).

4.4.3 Chronic Tension-Type Headache and Chronic Daily Headache

No trials formally evaluating the differential efficacy or safety of acupuncture in these headache populations that met inclusion criteria were identified.

4.5 Key Question 4: Cost-Effectiveness

4.5.1 Summary of results

- One poor to moderate quality cost utility analysis comparing acupuncture to usual care (UC) in patients with chronic migraine suggests that acupuncture may be cost-effective for a time horizon of one year at a willingness to pay a threshold of £30,000 with a probability of 84% based on data available from the associated RCT. ICERs ranged from £801/QALY (for a 10-year time horizon) to £12,333/QALY if a GP provided the service.
- Primary limitations of this study included: lack of comparison to more active treatments, limited data beyond one year, limited sensitivity analyses around model inputs, lack of clarity regarding continuation or discontinuation, and components of UC.
- Differences between the UK and US medical systems make it difficult to generalize this study's findings to the U.S. healthcare system.

4.5.2 Chronic Migraine

For the treatment of chronic migraine, one study, included in the 2017 report, compared acupuncture with UC.[118] No new full economic studies comparing acupuncture with other treatments for chronic migraine, chronic tension-type headache or chronic daily headache were identified for this update. The results for acupuncture versus UC for chronic migraine described below are excerpted from the prior report.

4.5.2.1 Study characteristics

One moderately well-done study from the U.K. evaluated the cost-effectiveness of acupuncture versus UC in patients with chronic migraine (mean 15.9 headache days/month).[117] Usual care was described as an "avoid acupuncture" strategy where patients received UC from their general practitioner but were not referred to acupuncture. Study funding came from the U.K. National Health Service, Health Technology Assessment Programme. Study characteristics, results, and conclusions are summarized in Table 15.

Extensive sensitivity analyses related to missing data were done, however, sensitivity analysis around assumptions and model in puts was less robust. A follow-up time horizon of 12 months was used; sensitivity analyses around longer time horizons were done. The authors cite the short follow-up time as a rationale for not discounting; however, a sensitivity analysis was conducted in which costs and QALYs were discounted at 6% and 1.5%, respectively, to reflect conventions of the U.K. central government. The analysis was from both a payer and a societal perspective.

Clinical effectiveness was reported in terms of quality-adjusted life years (QALY) based on the SF-36. Data were derived from the multicenter Vickers RCT (N = 301, moderately high risk of bias) which is included in this HTA report.[117] In the base case, no imputation was done for missing SF-36 data; thus the sample for the base case includes only those patients who completed the SF-36 on all three occasions (n=255).

Costing was based on 2002/2003 U.K. pound. Costs included non-prescription (over-the-counter) drugs and NHS and private healthcare visits (i.e., acupuncture, general practitioner [GP], outpatient, psychotherapy, physiotherapy, alternative medicine), and appear to be in part based on actual patient costs from the trial as well as the British National Formulary, Office for National Statistics, and various literature sources. The cost of prescription drugs, needles, and other consumables was not included.

One-way sensitivity analyses were performed varying the provider and staff time and grade associated with acupuncture treatment, GP cost per hour, cost of prescription drugs, an estimate of production loss, and the time horizon (extended to 2, 5, and 10 years); different strategies were used to adjust for missing data.

The quality of the study was assessed by two reviewers using the Quality of Health Economic Study (QHES) metric with a score 71/100 (Table 15; see Appendix Table D5 for full scoring details). The primary limitations include lack of comparison to more active treatments, limited availability of data for benefits and harms beyond one year, and limited sensitivity analyses around model inputs. Lack of clarity regarding the components of UC and differences between the U.K. and U.S. medical systems make it difficult to generalize this study's findings to the U.S. healthcare system.

4.5.2.2 Results

Base Case

Acupuncture was estimated to cost $403.40 and add 0.021 QALYs (equivalent to 8 quality-adjusted days) implying the additional cost per QALY to be $189.42. The cost difference per patient between acupuncture and UC was $189.42 (95% CI $102.24 to $276.61). Compared with UC, acupuncture yielded an incremental cost-effectiveness ratio (ICER) of $9180 (total cost = NHS plus patient) based on data from the SF-36; when considering just the NHS cost the ICER was $9951 (offset slightly by a small reduction in direct patient costs such as over-the-counter medication and visits to complementary and alternative medicine physicians).

Sensitivity Analysis

Authors report the probability that acupuncture is cost-effective at a ceiling of £30,000 is 92% based on imputation for missing values; it fell to 84% when completers only were analyzed. The ICER for data on completers only was £11,474/QALY and differed slightly from the ICER based on the imputation of missing values of £10,836/QALY. ICERs ranged from £801/QALY (for a 10-year time horizon) to £12,333/QALY if a GP provided the service. Although cost-effectiveness increases at later time horizons, RCT data on efficacy and harms only go to 1 year.

Conclusions and Limitations

One poor to moderate quality CUA comparing acupuncture to UC suggests that acupuncture may be cost-effective for a time horizon of one year at a willingness to pay a threshold of £30,000 with a probability of 84% based on data available from the associated RCT. ICERs ranged from £801/QALY (for a 10-year time horizon) to £12,333/QALY if a GP provided the service.

The primary limitations of this study include lack of comparison to more active treatments, limited availability of data for benefits and harms beyond one year, and limited sensitivity analyses around

model inputs. Given the chronic nature of CM, it is assumed that continued treatment may be needed, however, the circumstances for continuation or discontinuation are not clear. Lack of clarity regarding the components of UC and differences between the UK and US medical systems make it difficult to generalize this study's findings to the U.S. healthcare system.

Table 15. Overview of formal economic study comparing acupuncture with usual care

	Vickers 2004
Population	255 adults (aged 16-65 years) with chronic migraine* (mean headache days/month: 15.9)
Intervention(s)	Acupuncture
Comparator(s)	Usual care (NOS)
Country	UK and Wales
Funding	Government (National Health Service, HTA Programme)
Study design	Cost utility
Perspective	Payer (UK NHS) and Societal
Time horizon	12 months
Analytic model	Linear regression model
Effectiveness outcome	QALY
Effectiveness outcome components	SF-36
Source for effectiveness data	RCT (Vickers 2014)*
Costing year	2002/2003
Currency	UK £
Cost sources	Published literature (various, including Vickers 2014), Government
Components of cost data	Cost of acupuncture treatment
Discounting	None due to short time horizon (in a sensitivity analysis costs and QALYs were discounted at 6% and 1.5%, respectively)
Sensitivity analysis	Primarily done around missing values and related imputation; Limited analysis of assumptions
QHES	71/100
Results:	
BASE CASE	
Cost / QALY of intervention	£403.40 / 0.727
Cost / QALY of comparator	£217.20 / 0.708
ICER (Intervention vs. comparator)	£9,951/QALY (NHS perspective) £9,180/QALY (total cost perspective) (BoNTA considered cost-effective at a WTP threshold of €20,000 to €30,000/QALY)
SENSITIVITY ANALYSIS	
One-way SA	ICERs ranged from £801/QALY (for a 10 -year time horizon) to £12,333/QALY if a GP provided the service
Two-way SA	NR

	Vickers 2004
Probabilistic SA	Authors report the probability that acupuncture is cost effective at a ceiling of £30,000 is 92% with imputation for missing values; it fell to 84% when completers only were analyzed.
Conclusions and limitations	
AUTHOR'S CONCLUSION	Acupuncture led to increases in both QALYs and health service costs; the incremental cost-effectiveness was favorable and below the willingness-to-pay threshold. The estimated improvement in quality of life correlates with the observed reductions in headache severity and frequency.
STUDY LIMITATIONS	• The control group was described as "usual care to avoid acupuncture", but detailed components of such care are not provided; no comparison to more active treatments • Generalizability across settings and health systems and to U.S. are unclear • Limited time horizon (1 year); long term benefits and safety are not clear • The need for continued or periodic treatment over the course of time would likely be required. • Limited sensitivity analyses for economic model inputs • The time horizon is short given the chronic nature of CM, and lack of long-term follow-up data for benefits and harms.

*255 patients (out of 401) form the sample for the base-case analysis; the 255 patients represent the patients who completed the SF-36 on all three occasions.
HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NOS = not otherwise specified; NR = not reported; QALY = Quality Adjusted Life Years; SA = sensitivity analysis; SF-36 = short-form 36; UK = United Kingdom; WTP = willingness to pay.

4.5.3 Chronic Tension-Type Headache and Chronic Daily Headache

No trials performing formal economic analysis evaluating acupuncture in these headache populations that met inclusion criteria were identified.

5 Strength of Evidence (SOE)

The following strength of evidence (SOE) summaries have been based on the highest quality of studies available across the totality of the evidence identified from the prior report and this update report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by time frame and/or comparator. Details of other outcomes are available in the report.

Notes:

- Only primary outcomes were rated for SOE
- Only time frames for which there is evidence are represented in the SOE tables
- Unless otherwise specified, it is unclear from the publication whether the term headache refers specifically to a specific headache type (e.g., migraine) or to any headache.

5.1 Strength of Evidence Summary: Efficacy Results for Chronic Migraine

5.1.1 Strength of Evidence Summary: Efficacy of Acupuncture versus Sham and Active Controls: Chronic Migraine

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Responders: Proportion with ≥50% reduction in *any headache days* from baseline	1–36 wks.	**3 RCTs** Vickers 2004 (UC) Musil 2018 (WL+UC) Yang 2011 (Topiramate)	443	Yes[1] (-1)	Unknown (Short term) No (Long term)	No	Yes[3] (-1) (Short term) No (Long term)	<u>Short-term (1 wk.)</u> **1 RCT, N=66 (vs. topiramate)** RR 4.20 (95% CI 1.80 to 9.80) RD 48% (95% CI 28% to 69%) <u>Long-term (24-36 wks.)</u> **2 RCTs, N=377 (vs. UC/WL)** Pooled RR 2.14 (95% CI 1.56 to 2.95), I^2=0% Pooled RD 29% (95% CI 0% to 58%), I^2=86% <u>Any time point (1-36 wks.) or comparator</u> **3 RCTs, N=443 (vs. topiramate, UC/WL)**	⊕⊕◯◯ LOW (Short term) ⊕⊕⊕◯ MODERATE (Long-term)

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								Pooled RR 2.35 (95% CI 1.70 to 3.24), I^2=11% Pooled RD 35% (95% CI 11% to 59%), I^2=85% Conclusion: More acupuncture participants experienced ≥50% reduction in number of migraine days compared with active controls over the short and long term.	
Responders: Proportion with ≥50% reduction in *moderate/ severe headache days* from baseline	1–36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	Yes[1] (-1)	Unknown	No	Yes[3] (-1) (Short term) No (Long term)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** RR 2.50 (95% CI 1.44 to 4.34) RD 45% (95% CI 24% to 67%) Long-term (36 wks.) **1 RCT, N=301 (vs. UC)** RR 1.48 (95% CI 1.06 to 2.07) RD 13% (95% CI 2% to 23%) Any time point (1-36 wks.) or comparator **2 RCTs, N=367 (vs. topiramate, UC)** Pooled RR 1.83 (95% CI 1.11 to 3.04), I^2=60% Pooled RD 28% (95% CI –4% to 60%), I^2=86% Conclusion: More acupuncture participants experienced ≥50% reduction in number of *moderate or severe* migraine days compared	⊕⊕◯◯ LOW (Short and Long term)

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								with active controls over the short and long term	
Responders: Proportion with ≥50% reduction in *mild headache days* from baseline	36 wks.	**1 RCT** Vickers 2004 (UC)	301	Yes[1] (-1)	Unknown	No	No	RR 1.9 (95% CI 1.3 to 2.9) RD 16.9% (95% CI 7.2% to 26.6%) Conclusion: More acupuncture participants experienced ≥50% reduction in number of *mild* migraine days compared with usual care over the long term	⨁⨁◯◯ LOW
Responders: Proportion with ≥35% improvement in *headache score from baseline**	36 wks.	**1 RCT** Vickers 2004 (UC)	301	Yes[1] (-1)	Unknown	No	No	RR 1.7 (95% CI 1.3 to 2.2) RD 21.9% (95% CI 11.0% to 32.8%) Conclusion: More acupuncture participants experienced ≥35% improvement in headache score from baseline compared with usual care over the long term	⨁⨁◯◯ LOW
Reduction in *any headache days* per month	1–8 wks.	**3 RCTs** Habibabadi 2021 (Sham+UC) Naderinabi 2017 (Sodium valproate; Botulinum toxin A) Yang 2011 (Topiramate)	296	Yes[1] (-1)	Yes[2] (-1)	No	No†	Pooled MD –2.80 (95% CI –4.19 to –1.42), I^2=44% Conclusion: Acupuncture was associated with a greater reduction in mean headache days compared with sham/UC and with active controls (topiramate, sodium valproate, and Botulinum toxin A) at short term.	⨁⨁◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	12–36 wks.	**3 RCTs** Vickers 2004 (UC) Musil 2018 (WL+UC) Naderinabi 2017 (Sodium valproate; Botulinum toxin A)	527	Yes[1] (-1)	No	No	No†	Pooled MD –3.54 (95% CI –5.15 to –1.94), I^2=30% Conclusion: Acupuncture was associated with a greater reduction in mean headache days compared with active controls (WL/UC, sodium valproate, and Botulinum toxin A) at long term.	⨁⨁⨁◯ MODERATE
Reduction in *moderate/ severe headache days* per month	1–36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	Yes[1] (-1)	Unknown	No	Yes[3] (-1) (Short term) No (Long term)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** MD –2.30 (95% CI –3.68 to –0.92) Long-term (36 wks.) **1 RCT, N=301 (vs. UC)** MD –1.50 (95% CI –2.69 to –0.31) Any time point (1-36 wks.) or comparator **2 RCTs, N=367 (vs. topiramate, UC)** Pooled MD –1.84 (95% CI –2.74 to –0.94), I^2=0% Conclusion: Acupuncture was associated with a greater reduction in mean headache days of *moderate or severe intensity*	⨁⨁◯◯ LOW (Short and Long term)

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								compared with active controls at short and long term.	
Reduction in *mild headache days* per month (adjusted for baseline)	36 wks.	**1 RCT** Vickers 2004 (UC)	301	Yes[1] (-1)	Unknown	No	No	MD –1.6 (95% CI –2.6 to –0.5) Conclusion: Greater reduction in mild headache days with acupuncture vs. usual care long term.	⊕⊕◯◯ LOW
Reduction in *headache episodes/attacks* per month	4 wks.	**1 RCT** Habibabadi 2021 (Sham+UC)	80	Yes[1] (-2)‡	Unknown	No	Yes[3] (-1)	MD –6.12 (95% CI –9.91 to –2.33) Conclusion: Greater reduction in headache episodes/attacks with acupuncture vs. sham/UC short term.	⊕◯◯◯ INSUFFICIENT
	24 wks.	**1 RCT** Musil 2018 (WL+UC)	76	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD –0.90 (95% CI –2.05 to 0.25) Conclusion: No difference between groups (acupuncture and WL/UC) in headache episodes/attacks long term.	⊕⊕◯◯ LOW
Migraine Disability Assessment (MIDAS)§	1–24 wks.	**2 RCTs** Musil 2018 (WL+UC) Yang 2011 (Topiramate)	124	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Short-term (1 wk.) **1 RCT, N=66 (vs. topiramate)** MD –12.00 (95% CI –17.58 to –6.42) Long-term (24 wks.) **1 RCT, N=58 (vs. UC+WL)** MD –13.60 (95% CI –32.01 to 4.81) Any time point (1-24 wks.) or comparator **2 RCTs, N=124 (vs. topiramate, UC+WL)**	⊕⊕◯◯ LOW (Short and Long term)

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								Pooled MD –12.13 (95% CI –17.47 to –6.80), I^2=0% Conclusion: Greater reduction in mean MIDAS scores, suggesting improved function, was seen in the acupuncture group compared to active controls over the short, but not the long, term; this may be a clinically important difference.	

CI = confidence interval; MD = mean difference; MIDAS = Migraine Disability Assessment; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; UC = usual care; wks. = weeks; WL = waitlist.

*Defined as the summed total of headache severity recorded 4x/day on a 6-point Likert scale; this was the study protocol definition of responder

†It is unclear what constitutes a clinically meaningful difference in headache days or what would be consider a mild to substantial improvement; this estimate could be considered imprecise if the confidence interval ranged from mild to substantial.

‡This trial appeared to exclude patients who experienced certain adverse event/side effects and it is unclear what impact that loss-to-follow-up may have had on efficacy outcomes.

§The MIDAS assesses how severely migraines affect a patient's life and includes questions about the frequency and duration of headaches, as well as how often these headaches limit the patient's ability to participate in activities at work, at school, or at home.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.2 Strength of Evidence Summary: Efficacy Results for Chronic Tension-type Headache

5.2.1 Strength of Evidence Summary: Efficacy of Acupuncture versus Sham: Chronic Tension-type Headache

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Responders Proportion with >33% and >50% improvement from baseline on the HI*	4 wks.	1 RCT (Tavola 1992)	30	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	<u>>33% improvement on the HI</u> RR 1.4 (95% CI 0.9, 3.2) <u>>50% improvement on the HI</u> RR 1.1 (95% CI 0.6, 2.3) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	52 wks.			Yes[1] (-1)	Unknown	No	Yes[3] (-1)	<u>>33% improvement on the HI</u> RR 1.1 (95% CI 0.6, 2.3) <u>>50% improvement on the HI</u> RR 1.5 (95% CI 0.5, 4.3) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Reduction in headache *<u>episodes</u>* per month	4-6 wks.	2 RCTs (Tavola 1992, Karst 2000)	69	Yes[1] (-1)	Yes[2] (-1)	No	Yes[3] (-1)	Pooled MD –1.94 (95% CI –6.74, 2.85, I^2= 61%) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions. No difference between acupuncture and sham acupuncture in reduction of headache episode per month.	⊕◯◯◯ INSUFFICIENT
	26-52 wks.	1 RCT (Tavola 1992)	30	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Authors state that the frequency of headache episodes continued to decrease through 26 and 52 weeks post-treatment with no statistical	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								differences between groups; no data provided. <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	

CI = confidence interval; MD = mean difference; HI = Headache index; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; wks. = weeks.
*Authors definition: headache index = intensity (sum of the intensity of the crises in a month/number of crises) X duration (sum of the hours of headache in a month/number of crises) X frequency (the number of crises in a month)/30.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.2.2 Strength of Evidence Summary: Efficacy of Acupuncture versus Active Controls: Chronic Tension-type Headache

Outcome	Follow-up	RCTs	N	Serious Risk of Bias*	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Tension Type Headache: Acupuncture vs. Physical Training/Exercise									
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	Yes[1] (-2)	Unknown	No	Yes[3] (-1)	<u>12 weeks</u>: mean 6.25 and median 0.25 (range, 0.00–28.00) (n=30) versus mean 7.46 and median 5.00 (range, 0.00–28.00) (n=30); p=NS <u>26 weeks</u>: mean 7.58 and median 0 (range, 0.00–28.00) (n=30) versus	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias*	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								mean 9.37 and median 9.38 (range, 0.00–28.00) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	
Headache-free *days* per week				Yes[1] (-2)	Unknown	No	Yes[3] (-1)	12 weeks: mean 1.18 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.23 and median 0.50 (range, 0.00–7.00) (n=30); p=NS 26 weeks: mean 1.56 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.66 and median 1.00 (range, 0.00–7.00) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Chronic Tension Type Headache: Acupuncture vs. Physiotherapy									
Reduction in headache episodes†	4-9 wks.	1 RCT (Carlsson 1990)	62	Yes[1] (-2)	Unknown	No	Yes[3] (-2)	Authors state headache frequency was significantly (<0.001) reduced in both groups 4 to 9 weeks after treatment; however, no data were provided and no information regarding the between group difference was provided. Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias*	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Sickness Impact Profile (SIP)				Yes[1] (-2)	Unknown	No	Yes[3] (-2)	Authors state that the acupuncture group improved significantly ($p<0.05$) more than the physiotherapy group in the SIP category Sleep and Rest but significantly less with respect to the psychosocial categories Emotional Behavior, Work, Eating, and Recreation and Pastimes; overall SIP score and the Psychosocial dimension were improved in both groups but between group differences are unclear. No data was provided to support these statements. Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Chronic Tension Type Headache: Acupuncture vs. Relaxation Training									
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	Yes[1] (-2)	Unknown	No	Yes[3] (-1)	12 weeks: mean 6.25 and median 0.25 (range, 0.00–28.00) (n=30) versus mean 7.67 and median 2.0 (range, 0.00–29.00) (n=30); p=NS 26 weeks: mean 7.58 and median 0 (range, 0.00–28.00) (n=30) versus mean 8.29 and median 2.0 (range, 0.00–29.00) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias*	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Headache-free *days* per week				Yes[1] (-2)	Unknown	No	Yes[3] (-1)	12 weeks: mean 1.18 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.58 and median 0.13 (range, 0.00–7.25) (n=30); p=NS 26 weeks: mean 1.56 and median 0 (range, 0.00–7.00) (n=30) versus mean 1.73 and median 0.13 (range, 0.00–7.25) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	⨁◯◯◯ INSUFFICIENT

NS = not statistically significant; RCT = randomized controlled trial; SIP = Sickness Impact Profile; wks. = weeks.
*Though both RCTs were rated as moderately high risk of bias, they each suffered from a variety of methodological limitations that makes them at higher risk of bias compared with other RCTs.
†Headache frequency was measured on a 1 to 5 scale: almost never, once or twice a month, once a week, several times a week, and daily.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.3 Strength of Evidence Summary: Safety Results for Chronic Migraine

5.3.1 Strength of Evidence Summary: Safety of Acupuncture versus Sham and Active Controls: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Serious adverse events	1 to 36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	No serious adverse events occurred in any group (acupuncture, topiramate, UC); data and information not provided. Conclusion: Without knowing what constitutes a serious adverse event and the rarity of such events, it is unknown whether there was sufficient sample size to detect such events; firm conclusions are difficult.	⊕◯◯◯ INSUFFICIENT
Discontinuation due to adverse events	1 to 36 wks.	**2 RCTs** Vickers 2004 (UC) Yang 2011 (Topiramate)	367	Yes[1] (-1)	No	No	Yes[3] (-1)	**Acupuncture vs. UC (1 RCT):** 0.6% (1/161) vs. 0% (0/140) **Acupuncture vs. Topiramate (1 RCT):** 0% (0/33) vs. 9.1% (3/33) Conclusion: Although no statistical difference between groups in either trial, it is unclear whether there was sufficient sample size to detect a statistical difference.	⊕⊕◯◯ LOW
Death	1 wk.	**1 RCT** Yang 2011 (Topiramate)	66	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	No deaths occurred in either group (acupuncture vs. topiramate). Conclusion: Small sample size and short follow-up makes the detection of rare events difficult; insufficient evidence preclude firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Any side effect (minor, self-limiting)	1 to 12 wks.	**2 RCTs** Yang 2011 (Topiramate) Naderinabi 2017 (Sodium valproate; Botulinum toxin A)	216	Yes[1] (-1)	No	No	Yes[3] (-1)	**Acupuncture vs. Topiramate (1 RCT):** RR 0.09 (95% CI 0.02, 0.36) • Acupuncture: 6% (2/33); all due to local insertion of needles (pain, paresthesia, ecchymosis) • Topiramate: 66% (22/33); most common included paresthesia (48%), difficulty with memory (36%), dyspepsia (36%), fatigue (24%), dizziness (21%), somnolence (18%), and nausea (12%) **Acupuncture vs. Botulinum toxin (1 RCT):** RR 0.27 (95% CI 0.08, 0.92) • Acupuncture: 6% (3/50); bleeding or subcutaneous hematoma • Botulinum Toxin A: 22% (11/50); ptosis, facial masking or asymmetry **Acupuncture vs. Sodium Valproate (1 RCT):** • Acupuncture: 6% (3/50); bleeding or subcutaneous hematoma • Sodium Valproate: frequency of any non-serious AEs NR but authors list a variety of side effects that occurred (i.e., anorexia, weight gain, tremor, somnolence, insomnia, alopecia) and ranged from 4% to 18% of patients.	⊕⊕◯◯ LOW

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								Conclusion: Statistically fewer side-effects occurred following acupuncture versus topiramate and versus Botulinum toxin A. For sodium valproate, though not a direct comparison, it can be inferred that acupuncture had fewer side effects than sodium valproate with the data provided.	
Hematoma, facial hematoma	4 to 12 wks.	**2 RCTs** Habibabadi 2021 (Sham+UC) Musil 2018 acupuncture group only (WL+UC)	159	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	**Acupuncture vs. sham/UC, 1 RCT:** • No cases of hematoma in either group; however, authors state that patients were excluded from the study if they developed redness or infection at the site of the needle implant **Acupuncture vs. WL/UC, 1 RCT:** • One case of facial hematoma in acupuncture group: 1.3% (1/79) • NR in WL/UC group Conclusion: The evidence is insufficient to draw conclusions regarding the risk of hematoma following acupuncture. Methodological concerns in one trial [Habibabadi 2021] regarding the exclusion of patients due to side effects further limit our confidence in the results.	⊕◯◯◯ INSUFFICIENT
Headache	Unclear	**1 RCT** Vickers 2004	301	Yes[1] (-1)	Unknown	No	No	2.5% (4/161) [5 cases] vs. 0% (0/140)	⊕⊕◯◯ LOW

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		(UC)						Conclusion: No statistical difference between groups; it is unclear whether sample size played a role.	
Ear swelling, Ear pain, Erythema Ear infection	4 wks.	**1 RCT** Habibabadi 2021 (Sham+UC)	80	Yes[1] (-2)	Unknown	No	Yes[3] (-1)	No events occurred in the sham/UC group. In the auricular acupuncture group, the frequency of **ear swelling** ranged from 3% (1/40) to 10% (4/40) and **ear pain** from 5% (4/240) to 18% (7/40) across 1-, 2-, 3-, and 4-week follow-ups. No cases or **erythema or ear infection** were reported, *however, authors state that patients were excluded from the study if they developed redness or infection at the site of the needle implant* Conclusion: Ear swelling, ear pain and erythema are common, likely expected, AEs following auricular acupuncture; however, the evidence is considered insufficient to draw conclusions. Methodological concerns regarding the exclusion of patients due to side effects further limit our confidence in the results.	⨁◯◯◯ INSUFFICIENT

CI = confidence interval; MD = mean difference; MIDAS = Migraine Disability Assessment; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; UC = usual care; wks. = weeks; WL = waitlist.

*Neither study provided information on what constituted a serious adverse event or adverse events that caused discontinuation.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.4 Strength of Evidence Summary: Safety Results for Chronic Tension-type Headache

5.4.1 Strength of Evidence Summary: Safety of Acupuncture versus Active Control: Chronic Tension-type Headache

Outcome	Follow-up	RCTs	N	Serious Risk of Bias*	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Outcome
Chronic Tension Type Headache: Acupuncture vs. Physiotherapy									
Vasovagal reaction	4-9 wks.	1 RCT (Carlsson 1990)	62	Yes[1] (-2)	Unknown	No	Yes[3] (-2)	Authors state that a few patients in the acupuncture group had a slight vasovagal reaction; no other complications were noted. Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

RCT = randomized controlled trial; wks. = weeks.

*Though rated as moderately high risk of bias, this trial suffered from a variety of methodological limitations that makes it at higher risk of bias compared with other RCTs.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice.
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.5 Strength of Evidence Summary: Differential Efficacy and Safety for Chronic Migraine

Exposure	Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HTE-related	Conclusion	Quality
Chronic Migraine: Acupuncture versus Usual Care											
Baseline headache score; Headache type/diagnosis; **Age;** **Sex;** **Chronicity**	Headache score	36 wks.	1 RCT (Vickers 2004)	301	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Yes (-2)[5, 7]	Baseline headache score modified the treatment effect such that those with more severe symptoms at baseline showed significantly greater improvement with acupuncture vs. usual care (interaction p=0.004). Type of headache (chronic migraine or CTTH) did not modify treatment effect (no interaction); the small number of CTTH patients likely precluded detection of effect. Age, sex, and chronicity did not modify the treatment effect.	⊕○○○ INSUFFICIENT
Chronic Migraine: Acupuncture versus Topiramate											
Baseline headache days; **multiple other demographic**	≥50% reduction from baseline in	36 wks.	1 RCT (Yang 2013)	66	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Yes (-2)[5, 7]	Baseline headache days (overall and moderate/severe at baseline) may modify	⊕○○○ INSUFFICIENT

Exposure	Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HTE-related	Conclusion	Quality
and headache characteristics	moderate/ severe headache days									treatment effect; patients with higher (≥20 days/mo.) versus lower (<20 days/mo.) frequency showed greater improvement with acupuncture but not with topiramate overall (interaction p=0.002) and in those with moderate/severe headache days at baseline (interaction p=0.007).* Other variables explored did not modify the treatment effect (see full report)	

CTTH = chronic tension-type headache; HTE = heterogeneity of treatment effect

*Interaction was examined by logistic regression; the dichotomized outcome i.e., dependent variable was whether or not the reduced moderate/severe headache days was ≥50% of the baseline level.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate: wide (or unknown) confidence interval and/or small sample size
4. Indirect, intermediate or surrogate outcomes may be downgraded.

The following apply specifically to heterogeneity of treatment effect (HTE):

5. Subgroup analysis not preplanned (and/or no hypothesis), not considered in sample size calculation or unknown
6. Statistical test for homogeneity or interaction not performed
7. Multiple comparisons made

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