Washington State Health Care Authority

Treatment of chronic migraine and chronic tension-type headache

Final evidence report

April 14, 2017

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

Treatment of Chronic Migraine and Chronic Tension-Type Headache

Provided by:

Spectrum Research, Inc.

Prepared by:

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

April 14, 2017

With assistance from:
Krystle Pagarigan, BS
Mark Junge, BS

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.

TABLE OF CONTENTS

TABLES

FIGURES

Abbreviations

AE:	adverse event
BoNTA:	OnabotulinumtoxinA
CI:	confidence interval
CM:	chronic migraine
CTTH:	chronic tension-type headache
HA:	headache
F/U:	follow-up
HI:	Headache Index
HIT-6	Headache Impact Test 6 dimensions
HR:	hazards ratio
HR-QoL:	Health-Related Quality of Life
IQR:	inter-quartile range
LA:	local anesthetic
MD:	mean difference
MIDAS:	Migraine Disability Assessment
MIQ:	Migraine Impact Questionnaire
MSQ:	Migraine Specific Quality of Life Questionnaire
NC:	not calculable
NR:	not reported
NRS:	Numerical Rating Scale
NS:	not statistically significant
NSAID:	nonsteroidal anti-inflammatory drug
PREEMPT	Phase III REsearch Evaluating Migraine Prophylaxis Therapy
QoL:	quality of life
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
SMT:	spinal manipulation therapy
TMS:	transcranial magnetic stimulation
VAS:	Visual Analog Scale
WMD:	weighted mean difference

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. 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 both migraine and tension-type headache 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 chronic migraine and chronic tension-type headache. Interventions to be evaluated in this report include botulinum toxin injections, trigger point injections, transcranial magnetic stimulations, manipulation/manual therapy, acupuncture and massage. This report will focus on use of such interventions for the prevention of CTTH and CM

OnabotulinumtoxinA (onaBoNT-A, Botox) is a type of botulinum toxin that is FDA approved for the prophylaxis of with chronic migraine (≥ 15 days per months with headache lasting ≥4 hours a day) in adults.

Trigger point injections involve injection of local anesthetic or other injectate into trigger points which are muscle areas that are very irritable, show a band of tightness in the area of muscle itself, and, when pressed, produce a twitch within the affected muscle. Trigger point injections may be done in conjunction with peripheral nerve blocks which involves injection of medication on or near nerves. Peripheral nerve blocks are not included in this review.

Transcranial magnetic stimulation involves use of a portable device that is held to the scalp and sends a series of brief magnetic pulses through the skin. The FDA has approved three devices for treatment of pain associated with migraine with aura, which are the Cerena TMS device, the Spring TMS device, and the eNeura sTMS mini device.

Manual therapies, including manipulation, involve passive movement of joints and soft tissues by hands or equipment to treat musculoskeletal and disability including headache and may be used by physiotherapists, chiropractors, osteopathic physicians and others. Massage is often classified as a manual therapy and involves systematic and methodical manipulation of body tissues, including trigger points, usually with the hands.

Acupuncture involves the insertion of solid, filiform needles into the body (with or without manual or electrical stimulation) to directly or indirectly stimulates acupuncture points, including trigger points, and other tissues to promote health and treat organic or functional disorders.

Policy Context

Interventions for treatment of headaches include botulinum toxin injections, trigger point injections or dry needling, transcranial magnetic stimulations, acupuncture, manipulation, manual therapy and massage. The topic was proposed to determine the safety, efficacy and value of interventions for treatment of migraines and other headache types. The topic was selected based on medium/high concerns for safety, efficacy and cost.

Objectives

The primary aim of this assessment is to systematically review and synthesis published evidence on the efficacy, safety, and cost-effectiveness of botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults.

Key Questions

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 botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

2. What is the evidence regarding short- and long-term harms and complications of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

3. Is there evidence of differential efficacy, effectiveness, or safety of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo sham, waitlist or no treatment? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation.

4. What is the evidence of cost-effectiveness of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

Inclusion and exclusion criteria are summarized as follows and are detailed in the full report. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with chronic migraine (with or without aura) or chronic tension-type headache or co-existent chronic migraine and tension-type headache. While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions. 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.
- **Interventions:** Botulinum toxin injection, acupuncture, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), trigger point injection (TPI) or dry needling
- **Comparators:** Usual (standard) treatment(s), sham, placebo, waitlist or no treatment
- **Outcomes:** Primary/critical outcomes are 1) the proportion of treatment responders, 2) cessation/prevention of headache (including reduction in mean number of episodes and/or headache days), 3) function/disability (based on validated outcomes measures), 4) treatment related adverse events/harms, 5) quality of life. 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.

- **Studies:** Studies must report at least one of the primary outcomes. Focus will be on studies with the least potential for bias such as high quality systematic reviews of randomized controlled trials and randomized controlled trials and full economic studies.
- **Timing:** Focus will be on intermediate (>6 months) and long term (> 12months) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Methods

The scope of this report and final key questions were refined based on input from clinical experts and public comments received on draft key questions. Clinical expert input was sought to confirm critical outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. 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.

Pertinent studies were critically appraised independently by two reviewers evaluating the methodological quality and potential for bias based on study design as well as factors which may bias studies. 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 for was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[1,14] The strength of evidence was based on the highest quality evidence available for a given outcome. 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 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. There are also situations where the studies could be upgraded if the study had large magnitude of effect (strength of association). 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 no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

We summarized evidence separately for chronic migraine, chronic tension-type headache, and chronic daily headache (co-existent chronic migraine and tension-type headache). The interventions of interest were reported in the following order for each headache indication: botox, acupuncture, manual therapies/manipulation, massage, transcranial magnetic stimulation (TMS), and trigger-point injections (TPI) or dry needling.

We conducted meta-analyses when there were two or more studies with similar indications, interventions, control groups and outcomes. We grouped control treatments according to whether the control was a placebo/sham treatment or an active comparator (e.g., pharmacological treatment, physical therapy). 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.

Results

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

Overall, 27 randomized trials (in 32 publications) that reported efficacy and safety outcomes the efficacy and safety outcomes were included. The selection of the studies is summarized in the Table below. The comparisons evaluated and their respective studies are listed below; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. An additional three economic studies were included.

Comparisons	Studies
CHRONIC MIGRAINE	
OnabotulinumtoxinA vs. Placebo	4 RCTs (8 publications)[2-4,10-12,18,36]
OnabotulinumtoxinA vs. Amitriptyline	1 RCT[19]
OnabotulinumtoxinA vs. Topiramate	1 RCT[21]
Acupuncture vs. Usual Care	1 RCT[34]
Acupuncture vs. Topiramate	1 RCT[38]
Spinal Manipulation Therapy vs. Amitriptyline	1 RCT[23]
Transcranial Magnetic Stimulation vs. Sham	2 RCTs[22,33]
CHRONIC TENSION-TYPE HEADACHE	
OnabotulinumtoxinA vs. Placebo	5 RCTs[13,17,25,27,28]
Acupuncture vs. Sham	2 RCT[16,32]
Acupuncture vs. Physical Training*	1 RCT (2 publications)[30,31]

Comparisons	Studies
Acupuncture vs. Physiotherapy	1 RCT[7]
Acupuncture vs. Relaxation Training*	1 RCT (2 publications)[30,31]
Manual Therapy vs. Usual Care	1 RCT[8]
Trigger Point Injection vs. Placebo	1 RCT[15]
CHRONIC DAILY HEADACHE	
OnabotulinumtoxinA vs. Placebo	3 RCTs[20,24,29]
OnabotulinumtoxinA vs. Topiramate	1 RCT[6]
Massage vs. Sham	1 RCT[9]

*This study (Soderberg 2006, 2011) had 3 arms: an acupuncture, a physical training, and a relaxation training group.

KQ1 Summary of Results:

General findings for each headache type for the primary outcomes are briefly summarized by treatment and comparator below. The strength of evidence tables that follow provide information on effect sizes, general conclusions and additional information for the primary outcomes. Detailed findings, including results for secondary outcomes are found in the full report. We report following primary outcomes here:

- The proportion of treatment responders is a primary outcome of interest; it was variable defined across trials.
- Reduction in mean frequency of headache was the most common outcome reported. This may include frequency of attacks/episodes, overall headache days or headache days for a specific headache type (e.g. migraine days)
- Function as measured by validated measures

For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Most trials were at moderately high risk of bias; assessment details are provided in the full report.

Across studies, headache types and comparators, the majority of patients were female, with a mean age in most trials of 40 to 45 years old. In general a large proportion of study participants reported previous use of prophylactic medications and a few trials permitted concurrent use of them. Overuse of medications was variably defined and variably reported across trials; some trials excluding 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 employed placebo or 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 alternative treatments. Few trials compared interventions to active alternative treatments that might be used to treat headache conditions.

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. As a consequence, the terminology used in clinical studies has also varied. For the purposes of this 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 (CDH), which is generally consistent with the terminology used by authors.
With regard to the overall quality of retained studies (for KQ 1-3), only the PREEMPT 1 and 2 trials comparing BoNTA and placebo and one trial evaluating massage were considered to be at low risk of bias (good quality RCTs). The majority of trials (n= 15) were considered to be at moderately high risk of bias (poor quality RCTs); nine were considered to be at moderately low risk of bias (moderate quality RCTs). Detailed descriptions of study quality are provided in the report for each headache type and comparator set and in Appendix E.

The overall strength of evidence for most efficacy outcomes was considered low across interventions and comparators. Efficacy outcomes for which there was moderate quality evidence (whether positive or negative result) were confined to the comparator of BoNTA with placebo and based largely on the PREEMPT 1 and 2 trials. The strength of evidence tables below and more detailed strength of evidence evaluation in Section 5 of the report provide additional information.

Chronic Migraine

BoNTA versus Placebo

Two large Phase III trials and one small trial reported on the primary outcomes of interest.

No studies reported outcome of interest in the short term (≤8 weeks) or intermediate term (>8 to 12 weeks).

In the longer-term (>12 weeks), findings include the following:

- At 24 weeks, across 2 large RCTs, a ≥ 50 % reduction in number of *migraine days* and overall number of *headache days* per month was achieved by more BoNTA recipients compared with placebo (RD 12%, moderate evidence).
- With regard to mean headache days (3 trials) and migraine days (2 trials) per month a small difference between groups (<2 days) favoring BoNTA was observed through 24 weeks (moderate evidence for all outcomes)
- When migraine episodes and headache episodes were considered, there was not a difference between groups in the percent of patients who achieved ≥ 50 % reduction in the number of *migraine episodes* per month across 2 large trials or in one small trial over 4 months (moderate evidence). Similarly, there were no statistically significant differences in the reduction of mean number of *headache episodes* or *migraine episodes* per month through 24 weeks (3 trials). (moderate evidence for all outcomes)
- At 24 weeks BoNTA was associated with improved function based in Headache Impact Test-6 Scores and significantly fewer BoNTA recipients had severe HIT-6 scores compared with placebo across two trials (moderate evidence for both outcomes). One small trial reported greater

reduction in Migraine Disability Assessment Scale (MIDAS) scores following BoNTA versus placebo, suggesting better function by 16 weeks, but the result was not statistically significant (insufficient evidence), in part due to inadequate sample size.

- Over 60% of participants in the two largest trials reported medication overuse at baseline; the other small trial excluded those with medication overuse

BoNTA versus Active Control

- BoNTA versus Topiramate: one small RCT provided data on primary outcomes
  - No data on short- or intermediate-term outcomes were available
  - Longer-term outcomes were as follows:
  - At 12, 24, and 36 weeks,more BoNTA recipients achieved ≥ 50% reduction overall number of *headache days* compared with placebo, however the differences did not reach statistical significance in one small RCT. Differential attrition between treatment groups and substantial loss to follow-up may be contributing factors. Data available for the BoNTA and topiramate groups respectively: 80% versus 70% at 12 weeks, 70% versus 60% at 24 weeks and 63% versus 57% at 36 weeks.(low level of evidence at 12 weeks, insufficient at 24 and 36 weeks).
  - There were no differences at any time points up for the functional measures reported including MIDAS, HIT-6 and MIQ (low level of evidence at 12 weeks, insufficient at 24 and 36 weeks).
- BoNTA versus Amitriptyline: one small RCT provided data on primary outcomes
  - No data on short- or intermediate term outcomes were available
  - At long-term follow-up (12 weeks), there were no differences between groups with regard to the percent of patients with ≥ 50% reduction in the frequency of pain days or the percent of patients with ≥3 point reduction in pain intensity in one small RCT (low evidence for both outcomes)

Acupuncture versus Sham

- No trials were identified that met the inclusion criteria.

Acupuncture versus Active Control

- Acupuncture versus Usual Care: one RCT provided data on primary outcomes
  - No data on short- or intermediate term outcomes were available.
  - In the longer term (36 weeks), acupuncture resulted in a statistically greater improvement in all outcomes measured compared with usual care: proportion of patients achieving ≥50%

reduction in any, mild, and moderate/severe headache days; proportion of patients achieving ≥35% reduction in headache days; mean reduction from baseline in any, mild or moderate/severe headache days per month (low quality evidence for all outcomes).

- Acupuncture versus Topiramate: one small RCT provided data on primary outcomes
    - In the short-term (4 weeks), acupuncture resulted in a statistically greater improvement in all outcomes measured compared with topiramate (low quality evidence for all): proportion of patients achieving ≥50% reduction headache days (any and moderate/severe); and mean reduction from baseline in headache days (any and moderate/severe) per month and in the Migraine Disability Assessment (MIDAS); for the latter outcome, it is unclear if the difference is clinically meaningful.
    - No data on intermediate- or long-term outcomes were available

Spinal Manipulation Therapy versus Sham

- No trials were identified that met the inclusion criteria.

Spinal Manipulation Therapy versus Active Control

- Spinal Manipulation Therapy versus Amitriptyline: one small RCT provided data on primary outcomes
    - In the short-term (4 weeks), SMT resulted in a statistically greater proportion of patients achieving >20% and >40%, but not >60%, reduction in Headache Index scores from baseline compared with amitriptyline. There was no statistical difference between groups in the mean reduction in the percentage of days per month with headache. The strength of evidence was low for all outcomes.
    - No data on intermediate- or long-term outcomes were available.

Massage versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham

Two small RCTs provided data on primary outcomes over the short-term only for this comparison:

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

- At 8 weeks in a second RCT, no statistical differences were seen between low-frequency TMS and sham for reduction in migraine attacks and reduction in migraine days during the 8 weeks period following treatment; however, all data is of insufficient quality to draw conclusions.
- No data on intermediate- or long-term outcomes were available.

Transcranial Magnetic Stimulation versus Active Control

- No trials were identified that met the inclusion criteria.

Trigger Point Injection versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Chronic Tension-type Headache

BoNTA versus Placebo

Although five trials met the inclusion criteria, reporting on primary outcomes was limited. All but one trial enrolled 60 or fewer patients.

- Short-term outcomes are as follows:
  - Although more patients the BoNTA experienced ≥ 25% reduction in pain intensity at 8 weeks, results did not reach statistical significance in one small RCT (insufficient evidence).
  - At 4 weeks in one small trial, BoNTA was associated with significantly lower Headache Disability Index scores indicating improved function compared with placebo (insufficient evidence).
- Longer-term outcomes are as follows:
  - At 12 weeks), although more patients the BoNTA experienced ≥ 45% reduction in pain intensity, results did not reach statistical significance in one small RCT (insufficient evidence).
  - Across two RCTs, BoNTA was associated with a reduction in the mean number of headache days per month at 12 weeks (insufficient evidence).
  - In one small RCT, BoNTA was associated with significantly lower Headache Disability Index scores at 12 weeks indicating improved function compared with placebo (insufficient evidence).
- No data on intermediate-term outcomes were available.

BoNTA versus Active Control

- No studies were identified that met the inclusion criteria.

Acupuncture versus Sham

Two small RCTs provided data on primary outcomes for this comparison:

- In the short-term, no statistical differences were seen between the acupuncture and the sham group in the proportion of patients achieving >33% and >50% improvement from baseline on the Headache Index (HI) in one small trial with 4 weeks of follow-up, or in the pooled mean reduction in headache episodes per month across two small trials at 4-6 weeks follow-up (insufficient evidence for all outcomes).
- In the longer term, as reported by one small trial, no statistical differences were seen between groups in the proportion of patients achieving >33% and >50% improvement from baseline on the Headache Index at 52 weeks, or in the mean reduction in headache episodes per month at 26 and 52 weeks (insufficient evidence for all).
- No data for the intermediate-term was available.

Acupuncture versus Active Control

- Acupuncture vs. Physical Training/Exercise and vs. Relaxation Training: one small RCT provided data on primary outcomes for this comparison
    - No data for the short- or intermediate-term were available.
    - In the longer-term (12 and 26 weeks), no statistical differences were seen between the acupuncture and the physical training/exercise group or the relaxation training group in the number of headache-free periods and headache-free days per week (insufficient evidence for all outcomes and comparisons).
- Acupuncture vs. Physiotherapy: one small RCT provided data on primary outcomes for this comparison
    - Over the short- and intermediate term (4-9 weeks), the authors provide insufficient data to assess comparative efficacy for the reduction in number of headache episodes and overall Sickness Impact Profile (SIP) score. The authors state that the acupuncture group improved significantly 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; no data was provided to support these statements. All evidence is insufficient for this trial.
    - No data over the longer-term were available.

Manual Therapy/Manipulation versus Sham

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Usual Care

One small RCT provided data on primary outcomes for this comparison:

- No data for the short- or intermediate-term were available.
- At long-term follow-up (18 weeks) in one small trial, statistically greater improvements in all outcomes reported were seen in patients who received manual therapy compared with usual care: proportion with >50% reduction in headache days per 2 weeks, mean reduction in number of headache days per 2 weeks, the Headache Impact Test (HIT-6), and the Headache Disability Inventory (HDI); the difference between groups on the HIT-6, but not on the HDI, was clinically meaningful (low strength of evidence).

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria for either comparison.

Trigger Point Injections versus Sham

One small RCT provided data on primary outcomes for this comparison:

- At long-term follow-up (12 weeks) in one small trial, a statistically greater reduction in the number of headache days per month was seen following trigger point injections compared with sham; however the strength of evidence is insufficient.

Trigger Point Injections versus Active Control

- No studies were identified that met the inclusion criteria.

Chronic Daily Headache/Co-existent Chronic Migraine and Tension-type Headache

BoNTA vs. Placebo

Three RCTs provided limited data on primary efficacy outcomes.

- No data on short- or intermediate term outcomes were available.
- At long-term follow-up (24 weeks) in one RCT, there is low evidence that more BoNTA recipients had a ≥50% reduction frequency of headache days compared with placebo (low evidence)

- There was no statistically significant difference across two RCTS in the change in mean number of headache-free days over the long-term (24 weeks) (low evidence); while one of these trials reported a statistical difference, it didn't meet their criteria for clinical significance.

BoNTA vs. Active Control (Topiramate):

One small RCT provided limited data on primary outcomes.

- At short- (4 weeks) and long-term (12 weeks) follow-up in one small RCT, there was no difference between BoNTA and topiramate in the reduction of mean headache days per month (low evidence).
- At long-term follow-up (12 weeks) there no differences between groups with regard to function or disability based on HIT-6 or MIDAS scores in the same RCT (low evidence).
- No data on intermediate-term outcomes were available.

Acupuncture vs. Sham and vs. Active Control

- No trials were identified that met the inclusion criteria.

Manual Therapy/Manipulation vs. Sham and vs. Active Control

- No trials were identified that met the inclusion criteria.

Massage vs. Sham

One small RCT provided data on primary outcomes for this comparison.

- Over both the short- (3 weeks) and intermediate-term (9 weeks) in one small RCT, no statistical differences were seen between the massage and sham groups in the reduction in headache attacks per month and Headache Disability Index (low strength of evidence).
- No data on longer term outcomes were available

Massage vs. Active Control

- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation vs. Sham and vs. Active Control

- No trials were identified that met the inclusion criteria.

Trigger Point Injection vs. Sham and vs. Active Control

- No trials were identified that met the inclusion criteria.

KQ2: Summary of Results

All included comparative studies were evaluated for harms and complications. The overall strength of evidence for most efficacy outcomes was considered low or insufficient across interventions and comparators with the exception of treatment-related adverse events and serious adverse events following BoNTA compared with placebo which are primarily based on two large RCTs at low risk of bias.

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 strength of evidence determination for each outcome.

Chronic Migraine

BoNTA versus. Placebo

Two large Phase III trials provide the primary evidence regarding safety for this comparison.

- At long-term follow-up (24 weeks), across two RCTs, treatment-related and serious adverse events were 2 times more common following BoNTA compared with placebo (moderate evidence) and discontinuation of treatment due to treatment related adverse events was three times more common following BoNTA (low evidence). All results were statistically significant.
- Over the longer-term (24 weeks), treatment-related serious adverse events were rare; there was likely insufficient power to detect such events precluding firm conclusions (insufficient evidence).
- No deaths occurred in any of the trials

BoNTA versus Active Control

- BoNTA versus Topiramate (1 RCT):
  - At 36 weeks, although the result was not statistically significant, fewer BoNTA patients experienced drug-related adverse events compared with topiramate recipients and fewer BoNTA patients discontinued treatment, however sample size was small; Differential attrition between treatment groups and substantial loss to follow-up should be also considered when interpreting this finding. Data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks. (low evidence)
- BoNTA versus Amytriptyline (1 RCT):
  - Limited data were reported for adverse events over the long-term (12 weeks) in one small trial. More BoNTA recipients reported injection site pain and edema compared with amitriptyline; no one in the amitriptyline group experienced these effects (low evidence)

Acupuncture versus Sham

- No trials were identified that met the inclusion criteria.

Acupuncture versus Active Control

- Acupuncture versus Usual Care (1 RCT):
  - At long-term follow-up (36 weeks), authors report that no adverse events occurred in either group and no difference was seen between groups in the proportion of patients that withdrew from the trial due to adverse events; however, limited data was provided and sample size was small (insufficient evidence for both). No difference was seen in proportion of patients with headache following treatment (low evidence); again sample size was small.
- Acupuncture versus Topiramate (1 RCT):
  - In the short-term (4 weeks), authors reported that no adverse events or deaths occurred in either group, however limited data was provided and the sample size was small (insufficient evidence for both). Statistically fewer side-effects occurred following acupuncture compared with topiramate, but no statistical difference was seen between groups in the proportion of patients that withdrew from the trial due to adverse events (low strength of evidence for both outcomes); however, the sample size was small.

Manual Therapy/Manipulation versus Sham

- No trials were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Active Control

- Spinal Manipulation Therapy (SMT) versus Amitriptyline (1 RCT):
  - Over the short-term (4 weeks), withdrawal from the study due to adverse effects occurred with a lower frequency in patients who received SMT versus amitriptyline (low evidence). The frequency of any adverse event was not reported in a way that we could evaluate comparative efficacy (insufficient evidence).

Massage versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation (TMS) versus Sham

Two small RCTs provided limited evidence regarding safety for this comparison.

- At short-term follow-up (4 weeks), no statistical difference was seen between the TMS and the sham group in the frequency of study withdrawal due to adverse events in one trial; however the sample size was small (insufficient evidence). In this same trial, more patients receiving high-frequency TMS experienced discomfort (no to mild pain) during treatment compared with sham (low evidence).

- At short-term follow-up (8 weeks), as reported by a second small trial, no differences were seen between groups in the frequency of minor adverse events or of study withdrawal due to adverse events; however, all data was insufficient.

Transcranial Magnetic Stimulation (TMS) versus Active Control

- No trials were identified that met the inclusion criteria.

Trigger Point Injection (TPI) versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Chronic Tension-type Headache

BoNTA versus Placebo

- At short-term follow-up (8 weeks), in one trial, treatment-related adverse events were more in the BoNTA groups compared to placebo, though the differences were not statistically significant (low evidence) however, the risk of severe adverse events was similar between groups (low evidence) in the same trial.
- Over the short-term (8 weeks) in one small trial, there was no difference between groups with regard to injection site pain (insufficient evidence).
- At longer-term follow-up (12 weeks) across two small RCTs, there were no statistical differences between groups with regard to injection site pain (insufficient evidence)
- Vertigo was uncommon across two small RCTs; firm conclusions are not possible (insufficient evidence).

BoNTA versus Active Control

- No studies were identified that met the inclusion criteria.

Acupuncture versus Sham

- Adverse events were not reported by any of the trials included for efficacy.

Acupuncture versus Active Control

- Acupuncture vs. Physiotherapy (1 RCT)
  - Over the short- (4 weeks) and intermediate-term (9 weeks), one trial reported that a few patients in the acupuncture group had a slight vasovagal reaction; no other complications were noted and no data was provided (insufficient evidence).

- Acupuncture vs. Physical Training and vs. Relaxation (1 RCT)
  - Adverse events were not reported by the trial included for efficacy.

Manual Therapy/Manipulation versus Sham

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Active Control

- Manual Therapy (MT) vs. Usual Care (1 RCT)
  - Over the longer-term (18 weeks), one trial reported that no adverse events occurred in either the MT or usual care group; however no further data was provided (insufficient evidence).

Massage versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Trigger Point Injection versus Sham

One small trial provided limited evidence regarding safety for this comparison.

- At long-term follow-up (12 weeks), one trial reported that no adverse events occurred in either group; however no further data was provided (insufficient evidence). This same trial also reported a similar frequency of minor side effects between the TPI and the sham group but the sample was small (low strength of evidence).

Trigger Point Injection versus Active Control

- No studies were identified that met the inclusion criteria.

Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

BoNTA vs. Placebo

Two trials provided information on safety-related outcomes for this comparison.

- At long-term follow-up (24 weeks), treatment-related adverse events were over two-times more common following BoNTA compared with placebo across two RCTs; results were statistically significant (moderate evidence).
- The most common adverse event experienced in BoNTA recipients was muscle weakness (24%) followed by neck pain (19%) and neck rigidity (9.0%). Shoulder/arm pain (5.5%) and Dysphagia

(3%) were less common. All of these were significantly more common the BoNTA group compared with placebo. (low evidence for all outcomes)

BoNTA vs. Active Control (Topiramate)

One small RCT provided limited information on safety-related outcomes for this comparison.

- Through longer-term follow-up (12 weeks), nausea was two times more common with BoNTA than with topiramate however both groups experienced similar frequency of mild fatigue in one small RCT (Low evidence).

Acupuncture versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Massage versus Sham

One small RCT provided limited evidence regarding safety for this comparison.

- Through the intermediate-term (9 weeks), one small trial reported no statistical difference between the massage and the sham group in minor fever, mild soreness, and other discomfort; again, the sample was small (low strength of evidence).

Massage versus Active Control

- No studies were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Trigger Point Injection versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

KQ3: Summary of Results

For this key question, RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation.

None of the trials comparing BoNTA with either placebo or an active treatment provided information on differential effectiveness or safety.

Two trials comparing acupuncture with an active control (usual care; topiramate)[34,37,38] for chronic migraine and one trial comparing manual therapy (MT) with usual care for the treatment of chronic tension-type headache[8] provided information on differential efficacy; no differential safety data was reported.

Acupuncture versus Active Control for Chronic Migraine

- Acupuncture vs. Usual Care (1 RCT):
  - 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; all other variables (headache diagnosis, age, sex, chronicity) did not modify the treatment effect (insufficient strength of evidence).
- Acupuncture vs. Topiramate (1 RCT):
  - Baseline headache days (any and moderate/severe) was found to modify treatment effect such that patients with higher (≥20 days/mo.) as compared with lower (<20 days/mo.) frequency showed significantly greater improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect (insufficient strength of evidence).

Manual Therapy versus Usual Care for Chronic Tension Type Headache

- Manual Therapy vs. Usual Care (1 RCT):
  - No differential effect of treatment was seen for the subgroup of patients with comorbid migraine versus without migraine; no formal test for interaction was performed (insufficient strength of evidence).

KQ4: Summary of Results

For the treatment of chronic migraine, three cost utility analyses (CUA) met the inclusion criteria; two compared Botox with placebo and one compared acupuncture with usual care. Two of the included economic studies were considered to be at poor to moderate quality and the third was very poor quality.

No economic studies that met our inclusion criteria were identified for the treatment of chronic tension-type headache or chronic daily headache.

BoNTA versus Placebo for Chronic Migraine

One poor to moderate quality[5] and one very poor quality[26] cost-utility analysis compared BoNTA versus placebo. The higher quality UK study suggests that BoNTA may be cost-effective at a willingness to pay threshold of €20,000 to €30,000/QALY). ICERs were higher for patients who had received three or more prior treatments. Based on sensitivity analysis, ICERs ranged from £4945/QALY (if no effect of placebo on # of HA days to £29,175/QALY when utilities for both BoNTA and placebo were the same in a given health state.

Primary limitations include lack of comparison to an active agent such as topiramate, lack of consideration of indirect costs (e.g., absenteeism, lost productivity, emergency department visit), unclear modeling of harms and lack of clear information on long-term (beyond 24 weeks) benefits and harms of BoNTA. Given the chronic nature of CM, it is assumed that continued treatment may needed, however the circumstances for continuation or discontinuation are not clear.

Acupuncture versus Usual Care for Chronic Migraine

One poor to moderate quality CUA 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.[34,35] 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, lack of consideration of indirect costs (e.g., absenteeism, lost productivity, emergency department visits), 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 needed, however the circumstances for continuation or discontinuation are not clear. Lack of clarity regarding the components of usual care and differences between the UK and US medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.

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***. Additional information on lower quality studies and secondary outcomes is available in the report. Summaries for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

Key Question 1: Strength of Evidence Summary: Chronic Migraine Efficacy Results

Efficacy of BoNTA: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: BoNTA versus Placebo						
Responders Percent with ≥ 50 % reduction in number of *migraine episodes*	>12 weeks	3 RCTs PREEMPT 1 and 2 (Aurora 2011), Freitag 2008	N= 1236 (completers) and 41	Indirectness[4] (-1)	24 Weeks: 2 RCTs (n =1236), low risk of bias Pooled RR 1.1, 95% CI 1.0, 1.2 Pooled RD 4.7%, 95% CI -0.8%, 10.2%) 16 Weeks: 1 RCT (n = 41), moderately high risk of bias RR 2.0, 95% CI 0.6, 6.8 Conclusion: No statistical difference between BoNTA and placebo.	⊕⊕⊕○ MODERATE
Responders Percent with ≥ 50 % reduction in number of *migraine days, overall number of headache days*	24 weeks	2 RCTs PREEMPT 1 and 2 (Aurora 2011)	N =1236 (completers)	Indirectness[4] (-1)	Migraine days: Pooled RR 1.3 95% CI 1.1, 1.5 RD 12.3% (6.9%, 17.8%) Headache days: Pooled RR 1.3 (95% CI 1.2, 1.5 RD 12.0% (6.5%, 17.4%) Conclusion: More BoNTA participants experienced ≥50% reduction in **number of migraine days** and **overall headache days** compared with placebo; the relative effect size is small; the RD between groups is 12%	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Reduction in mean *HA episodes* per month	24 weeks	2 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010)	N =1384	Indirectness[4] (-1)	Pooled MD -0.27 (95% CI -1.05, 0.51) Conclusion: There was no statistical difference in mean number of **HA episodes** for BoNTA and placebo	⊕⊕⊕○ MODERATE
Reduction in mean *HA days* per month	16 weeks 24 weeks	3 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010), Freitag 2008	N= 1420	Indirectness[4] (-1)	Pooled MD -1.77 (95% CI -2.49, -1.06) Conclusion: A small reduction in the mean number **HA days** favoring BoNTA group compared to placebo was observed.	⊕⊕⊕○ MODERATE
Reduction in mean *migraine episodes* per month	16 weeks 24 weeks	2 RCTs PREEMPT 1(Aurora 2010), Freitag 2008	N=715	Inconsistency[2] (-1), Indirectness[4] (-1)	Pooled MD -1.29 (95% CI -4.22, 1.64) Conclusion: No statistical difference was observed for the pooled estimate or in the larger trial that was a low risk of bias in the number of **migraine episodes**. The smaller trial at moderately high risk of bias reported a significant decrease in the BoNTA group. The quality rating is based on the larger, low risk of bias trial.	⊕⊕⊕○ MODERATE
Reduction in mean *migraine days* per month	24 weeks	2 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010)	N =1384	Indirectness[4] (-1)	Pooled MD -1.79 (95% CI -2.61, -0.96) Conclusion: A small reduction in the mean number of **migraine days** favoring BoNTA group compared to placebo was observed.	⊕⊕⊕○ MODERATE
Percentage of Participants with a Severe HIT-6 Score (≥60) †	24 weeks	2 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010)	N =1384	Indirectness[4] (-1)	Pooled RR 0.86 (95% CI 0.81, 0.92) Conclusion: Significantly fewer patients in the BoNTA group still had severe HIT scores at 24 weeks compared to placebo; At baseline, 94%	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
					of participants in both groups had a severe score.	
Headache Impact Test-6 (HIT) †	24 weeks	2 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010)	N =1384	Indirectness[4] (-1)	MD -2.39 (95% CI -3.40, -1.39) Conclusion: Greater reduction in mean HIT scores, suggesting improved function, was seen in the BoNTA group compared to placebo; this may be a clinically important difference.	⊕⊕⊕○ MODERATE
Migraine Disability Assessment Scale (MIDAS) (0-27 [worst])	16 weeks	1 RCT (Freitag 2008)	N = 41	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	Mean change from baseline BoNTA: -11 placebo: +2 Conclusion: Although the mean change in MIDAS scores suggests improved function in the BoNTA group compared to placebo, authors report that the result was not statistically significant.	⊕○○○ IINSUFFICIENT
Chronic Migraine: OnabotulinumtoxinA (BoNTA) versus Topirimate						
Responders Percent with ≥ 50 % reduction in number of *headache days* per month	12, 24, 36 weeks	1 RCT (Mathew 2009)	N=60	Risk of Bias[1] (-1), Imprecision[3] (-1)	12 weeks: BoNTA 38.5%, Topiramate 22.7% RR 1.7, 95% CI 0.7, 4.2 24 weeks: BoNTA 58.3%, Topiramate 31.8% RR 1.8, 95% CI 0.9, 3.7 36 weeks: BoNTA 40.9%, Topiramate 42.9% RR 1.0, 95% CI 0.5, 1.9 Conclusion: At 12 and 24 weeks, more BoNTA recipients achieved **≥ 50 reduction in headache days, however,** there were no statistical differences between groups at any time point however this may partly be a function of sample size. There was	12 weeks: ⊕⊕○○ LOW 24 and 36 weeks ⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
					substantial attrition and differential loss to follow-up: data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks.	
Functional Measures (MIDAS, HIT-6, MIQ)	4- 36 weeks			Risk of Bias[1] (-1), Imprecision[3] (-1)	MIDAS: 12 weeks: MD 22.8, 95% CI -2.5, 48.1 24 weeks: MD 35.0, 95% CI -3.2, 73.2 HIT-6 12 weeks: MD 3.2, 95% CI -1.1, 7.5 24 weeks: MD 4.8, 95% CI 0.1, 9.6 36 weeks: MD 5.3, 95% CI 0.8, 9.8 MIQ: 4 weeks: MD -0.2, 95% CI -1.7, 1.3 24 weeks: MD -1.8, 95% CI -3.2, -0.4 Conclusion: There were no differences between groups for any functional measure at any time point. As noted above, there was substantial attrition and differential loss to follow-up.	12 weeks: ⊕⊕◯◯ LOW 24 and 36 weeks ⊕◯◯◯ INSUFFICIENT
Chronic Migraine: OnabotulinumtoxinA (BoNTA) versus Amitriptyline						
Responders: Percent of patients with ≥ 50% reduction in the frequency of pain days	12 weeks	1 RCT (Magalhaes 2010)	N=72	Risk of Bias[1] (-1), Imprecision[3] (-1),	RR 0.9 (95% CI 0.1, 8.0) Conclusion: There were no differences between groups	⊕⊕◯◯ LOW
Responder: Percent of patients with ≥3 point				Risk of Bias[1] (-1), Imprecision[3] (-1),	RR 1.1 (95% CI 0.3, 3.8). Conclusion: There were no differences between groups	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
reduction in pain intensity						

MIDAS = Migraine Disability Assessment Scale, greater number of days, greater disability (scale 0-27(worst), HIT-6 = Headache Impact Test-6,36-78(worst) higher score, greater impact on activities of daily living; between-group difference in change scores of 2.3 units may be considered clinically significantin patients with ≥ 15 headache days/month; MIQ = Migraine Impact Questionnaire (scale 0-100)

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers. Authors of the PREEMPT 1 and 2 trials imputed values for missing participants using last observation carried forward for ITT analysis

† Headache Impact Test-6 (HIT) measures the impact headache has on function. Higher scores = higher impact on activities of daily living; Scoring interpretation- Little or no impact: <46, Some impact: 50 – 55, Substantial impact: 56 – 59, Severe impact: 60 –78; a between-group difference in change scores of 2.3 units may be considered clinically significant in patients with ≥ 15 headache days/month.

‡ Results could not be pooled due to differences in data reporting between the trials.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

Efficacy of Acupuncture: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: Acupuncture vs. Usual Care						
Responders Proportion with ≥50% reduction in *any, mild, and moderate/ severe headache days* from baseline	36 wks.	1 RCT (Vickers 2004)	301	Risk of Bias[1] (-1), Indirectness[4] (-1)	<u>Any headache days</u>: RR 2.0 (95% CI 1.3, 3.2) RD 15.4% (95% CI 6.2%, 24.7%) <u>At least mild headache days</u>: RR 1.9 (95% CI 1.3, 2.9) RD 16.9% (95% CI 7.2%, 26.6%) <u>Moderate/Severe headache days</u>: RR 1.5 (95% CI 1.1, 2.1) RD 12.7% (95% CI 2.2%, 23.2%) <u>Conclusion</u>: Statistically greater improvement with acupuncture vs. usual care	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
					for all three measures 36 weeks post-treatment.	
Responders Proportion with ≥35% reduction in *headache days* from baseline				Risk of Bias[1] (-1), Indirectness[4] (-1)	RR 1.7 (95% CI 1.3, 2.2) RD 21.9% (95% CI 11.0%, 32.8%) Conclusion: Statistically greater improvement with acupuncture vs. usual care 36 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in any, mild or moderate/ severe *headache days* per month (adjusted for baseline score)				Risk of Bias[1] (-1), Indirectness[4] (-1)	Any headache days: MD 1.8 (95% CI 0.6, 2.9) At least mild headache days: MD 1.6 (95% CI 0.5, 2.6) Moderate/Severe headache days: MD 1.2 (95% CI 0.4, 2.1) Conclusion: Statistically greater improvement with acupuncture vs. usual care for all three measures 36 weeks post-treatment.	⊕⊕◯◯ LOW
Chronic Migraine: Acupuncture vs. Topiramate						
Responders Proportion with ≥50% reduction in *any or moderate/ severe headache days* from baseline	4 wks.	1 RCTs (Yang 2011)	66	Risk of Bias[1] (-1), Imprecision[3] (-1)	Any headache days: RR 4.2 (95% CI 1.8, 9.8) RD 48.5% (95% CI 28.0%, 69.0%) Moderate/Severe headache days: RR 2.5 (95% CI 1.4, 4.3) RD 45.5% (95% CI 24.0%, 66.9%) Conclusion: Statistically greater improvement with	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
					acupuncture vs. topiramate for both measures 4 weeks post-treatment.	
Reduction in *any or moderate/ severe headache days* per month				Risk of Bias[1] (-1), Imprecision[3] (-1)	Any headache days: MD 2.8 (95% CI 1.2, 4.4) Moderate/Severe headache days: MD 2.7 (95% CI 1.1, 4.3) Conclusion: Statistically greater improvement with acupuncture vs. topiramate for both measures 4 weeks post-treatment.	⊕⊕◯◯ LOW
Migraine Disability Assessment (MIDAS)*				Risk of Bias[1] (-1), Imprecision[3] (-1)	MD 12.6 (95% CI 7.7, 17.5) Conclusion: Statistically greater improvement with acupuncture vs. topiramate 4 weeks post-treatment; it is unclear if this difference is clinically meaningful.	⊕⊕◯◯ LOW

*The MIDAS (Migraine Disability Assessment Scale) 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; regarding interpretation, greater number of days = greater disability (scale 0-27 (worst)).

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

Efficacy of Manual Therapy/Manipulation: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: Spinal Manipulation Therapy (SMT) vs. Amitriptyline						
Responders Proportion with >20%, >40%, and >60% reduction in HI scores* from baseline	4 wks.	1 RCT (Nelson 1998)	108	SRisk of Bias[1] (-1), Imprecision[3] (-1)	<u>>20% reduction in HI score</u> RR 1.7 (95% CI 1.2, 2.4) RD 30.1% (95% CI 12.4%, 47.9%) <u>>40% reduction in HI score</u> RR 1.7 (95% CI 1.1, 2.6) RD 24.3% (95% CI 6.0%, 42.7%) <u>>60% reduction in HI score</u> RR 1.4 (95% CI 0.6, 3.1) RD 6.4% (95% CI -8.4%, 21.2%) <u>Conclusion</u>: Statistically greater proportion of patients achieved >20% and >40%, but not >60%, reduction in HI scores with SMT vs. amitriptyline 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in <u>*percentage of days per month*</u> with headache				Risk of Bias[1] (-1), Imprecision[3] (-1)	MD 3.6% (95% CI -6.8%, 14.0%) <u>Conclusion</u>: No statistical difference between SMT and amitriptyline at 4 weeks post-treatment.	⊕⊕◯◯ LOW

*Headache Index (HI) scores: The weekly sum of each patients headache pain score (rated on a 0-10 scale) on the days they report having a headache.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Efficacy of Transcranial Magnetic Stimulation: Chronic Migraine

Outcome	Follow-up	CTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: Transcranial Magnetic Stimulation (TMS) vs. SHAM*						
Responders Proportion with >50% reduction in *migraine attacks* from baseline	4 wks.	1 RCT (Misra 2013)	95	Imprecision[3] (-1), Indirectness[4] (-1)	RR 2.4 (95% CI 1.3, 3.2) RD 45.4% (95% CI 27.7%, 63.1%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Responders Proportion with >50% improvement in *headache severity*† from baseline				Imprecision[3] (-1), Indirectness[4] (-1)	RR 2.8 (95% CI 1.7, 4.6) RD 49.5% (95% CI 32.1%, 67.0%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *migraine attacks per month* from baseline				Imprecision[3] (-1), Indirectness[4] (-1)	MD -3.7 (95% CI -6.07, -1.33) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *migraine attacks per 2 weeks* from baseline	8 wks.	1 RCT (Teepker 2010)	27	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	MD -0.91 (95% CI -4.27, 2.46) Conclusion: Insufficient evidence precludes firm conclusions. MD -3.7 (95% CI -10.1, 2.8) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Reduction in *migraine days per 8 weeks*				Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	MD -0.91 (95% CI -4.27, 2.46) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

Functional disability rating of normal or mild§	4 wks.	1 RCT (Misra 2013)	93	Imprecision[3] (-1), Indirectness[4] (-1)	RR 4.4 (95% CI 2.2., 9.1) RD 49.9% (95% CI 32.7%, 67.1%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW

*Results could not be pooled due to heterogeneity in patient populations and treatment regimens, variation in the definition of primary outcomes and differences in study quality.
†Headache severity: pain on 0-100 VAS, considering frequency and average severity.
§Functional disability was graded on a 0 to 4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe impairment of activities of daily living (ADL), 4 = inability to perform ADL requiring bed rest) and recorded by the patient in a daily headache diary.
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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Key Question 1 Strength of Evidence Summary: Chronic Tension-Type Headache Efficacy Results

Efficacy of BoNTA: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Tension-Type Headache: BoNTA vs. Placebo						
Percent of patients with ≥ 25% reduction in pain intensity	4, 8 weeks (short term)	1 RCT (Schmitt 2001)	N = 59	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	4 weeks: BoNTA 36.7%, placebo 27.6%; RR 1.3, 95% CI 0.6, 2.8 8 Weeks: BoNTA 50.0%, placebo 31.0%; RR 1.3, 95% CI 0.6, 2.8 Conclusion: Although more patients the BoNTA experienced **≥ 25% reduction in pain intensity,** results did not reach statistical significance**.** Sample size is small.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Percent of patients with ≥ 45% reduction in pain intensity	12 weeks	1 RCT (Padberg 2004)	N = 40	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	12 Weeks: BoNTA 31.6%, placebo 14.3%; RR 1.3, 95% CI 0.6, 2.8 Conclusion: Although more patients the BoNTA experienced **≥ 45% reduction in pain intensity,** results did not reach statistical significance**.** Sample size is small.	⊕◯◯◯ INSUFFICIENT
Reduction in % of *HA days* per month	12 weeks	1 RCT (Padberg 2004)	N = 40	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 12±20%, placebo 5±14%; MD: 7.0, 95% CI: -4.0, 18.0 Conclusion: Although the BoNTA group had a greater percent reduction in HA days, statistical significance wasn't reached; small sample size is noted.	⊕◯◯◯ INSUFFICIENT
Reduction in mean *HA days* per month	4 weeks, ≥ 12 weeks	2 RCTs (Hamdy 2009, Kokoska 2004)	N = 68	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	4 weeks: MD 3.22 (95% CI -4.84, -1.60 (1 RCT, N=28) 12-24 weeks: Pooled MD-2.98, 95% CI -5.96, -0.01 (2 RCTs, N=68) Conclusion: BoNTA may be associated with fewer HA days; studies were small and at moderately high risk of bias.	⊕◯◯◯ INSUFFICIENT
Functional Measure: Mean HDI Scores†	4, 12 weeks	1 RCTs (Hamdy 2009)	N = 28	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	4 weeks: MD -11.85 (95% CI -22.23, -1.47) 12 weeks: MD -18.28 (95% CI -31.11, -5.45) Conclusion: Mean HDI scores at 4 and 12 weeks were significantly lower in the BoNTA group, indicating improvement in function	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
					compared with placebo. The percent reduction in HDI score was greater in the BoNTA group (40.6%) compared with placebo group (6.6%) at 12 weeks	

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers.
† HDI = Henry Ford Hospital Headache Disability Inventory, scale 0-100 (worst); 16 point improvement may be considered clinically significant

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Efficacy of Acupuncture: 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	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-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.	⊕◯◯◯ INSUFFICIENT
	52 wks.				<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%)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion	Quality
					>50% improvement on the HI RR 1.5 (95% CI 0.5, 4.3) RD 13.3% (95% CI -20.1%, 46.7%) Conclusion: Insufficient evidence precludes firm conclusions.	
Reduction in headache *episodes* per month	4-6 wks.	2 RCTs (Tavola 1992, Karst 2000)	69	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	Pooled MD -1.94 (95% CI -6.74, 2.85) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	26-52 wks.	1 RCT (Tavola 1992)	30	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-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. Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Chronic Tension Type Headache: Acupuncture vs. Physical Training/Exercise						
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	Risk of Bias[1] (-2), 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

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion	Quality
Headache-free *days* per week				Risk of Bias[1] (-2), 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 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	Risk of Bias[1] (-1) 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.	⊕◯◯◯ INSUFFICIENT
Sickness Impact Profile (SIP)				Risk of Bias[1] (-1) 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	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion	Quality
					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.	
Chronic Tension Type Headache: Acupuncture vs. Relaxation Training						
Headache-free *periods* per week	12-26 wks.	1 RCT (Soderberg 2006, 2011)	60	Risk of Bias[1] (-2), 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.	⊕○○○ INSUFFICIENT
Headache-free *days* per week				Risk of Bias[1] (-2), 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 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

* 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.

† 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 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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

Efficacy of Manual Therapy/Manipulation: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Tension Type Headache: Manual Therapy (MT)/Manipulation vs. Usual Care						
Responders Proportion with >50% reduction in *headache days per 2 weeks* from baseline	18 wks.	1 RCT (Castien 2011)	82	Imprecision[3] (-1), Indirectness[4] (-1)	RR 2.0 (95% CI 1.3, 3.0) RD 41.0% (95% CI 21.0%, 61.1%) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in number of *headache days per 2 weeks*				Imprecision[3] (-1), Indirectness[4] (-1)	MD 4.9 (95% CI 2.98, 6.95) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Impact Test (HIT-6)				Imprecision[3] (-1), Indirectness[4] (-1)	MD 5.0 (95% CI 1.16, 9.02) Conclusion: Statistically and clinically* greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Disability Inventory (HDI)				Imprecision[3] (-1), Indirectness[4] (-1)	MD 10.1 (95% CI 0.64, 19.5) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment; however, the difference did not meet the author-defined MCID of ≥16 point reduction.	⊕⊕◯◯ LOW

HIT-6 = Headache Impact Test-6,36-78(worst) higher score, greater impact on activities of daily living; between-group difference in change scores of 2.3 units may be considered clinically significantin patients with ≥ 15 headache days/month.
*The Minimal Clinically Important Difference (MCID) as defined by the authors was a >2.3-point decrease on the HIT-6.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Efficacy of Trigger Point Injections: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Tension Type Headache: Trigger Point Injections (TPI) vs. Sham						
Reduction in number of *headache days per month*	12 wks.	1 RCT (Karadas 2013)	48	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	MD 11.2 (95% CI 9.2, 13.2) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Key Question 1 Strength of Evidence Summary: Chronic Daily Headache Efficacy Results

Efficacy of BoNTA: Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Daily Headache: BoNTA versus Placebo						
Responders Percent of patients with ≥ 50 % reduction frequency of	24 weeks	1 RCT (Mathew 2005)	N = 355	Risk of Bias[1] (-1), Indirectness[4] (-1)	BoNTA 40.3%, Placebo 25.3% RR 1.6, 95% CI 1.1, 2.2) Conclusion: More BoNTA recipients had a ≥ 50 % reduction frequency of	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
headache days					headache days compared with placebo.	
Change in mean number of headache-free days	24 weeks	2 RCTs (Mathew 2005, Silberstein 2005) †	N = 793	Risk of Bias[1] (-1), Indirectness[4] (-1)	Pooled MD 0.74 (95% CI -1.51, 2.99). Conclusion: Based on pooled data, there was no difference between groups. A statistically significant difference favoring BoNTA at 24 weeks was reported in Mathew (MD 1.64, 95% CI 0.12, 3.16), however, it did not meet their threshold of 3 days as being clinically significant. There were no differences between treatments at any other time point in this trial. Data from Silberstein were not available at other time frames and data across placebo non-responders and placebo responders could not be pooled.	⊕⊕◯◯ LOW
Chronic Daily Headache: BoNTA versus Topiramate						
Reduction in frequency of headache days per month	4 and 12 weeks	1 RCT (Cady 2011)	N =59	Risk of Bias[1] (-1), Imprecision[5] (-1)	Means 4 weeks: BoNTA -3.0 Topiramate -4.4 12 weeks: BoNTA -8.0 Topiramate – 8.1 Conclusion: No significant differences between the groups in the reduction of headache days per month; authors do not provide data to calculate effect size.	⊕⊕◯◯ LOW
Function: HIT-6 and MIDAS	12 weeks			Risk of Bias[1] (-1), Imprecision[5] (-1)	HIT-6: BoNTA -6.3, Topiramate -6.0 MIDAS: BoNTA -38.5, Topiramate -26.7 Conclusion: No significant differences between the groups for either measure; authors do not provide sufficient data for effect size calculation.	⊕⊕◯◯ LOW

MIDAS = Migraine Disability Assessment Scale, greater number of days, greater disability (scale 0-27(worst), HIT-6 = Headache Impact Test-6,36-78(worst) higher score, greater impact on activities of daily living; between-group difference in change scores of 2.3 units may be considered clinically significantin patients with ≥ 15 headache days/month.

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers.

† Both trials had a 30 day placebo run-in phase and identified placebo responders and placebo nonresponders. Pooling across these groups was done where data for Mathew, however Silberstein did not provide data on placebo responders, thus the pooled estimate in the table includes only placebo nonresponders for this trial .Placebo nonreponders comprised the majority (>75%) of the study population in the Silberstein trial.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Efficacy of Massage: Chronic Daily Headache/Co-existent Chronic Migraine and Tension-Type Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion	Quality
Chronic Daily Headache: Massage vs. Sham						
Reduction in number of *headache attacks per month* (adjusted for baseline scores)	3-9 wks.	1 RCT (Chatchawan 2014)	72	Imprecision[3] (-1), Indirectness[4] (-1)	3 weeks: MD 2.6 (95% CI -0.04, 5.2) 9 weeks: MD 0.2 (95% CI -1.1, 0.78) Conclusion: No statistical difference between massage versus sham at 3 and 9 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Disability Index (adjusted for baseline scores)				Imprecision[3] (-1), Indirectness[4] (-1)	3 weeks: MD 1.9 (95% -6.3, 10.0) 9 weeks: MD 0.4 (95% CI -7.3, 8.0) Conclusion: No statistical difference between massage versus sham at 3 and 9 weeks post-treatment.	⊕⊕◯◯ LOW

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Key Question 2 Strength of Evidence Summary: Serious or Potentially Serious Adverse Events Results

BoNTA vs. Placebo Safety Results: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: BoNTA vs. Placebo						
Treatment-related adverse events (AE)†	24 weeks	2 RCTs PREEMPT 1 (Aurora 2010), PREEMPT 2 (Denier 2010)	N =1379	Indirectness[4] (-1)	BoNTA 29.4 %, Placebo 12.7% Pooled RR 2.32 (95% CI 1.85, 2.91) Conclusion: Treatment-related adverse events over were twice as common in the BoNTA group compared to placebo	⊕⊕⊕◯ MODERATE
Serious adverse events‡				Indirectness[4] (-1)	BoNTA 4.8 %, Placebo 2.3 % Pooled RR 2.07 (95% CI 1.15, 3.73) Conclusion: Serious adverse events were significantly more common in the BoNTA group compared to placebo.	⊕⊕⊕◯ MODERATE
Treatment-Related Serious Adverse Events‡				Indirectness[4] (-1), Imprecision[3] (-2)	BoNTA 0.15%, Placebo 0% Pooled RR 3.09 (95% CI 0.13, 75.71 Conclusion: Such events were rare; none were reported in PREEMPT 1 and only one event in the BoNTA reported for PREEMPT 2. There was likely insufficient power to detect such events; firm conclusions are not possible.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Discontinuation Related to Adverse Events				Indirectness[4] (-1), Imprecision[3] (-2)	BoNTA 3.8%, Placebo 1.2 % Pooled RR 3.19 (95% CI 1.33, 7.05), Conclusion: Discontinuation of treatment related to AEs was 3 times more common for the BoNTA group compared to placebo	⊕⊕⊕◯ ⊕⊕◯◯ LOW

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† Treatment-related AEs were defined as events reported by ≥2% of patients. For both Aurora 2010 and Diener 2010, the treatment-related adverse events that occurred at a rate ≥ 5% were neck pain (5.9% in Aurora 2010, 7.5% in Diener 2010) and muscle weakness (5.9% in Aurora 2010, 5.2 in Diener 2010) in the onabotulinumtoxinA group. Other common treatment-related AEs were eyelid ptosis, muscle tightness, and injection-site pain. The treatment-related serious AEs reported in the DoNTA group was migraine requiring hospitalization. No information was given describing what constituted a treatment-related serious adverse event

‡ Aurora 2010 and Diener 2010 did not provide detail on what constituted a serious adverse event

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

BoNTA vs. Active Control Safety Results: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: BoNTA vs. Topiramate						
Drug-related adverse events or possible/probable drug –related adverse events†	36 weeks	1 RCT (Mathew 2009)	N=60	Risk of Bias[1] (-1), Imprecision[3] (-1)	Drug-related BoNTA 69.2% Topiramate 86.2% RR 0.8, 95% CI 0.6, 1.1 Possible/probable drug-related BoNTA 84.6% Topiramate 89.7% RR 0.9, 95% CI 0.8, 1.2 Conclusion: Although not statistically different, fewer BoNTA patients experienced drug-related AEs compared with topirimate recipients; sample size may preclude detection of statistical differences. Differential attrition between treatment groups and substantial loss to follow-up should be considered when interpreting this finding. Data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks	⊕⊕◯◯ LOW
Discontinuation Related to Adverse Events‡				Risk of Bias[1] (-1), Imprecision[3] (-1)	BoNTA 7.7%, Topiramate 24.1% RR 0.3, 95% CI 0.1, 1.4 Conclusion: Discontinuation of treatment was not statistically different, however fewer BoNTA recipients discontinued treatment than topiramate recipients; sample size may be a factor.	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Migraine: BoNTA vs. Amitriptyline						
Injection site pain	12 weeks	1 RCT (Magalhaes 2010)	N = 72	Risk of Bias[1] (-1), Imprecision[3] (-1)	BoNTA 35.0% vs amitriptyline 0.0% Conclusion: More BoNTA recipients experienced injection site pain;	⊕⊕◯◯ LOW
Edema				Risk of Bias[1] (-1), Imprecision[3] (-1)	BoNTA 14.0% vs amitriptyline 0.0% Conclusion: More BoNTA recipients experienced injection edema.	⊕⊕◯◯ LOW

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

†The most common (≥3 events) drug-related adverse events reported on the BoNTA group were weakness in eyebrow/eyelids, weakness in forehead/neck, paresthesias, pain in head, and sleepiness (including tiredness and fatigue) and dizziness. Adverse events reported in the topiramate group were sleepiness (including tiredness and fatigue) and dizziness, depression/mood disturbance, appetite/weight loss, cognitive deficits, night sweats, dry mouth/thirst, blurred vision/vision problems

‡ Mathew 2009 did not provide information on what constituted AEs that caused discontinuation

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Acupuncture versus Active Control Safety Results: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Migraine: Acupuncture vs. Usual Care						
Serious adverse events	36 wks.	1 RCT (Vickers 2004)	301	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	No serious adverse events occurred in either group; data and information not provided. Conclusion: Without knowing what constitutes a serious adverse event and the rarity of such	⊕◯◯◯ INSUFFICIENT

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					events, it is unknown whether there was sufficient sample size to detect such events; firm conclusions are difficult.	
Discontinuation due to adverse events				Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	0.6% (1/161) vs. 0% (0/140) Conclusion: Although no statistical difference between groups, it is unclear whether there was sufficient sample size to detect a statistical difference.	⊕◯◯◯ INSUFFICIENT
Headache				Risk of Bias[1] (-1), Indirectness[4] (-1)	2.5% (4/161) vs. 0% (0/140) Conclusion: No statistical difference between groups; it is unclear whether sample size played a role.	⊕⊕◯◯ LOW
Chronic Migraine: Acupuncture vs. Topiramate						
Serious adverse events	4 wks.	1 RCTs (Yang 2011)	66	Risk of Bias[1] (-1), Imprecision[3] (-2),	No serious adverse events occurred in either group; 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

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Death				Risk of Bias[1] (-1), Imprecision[3] (-2),	No deaths occurred in either group. Conclusion: Small sample size makes the detection of rare events difficult; insufficient evidence preclude firm conclusions.	⊕◯◯◯ INSUFFICIENT
Discontinuation due to adverse events				Risk of Bias[1] (-1), Imprecision[3] (-1)	0% (0/33) vs. 9% (3/33) Conclusion: No statistical difference between groups; small sample size may have precluded detection of a statistical difference.	⊕⊕◯◯ LOW
Any side effect				Risk of Bias[1] (-1), Imprecision[3] (-1),	RR 0.1 (95% CI 0.02, 0.4) • Acupuncture: 6% (2/33); all due to local insertion of needles (pain, paresthesia, ecchymosis) • Topiramate: 66% (22/33); to include paresthesia (48%), difficulty with memory (36%), dyspepsia (36%), fatigue (24%), dizziness (21%), somnolence (18%), and nausea (12%) Conclusion: Statistically fewer	⊕⊕◯◯ LOW

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					side-effects occurred following acupuncture versus topiramate.	

*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 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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Manual Therapy/Manipulation versus Amitriptyline Safety Results: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Migraine: Spinal Manipulation Therapy (SMT) vs. Amitriptyline						
Discontinuation due to adverse events	4 wks.	1 RCT (Nelson 1998)	108	Risk of Bias[1] (-1), Imprecision[3] (-1)	0% (0/77) vs. 11% (7/65) Conclusion: Lower frequency of withdrawal from study due to adverse events in the SMT versus amitriptyline group.	⊕⊕◯◯ LOW
Any adverse event				Risk of Bias[1] (-1), Imprecision[3] (-2)	Authors report that 58% (79/136) of patients who received amitriptyline (alone or in combination with acupuncture)† experienced medication side effects important enough to document (no further details provided); adverse effects following SMT were much more benign/mild, infrequent, and transitory (no further details provided). Conclusion: Lack of comparative data limits ability to draw conclusions.	⊕◯◯◯ INSUFFICIENT

*Author does not provided information on what constituted adverse events that caused discontinuation; specifics regarding any adverse events were not reported.

†The combination group (amitriptyline plus acupuncture) was excluded because it did not meet the inclusion criteria.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

Transcranial Magnetic Stimulation versus Sham Safety Results: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Migraine: Transcranial Magnetic Stimulation (TMS) vs. SHAM†						
Discontinuation due to adverse events	4 wks.	1 RCT (Misra 2013)	95	Imprecision[3] (-2), Indirectness[4] (-1)	2.1% (1/47) vs. 0% (0/48) Conclusion: Although no statistical difference between groups, it is unclear whether there was sufficient sample size to detect a statistical difference.	⨁◯◯◯ INSUFFICIENT
Discomfort during treatment				Imprecision[3] (-1), Indirectness[4] (-1)	100% (47/47) vs. 15% (7/48) RR 6.9 (95% CI 3.5, 13.6) Conclusion: More patients receiving high-frequency TMS experienced discomfort during treatment (no to mild pain)‡ compared with sham.	⨁⨁◯◯ LOW
Discontinuation due to adverse events	8 wks	1 RCT (Teepker 2010)	27	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	7.1% (1/14) vs. 7.7% (1/13) RR 0.9 (95% CI 0.1, 13.4) Conclusion: No difference between groups; however evidence is insufficient to draw a firm conclusion	⨁◯◯◯ INSUFFICIENT
Minor adverse events §				Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	• Assessment of visual motor threshold is uncomfortable: 35.7% (5/14) vs. 30.8% (4/13); RR 1.1 (95% CI 0.4, 3.4)	⨁◯◯◯ INSUFFICIENT

Outcome*	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality

					• Headache: 0% (0/14) vs. 15.4% (2/13)
					• Vigorous dreams: 7.1% (1/14) vs. 0% (0/13)
					• Phonophobia: 7.1% (1/14) vs. 0% (0/13)
					• One event was reported in each group for the following:
					  ○ Sitting is long-lasting and uncomfortable
					  ○ Sleepiness
					  ○ Amyostasia
					  ○ Testiness
					7.1% (1/14) vs. 7.7% (1/13); RR 0.9 (95% CI 0.1, 13.4)
					<u>Conclusion</u>: No statistical differences between group; however, insufficient evidence precludes firm conclusions.	

*Authors do not provided information on what constituted adverse events that caused discontinuation; specifics regarding any adverse events were not reported.
†Results could not be pooled due to heterogeneity in patient populations and treatment regimens, variation in the definition of primary outcomes and differences in study quality.
‡Mean scores on the Faces Pain Scale were 3.10 ± 0.71 versus 0.14 ± 0.35, respectively, p=0.0001.
§It was unclear if patients could have more than one event.
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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

BoNTA versus Placebo Safety Results: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Tension-Type Headache: BoNTA vs. Placebo						
Treatment-related adverse events†	8 weeks	1 RCT (Silberstein 2006)	N=200	Risk of Bias[1] (-1), Indirectness[4] (-1)	BoNTA 34% , placebo 22.0% RR 1.5, 95% CI 0.9, 2.7 Conclusion: Treatment-related AEs were more in the BoNTA groups compared to placebo, though the differences were not statistically significant.	⊕⊕◯◯ LOW
Severe Adverse events‡	8 weeks	1 RCT (Silberstein 2006)	N=200	Risk of Bias[1] (-1), Indirectness[4] (-1)	BoNTA 13.6% , placebo 14.0% RR 1.0, 95% CI 0.5, 2.0 Conclusion: The frequency of severe AEs was similar between groups	⊕⊕◯◯ LOW
Pain at injection site	4, 8 , 12 weeks	3 RCTs (Schmitt 2001, Hamdy 2009, Padberg 2004	N= 127	Risk of Bias[1] (-1), Indirectness[4] (-1), Imprecision[3] (-1)	4 weeks: (1 RCT n =59) BoNTA 6.7% , placebo 3.4% RR 1.9, 95% CI 0.2, 20.2 8 Weeks: (1 RCT n =59) BoNTA 0 %, placebo 0 %; 12 weeks: (2 RCTS n = 68) BoNTA 18.1% , placebo 28.6% RR 0.65, 95% CI 0.3, 1.5 Conclusion: There were no statistical differences at any time.	⊕◯◯◯ INSUFFICIENT
Vertigo	4, 8 , 12 weeks	2 RCTs (Schmitt 2001, Padberg 2004)	N = 59 N= 40	Risk of Bias[1] (-1), Indirectness[4] (-1), Imprecision[3] (-1)	4 weeks: (1 RCT n =59) BoNTA 6.7% , placebo 3.4% RR 1.9, 95% CI 0.2, 20.2 8 Weeks: (1 RCT n =59) BoNTA 0 %, placebo 0 %; 12 weeks: (1 RCT n = 40) BoNTA 0%% , placebo 4.8% (n = 1) Conclusion: Vertigo was uncommon; firm conclusions are not possible given small samples sizes	⊕◯◯◯ INSUFFICIENT

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† The relationship of an adverse event to the treatment was assessed by the investigator. The most frequently reported treatment-related adverse events across all groups were neck pain and muscular weakness. Additional treatment-related

adverse events reported in ≥ 3% of patients in any treatment group were neck rigidity, headache, pain dizziness, injection-site pain, dysphagia, paraethesia, asthenia, hypertonia, nausea, pharyngitis, and burning at the injection site.
‡ Serious adverse events were defined as an event that was fatal, life threatening, permanently disabling, resulted in hospitalization, or resulted in prolongation of existing hospitalization. Silberstein 2006 did not give details of specific serious adverse events that occurred in subjects.
§Data were only available from one study at 4 and 8 weeks (Schmitt) and one study at 12 weeks (Padberg); consistency across studies cannot be assessed.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Acupuncture versus Active Control Safety Results: 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	Risk of Bias[1] (-1), 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

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Manual Therapy/Manipulation versus Active Control: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Outcome
Chronic Tension Type Headache: Manual Therapy (MT)/Manipulation vs. Usual Care						
Any adverse events	18 wks.	1 RCT (Castien 2011)	82	Indirectness[4] (-1), Imprecision[3] (-2)	No adverse events occurred in either treatment group; no other information was 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

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Trigger Point Injections versus Sham Safety Results: Chronic Tension-Type Headache

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Outcome
Chronic Tension Type Headache: Trigger Point Injections (TPI) vs. Sham						
Serious adverse events*	12 wks.	1 RCT (Karadas 2013)	48	Risk of Bias[1] (-1), Imprecision[3] (-1), Indirectness[4] (-1)	No serious adverse events occurred in either group; 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
Minor side effects†				Risk of Bias[1] (-1), Indirectness[4] (-1)	• Injection site/injection pain: 12.5% (3/24) vs. 16.7% (4/24); RR 0.8 (95% CI 0.2, 3.0) • Dizziness: 8.3% (2/24) vs. 8.3% (2/24); RR 1.0 (95% CI 0.2, 6.5) • Back pain: 8.3% (2/24) vs. 12.5% (3/24); RR 0.7 (95% CI 0.1, 3.6) • Cervical muscle spasm: 0% (0/24) vs. 4.2% (1/24) • Any event: 29.2% (7/24) vs. 41.7% (10/24); RR 0.7 (95% CI 0.3, 1.5) Conclusion: No statistical difference between the groups; small sample size may have precluded detection of a statistical difference.	⊕⊕◯◯ LOW

*Authors do not provided information on what constituted a serious adverse event.
†It was unclear if patients could have more than one event.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

BoNTA versus Placebo Safety Results: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Daily Headache: BoNTA vs. Placebo						
Treatment-related adverse events †	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Indirectness[4] (-1)	BoNTA 56.8% , placebo 22% RR 2.47, 95% CI 1.98, 3.09 Conclusion: Treatment-related AEs over two times more common in the BoNTA groups compared to placebo.	⊕⊕⊕◯ MODERATE
Dysphagia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 3.3% , placebo 0.3% RR 7.30 (1.40, 38.04) Conclusion: Dysphagia occurred in 3.3% of BoNTA recipients; it was significantly more common with BoNTA than placebo.	⊕⊕◯◯ LOW
Neck Pain	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 19.1% , placebo 1.1% RR 14.66 (95% CI 5.47, 39.27) Conclusion: Neck pain occurred in 19% of BoNTA recipients and was more common compared with placebo	⊕⊕◯◯ LOW
Neck Rigidity	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 9.0 % , placebo 0.8% RR 7.96 (95% CI 1.60, 39.66 Conclusion: Neck rigidity occurred in 9.0% of BoNTA recipients ; it was significantly more common with BoNTA than placebo	⊕⊕◯◯ LOW
Shoulder/arm pain	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 5.5% , placebo 0.5 % RR 8.88 (95% CI 2.11, 37.40 Conclusion: Shoulder or arm pain occurred in 5.5% of BoNTA recipients; it was significantly more common with BoNTA than placebo.	⊕⊕◯◯ LOW
Muscle Weakness	24 weeks	2 RCT (Mathew 2005,	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 24% , placebo 0.3%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
		Silberstein 2005)			RR 53.72 (95% CI 10.82, 266.73), Conclusion:Muscle weakness occurred in 24% of BoNTA patients; it was significantly more common with BoNTA than placebo	
Hyperesthesia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	BoNTA 6.0% , placebo 1.4% RR 3.91 (95% CI 1.50, 10.24 Conclusion: Hyperesthesia occurred in 6.0% of BoNTA recipients and was more common compared with placebo.	⊕⊕◯◯ LOW
Headache, Injection site pain, hypertonia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Imprecision[3] (-1), Indirectness[4] (-1)	Headache: BoNTA 6.9 % , placebo 5.3% RR 1.34, 95% CI 0.78, 2.30 Injection site pain: BoNTA 5.6% , placebo 3.9% RR 1.16 (0.63, 2.14) Hypertonia: BoNTA 7.2% , placebo 1.4 % RR 4.95 (95% CI 0.72, 34.09) Conclusion: There were no statistical differences between groups for these adverse events	⊕⊕◯◯ LOW

*Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† In Mathew 2005, the most frequently reported adverse events for the BoNTA group were muscular weakness, neck pain, headache, and blepharoptosis. The most frequently reported adverse events for the placebo group were headache and injection-site hemorrhage. Additional treatment-related adverse events reported by ≥ 3 patients in either group were neck rigidity, shoulder/arm pain, injection site pain, pain, face pain, dysphagia, muscular weakness, hypertonia, hyperesthesia, dizziness, pharyngitis, skin tightness, and visual disturbance. In Silberstein 2005, the relationship of adverse events to the study treatment was assessed by the investigator. The most frequently reported treatment related AEs in the BoNTA group were muscular weakness (in areas of injection sites), neck pain, neck rigidity, injection pain, hypertonia, headache, shoulder/arm pain, and hypesthesia. The most frequently reported adverse events in the placebo group were injection-site pain and headache. Additional treatment related AEs reported by ≥ 3% of patients in either treatment group were blepharoptosis, dysphagia, asthenia, back pain, injection-site stinging, and migraine

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

BoNTA versus Topiramate Safety Results: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Reasons for Downgrading	Conclusion*	Quality
Chronic Daily Headache: BoNTA versus Topiramate						
Nausea†	12 weeks	1RCT (Cady 2011)	N= 59	Indirectness[1] (-1), Imprecision[3] (-1)	BoNTA 59.1% , topiramate 27.3% RR: 2.2, 95% CI 1.0, 4.7 Conclusion: Nausea was two times more common with BoNTA than with topirimate	⊕⊕◯◯ LOW
Mild fatigue	12 weeks	1RCT (Cady 2011)	N= 59	Indirectness[1] (-1), Imprecision[3] (-1)	BoNTA 72.7%, topiramate 68.2%, RR: 1.0, 95% CI 0.7, 1.6 Conclusion: There was no difference between groups.	⊕⊕◯◯ LOW

*Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† The most frequently reported adverse events for both groups were mild fatigue, nausea, difficulty concentrating or with memory, and mood swings. Cady 2011 did not give details on additional adverse events.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Massage versus Sham Safety Results: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion*	Quality
Chronic Daily Headache: Massage vs. Sham						
Minor fever, mild soreness, and other discomfort	3-9 wks.	1 RCT (Chatchawan 2014)	72	Imprecision[3] (-1), Indirectness[4] (-1)	17% (6/36) vs. 14% (5/36) RR 1.2 (95% CI 0.4, 3.6) Conclusion: No statistical difference between the massage and the sham ultrasound group.	⊕⊕◯◯ LOW

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Key Question 3 Strength of Evidence Summary: Differential Efficacy and Harms

Exposure	Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Chronic Migraine: Acupuncture versus Usual Care, Differential Efficacy and Harms							
Baseline headache score; Headache diagnosis; Age; Sex; Chronicity	Headache score	36 wks.	1 RCT (Vickers 2004)	301	Risk of Bias[1] (-1), Imprecision[3] (-1) Indirectness[4] (-1), HTE-related[5] (-1)	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). Improvements following acupuncture compared with usual care were larger for patients with a migraine (4.9; 95% CI 2.4, 7.5; n=284) versus a CTTH (1.1, 95% CI -2.4, 4.5); n=17) diagnosis; however no interaction was seen and the small number of CTTH patients may have precluded an effect in this population. Age, sex and chronicity did not modify the treatment effect.	⊕○○○ INSUFFICIENT
Chronic Migraine: Acupuncture versus Topiramate, Differential Efficacy and Harms							
Baseline headache days; various other demographic and headache characteristics	≥50% reduction from baseline in moderate/ severe headache days	36 wks.	1 RCT (Yang 2013	66	Imprecision[3] (-1) Indirectness[4] (-1), HTE-related[5] (-1)	Baseline headache days (any and moderate/severe) was found to modify treatment effect such that patients with higher (≥20 days/mo.) as	⊕○○○ INSUFFICIENT

Exposure	Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
						compared with lower (<20 days/mo.) frequency showed significantly greater improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect	
Chronic Tension Type Headache: Manual Therapy versus Usual Care, Differential Efficacy and Harms							
Comorbid migraine	Headache days	18 wks.	1 RCT (Castien 2011)	82	Risk of Bias[1] (-1), Imprecision[3] (-1) Indirectness[4] (-1), HTE-related[5] (-1)	No differential effect of treatment was seen for the subgroup of patients with comorbid migraine versus without migraine: mean difference in reduction in headache frequency was 5.1 days (95% CI 1.1, 9.2) versus 6.3 days (95% CI 4.2, 8.5), respectively; no formal test for interaction was performed.	⊕◯◯◯ INSUFFICIENT

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 for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Comparisons of an intervention to placebo or usual care is considered indirect.

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

5. Subgroup analysis not preplanned or unknown
6. Statistical test for homogeneity or interaction not performed

REFERENCES

1. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
2. Aurora SK, Dodick DW, Diener HC, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta neurologica Scandinavica 2014;129:61-70.
3. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia : an international journal of headache 2010;30:793-803.
4. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache 2011;51:1358-73.
5. Batty AJ, Hansen RN, Bloudek LM, et al. The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK. J Med Econ 2013;16:877-87.
6. Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011;51:21-32.
7. Carlsson J, Augustinsson LE, Blomstrand C, Sullivan M. Health status in patients with tension headache treated with acupuncture or physiotherapy. Headache 1990;30:593-9.
8. Castien RF, van der Windt DA, Grooten A, Dekker J. Effectiveness of manual therapy for chronic tension-type headache: a pragmatic, randomised, clinical trial. Cephalalgia : an international journal of headache 2011;31:133-43.
9. Chatchawan U, Eungpinichpong W, Sooktho S, Tiamkao S, Yamauchi J. Effects of Thai traditional massage on pressure pain threshold and headache intensity in patients with chronic tension-type and migraine headaches. Journal of alternative and complementary medicine 2014;20:486-92.
10. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia : an international journal of headache 2010;30:804-14.
11. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50:921-36.
12. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache 2008;48:201-9.
13. Hamdy SM, Samir H, El-Sayed M, Adel N, Hasan R. Botulinum toxin: could it be an effective treatment for chronic tension-type headache? The journal of headache and pain 2009;10:27-34.
14. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://handbook.cochrane.org.2011.
15. Karadas O, Inan LE, Ulas U, Odabasi Z. Efficacy of local lidocaine application on anxiety and depression and its curative effect on patients with chronic tension-type headache. European neurology 2013;70:95-101.
16. Karst M, Rollnik JD, Fink M, Reinhard M, Piepenbrock S. Pressure pain threshold and needle acupuncture in chronic tension-type headache--a double-blind placebo-controlled study. Pain 2000;88:199-203.
17. Kokoska MS, Glaser DA, Burch CM, Hollenbeak CS. Botulinum toxin injections for the treatment of frontal tension headache. The journal of headache and pain 2004;5:103-9.

18. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology 2011;77:1465-72.
19. Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical neurology and neurosurgery 2010;112:463-6.
20. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 2005;45:293-307.
21. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache 2009;49:1466-78.
22. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. Journal of neurology 2013;260:2793-801.
23. Nelson CF, Bronfort G, Evans R, Boline P, Goldsmith C, Anderson AV. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. Journal of manipulative and physiological therapeutics 1998;21:511-9.
24. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia : an international journal of headache 2004;24:60-5.
25. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia : an international journal of headache 2004;24:675-80.
26. Ruggeri M. The cost effectiveness of Botox in Italian patients with chronic migraine. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2014;35 Suppl 1:45-7.
27. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 2001;41:658-64.
28. Silberstein SD, Gobel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia : an international journal of headache 2006;26:790-800.
29. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clinic proceedings 2005;80:1126-37.
30. Soderberg E, Carlsson J, Stener-Victorin E. Chronic tension-type headache treated with acupuncture, physical training and relaxation training. Between-group differences. Cephalalgia : an international journal of headache 2006;26:1320-9.
31. Soderberg EI, Carlsson JY, Stener-Victorin E, Dahlof C. Subjective well-being in patients with chronic tension-type headache: effect of acupuncture, physical training, and relaxation training. The Clinical journal of pain 2011;27:448-56.
32. Tavola T, Gala C, Conte G, Invernizzi G. Traditional Chinese acupuncture in tension-type headache: a controlled study. Pain 1992;48:325-9.
33. Teepker M, Hotzel J, Timmesfeld N, et al. Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia : an international journal of headache 2010;30:137-44.
34. Vickers AJ, Rees RW, Zollman CE, et al. Acupuncture for chronic headache in primary care: large, pragmatic, randomised trial. Bmj 2004;328:744.
35. Vickers AJ, Rees RW, Zollman CE, et al. Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis. Health Technol Assess 2004;8:iii, 1-35.

36. Vo AH, Satori R, Jabbari B, et al. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviation, space, and environmental medicine 2007;78:B113-8.
37. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical journal of pain 2013;29:982-7.
38. Yang CP, Chang MH, Liu PE, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. Cephalalgia : an international journal of headache 2011;31:1510-21.

1. Appraisal

1.1 Background and Rationale

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. 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, 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 chronic migraine and chronic tension-type headache. Interventions to be evaluated in this report include botulinum toxin injections, trigger point injections, transcranial magnetic stimulations, manipulation/manual therapy, acupuncture and massage. This report will focus on use of such interventions for the prevention of CTTH and CM

OnabotulinumtoxinA (onaBoNT-A, Botox) is a type of botulinum toxin that is FDA approved for the prophylaxis of with chronic migraine (≥ 15 days per months with headache lasting ≥4 hours a day) in adults. It has been associated with reduction in the number chronic migraine headaches attacks.

Trigger point injections involve injection of local anesthetic or other injectate into trigger points which are muscle areas that are very irritable, show a band of tightness in the area of muscle itself, and, when pressed, produce a twitch within the affected muscle. Trigger point injections may be done in conjunction with peripheral nerve blocks which involves injection of medication on or near nerves. Peripheral nerve blocks are not included in this review.

Transcranial magnetic stimulation involves use of a portable device that is held to the scalp and sends a series of brief magnetic pulses through the skin. The FDA has approved three devices for treatment of

pain associated with migraine with aura, which are the Cerena TMS device, the Spring TMS device, and the eNeura sTMS mini device.

Manual therapies, including manipulation, involve passive movement of joints and soft tissues by hands or equipment to treat musculoskeletal and disability including headache and may be used by physiotherapists, chiropractors, osteoapths and others. Massage is often classified as a manual therapy and involves systematic and methodical manipulation of body tissues, including trigger points, usually with the hands.

Acupuncture involves the insertion of solid, filiform needles into the body (with or without manual or electrical stimulation) to directly or indirectly stimulate acupuncture points, including trigger points, and other tissues to promote health and treat organic or functional disorders.

Policy Context

Interventions for treatment of headaches include botulinum toxin injections, trigger point injections or dry needling, transcranial magnetic stimulations, acupuncture, manipulation, manual therapy and massage. The topic was proposed to determine the safety, efficacy and value of interventions for treatment of migraines and other headache types. The topic was selected based on medium/high concerns for safety, efficacy and cost.

Objectives

The primary aim of this assessment is to systematically review and synthesis published evidence on the efficacy, safety, and cost-effectiveness of botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults.

1.2 Key Questions

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 botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?
2. What is the evidence regarding short- and long-term harms and complications of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?
3. Is there evidence of differential efficacy, effectiveness, or safety of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment

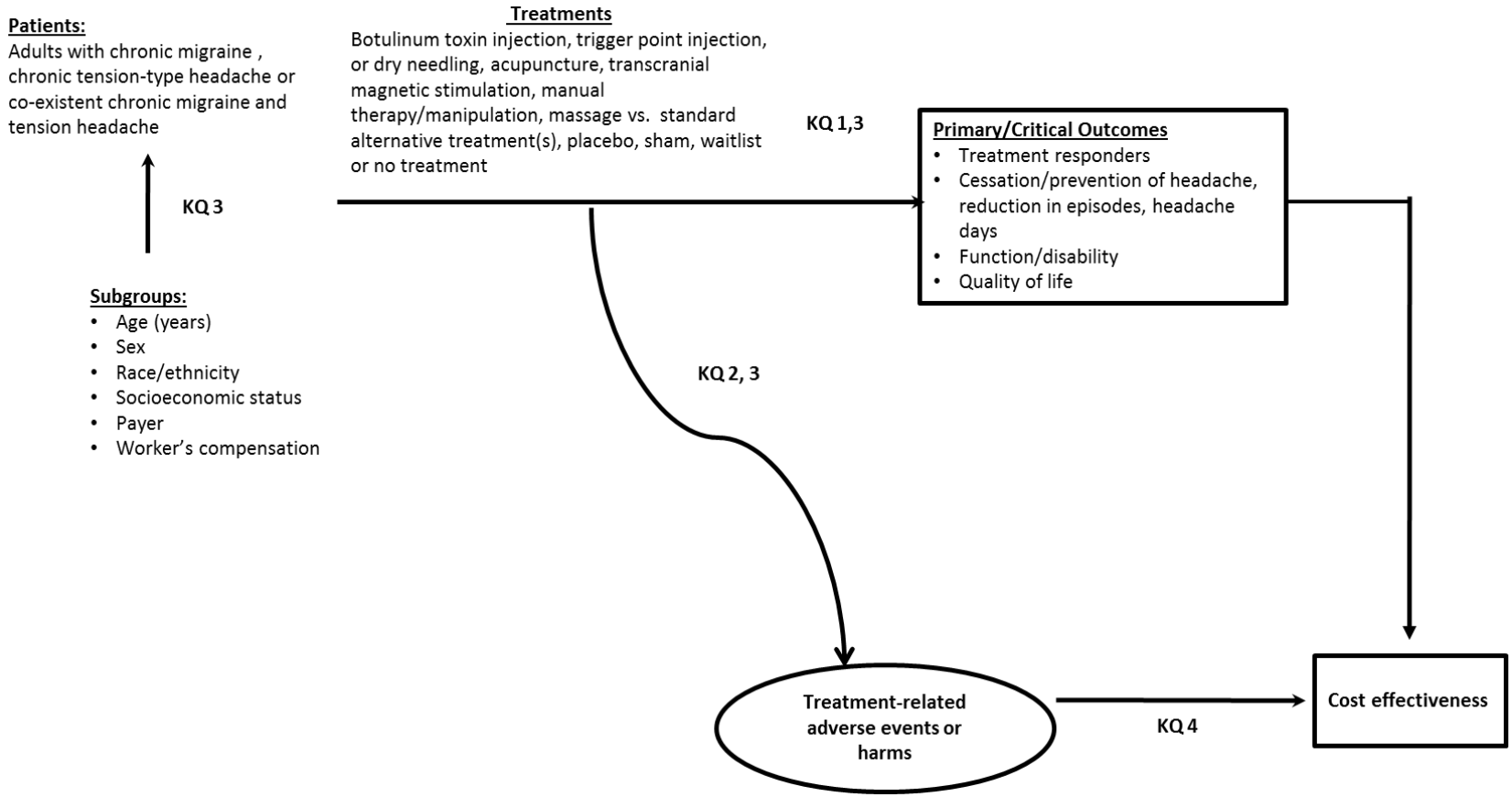
options, placebo sham, waitlist or no treatment? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation.

4. What is the evidence of cost-effectiveness of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

Inclusion and exclusion criteria are summarized as follows (see full report for details):

- **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. While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions. 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.
- **Interventions:** Botulinum toxin injection, acupuncture, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), trigger point injection (TPI) or dry needling
- **Comparators:** Standard alternative treatment(s), sham, placebo, waitlist or no treatment
- **Outcomes:** Primary/critical outcomes are 1) the proportion of treatment responders, 2) cessation/prevention of headache (including reduction in episodes and headache days), 3) function/disability (based on validated outcomes measures), 4) treatment related adverse events/harms, 5) quality of life. 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.
- **Studies:** Studies must report at least one of the primary outcomes**.** Focus will be on studies with the least potential for bias such as high quality systematic reviews of randomized controlled trials and randomized controlled trials and full economic studies.
- **Timing:** Focus will be on intermediate (>6 months) and long term (> 12months) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Figure 1. Analytic framework



1.3 Outcomes Assessed

The primary outcomes of interest for this report are listed below; these were designated as primary outcomes based on clinical expert input.

- 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. BURMIG, burden of migraine; HADLI, Headache Activities of Daily Living Index; HDI, Headache Disability Index (Inventory); HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test; MIDAS, Migraine Disability Scale) such as those listed in the table below.
- Harms, treatment-related adverse events, treatment discontinuation due to adverse events

The studies included in this assessment used a variety of measures to evaluate treatment outcomes, which are outlined in Table 1 which 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[30]	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
Burden of Migraine (BURMIG)/ EUROLIGHT[21,22]	Patient	77 items (BURMIG), assessing headache characteristics, migraine associated disability, comorbidities, management, and the consequences of headache on the patient lives. 103 items (EUROLIGHT) assessing primary headache disorders in terms of burden, quality of life, anxiety and depression, and disease management.	Unclear	Unclear	
Clinical Global Impression (CGI)[81]	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	
Hamilton Anxiety Scale[84]	Clinician	14 items rated on a 0-4 scale • Anxious mood • Tension • Fears • Insomnia • Intellectual • Depressed mood • Somatic (muscular) • Somatic (sensory) • Cardiovascular symptoms • Respiratory symptoms • Gastrointestinal symptoms	0 – 56 points	Higher score = higher level of anxiety	

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
		• Genitourinary symptoms • Autonomic symptoms • Behavior at interview			
Hamilton Depression Scale[85]	Clinician	17 items rated on either a 0 – 2 or 0 – 4 scale: • Depressed mood • Guilt feelings • Suicide • Insomnia early • Insomnia middle • Insomnia late • Work and activities • Retardation: psychomotor • Agitation • Anxiety (psychological) • Anxiety somatic • Somatic symptoms (gastrointestinal) • Somatic symptoms general • Genital symptoms • Hypochondriasis • Loss of weight • Insight	0 – 52 points	Higher score = higher level of depression	
Headache Activities of Daily Living Index (HADLI)[169]	Patient	9 items (0 – 5 points each) • Personal care • Lifting • Reading (include computers) • Sleeping • Exercising • Social activities • Work • Driving (include traveling) • Recreation	0 – 45 points, converted to a total percent score of 100	Unclear	
Headache Disability Questionnaire (HDQ)[132]	Patient	9 items (0 – 10) regarding headache pain severity and impact on daily activities (e.g., household work, school, socializing).	0 – 90 points	Higher score = greater impact of headache on quality of life and activities of daily living	
Headache Impact Test-6 (HIT-6)[33]	Patient	Six items, each rated and scored "Never" (6 points), "Rarely" (8 points), "Sometimes" (10 points), "Very often" (11 points), or "Always" (13 points) regarding headache pain severity, impact on daily activities (e.g., household work, school, socializing), desire for rest, feelings of tiredness, feelings of irritation, and ability to concentrate.	36 – 78 points	• Higher scores = higher impact on activities of daily living • Little or no impact: <46 • Some impact: 50 – 55 • Substantial impact: 56 – 59	MID for chronic daily headache defined as ≥ 15 days per month: -2.3 (-4.3, -0.3)

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
				• Severe impact: 60 – 78	
Headache Index (HI) Score[129]	Patient	Weekly sum of daily 11-box ordinal scale (0 = no pain, 10 = unbearable pain)	0 – 70 points	Lower score = lesser pain	NR
Henry Ford Hospital Headache Disability Inventory (HDI)[54,93]	Patient	25 items ("No" [0 points], "Sometimes" [2 points], "Yes" [4 points]) assessing the impact of headache on daily living, including feelings of anger, outlook on the world, restriction in activities of daily living, physical tension, etc.	0 – 100 points, can be converted to a total percent score of 100	For total points: The lower the score, the lower the disability; a decrease of at least 16 points is considered to be a clinically significant improvement[54]. For total percent: • 10 – 28% = mild disability • 30 – 48% = moderate disability • 50 – 68% = severe disability • >70% = complete disability	NR
Hospital Anxiety and Depression Scale (HADS)[157]	Patient	Anxiety: 7 questions with a four point (0—3) response scale Depression: 7 questions with a four point (0—3) response scale	Anxiety: 0—21 points Depression: 0—21 points	Greater number = greater severity of disorder: • 0—7 points = normal • 8—10 points = indicative of presence of disorder • ≥ 11 points = probable presence of disorder	NR
Migraine Disability Assessment Scale (MIDAS)[163]	Patient	Five items (number of days reported for each), assesses how many days of work/school, productivity, 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:	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
				• 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	
Migraine Specific Questionnaire (MSQ)[95]	Patient	3 health related quality of life (HRQoL) dimensions, each with subgroups: • Role Function-Restrictive dimension: 7 items that describe the degree migraine limits performance of normal activities • Role Function-Preventive dimension: 5 items that describe the degree migraine interrupts normal activities • Emotion Function dimension: 4 items that measure the emotional effect of migraine	0 – 100 points	Higher score = higher quality of life	Chronic Migraine[7]: • Role Function-Restrictive: 10.9 (9.4, 12.4) • Role Function-Preventative: 8.3 (6.7, 9.9) • Role Function-Emotional: 12.2. (10.2, 14.3)
Minor Symptom Profile Questionnaire (MSEP)[159]	Patient	24 total items ranked on a visual analog scale with three major dimensions and 9 independent items: • Contentment (5 items): Happiness, tranquility, self-control, decisiveness, self-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	0 –10 cm or 0 – 100 mm	Lower score = positive feelings	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
		• Appetite • Sweating • Physical competence			
Mood Adjective Check List (MACL)[52]	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	
Physician Global Assessment[50]	Physician	9 point scale as follows: • + 4 Clearance of signs and symptoms (about 100% improvement) • + 3 Marked improvement (about 75% improvement) • + 2 Moderate improvement (about 50% improvement) • +1 Slight improvement (about 25% improvement) • 0 Unchanged • -1 Slight worsening (about 25% worse) • -2 Moderate worsening (about 50% worse) • -3 Marked worsening (about 75% worse) • -4 Very marked worsening (about 100% worse)	-4 to 4 points	Higher score = greater response to treatment	
Psychosocial Adjustment to Illness Scale (PAIS)[63]	Clinician	7 domains, total of 46 items rated on a 4 point scale (0 – 3 points): • 1st domain: Health care orientation • 2nd domain: Vocational environment • 3rd domain: Domestic environment • 4th domain: Sexual relationships • 5th domain: Extended family relationships • 6th domain: Social environment • 7th domain: Psychological distress	0 – 138 points	Higher score = lower psychosocial adjustment to illness	

Sickness Impact Profile (SIP)[35]	Patient	12 categories (136 statements):
		• Physical dimension categories
		  ○ Ambulation
		  ○ Body care
		  ○ Movement
		• Psychosocial dimension categories
			0 – 100 points (subscale score)	Higher score = greater disability	NR

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID*
		○ Emotional behavior ○ Social interaction ○ Alertness behavior ○ Communication • Independent categories ○ Eating ○ Work ○ Sleep and rest ○ Home management ○ Recreation and pastime			
Short Form-36 (SF-36)[175,176]	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
West Haven-Yale Multidimensional Pain Inventory Instrument[101]	Patient	3 parts: • Part I (0 – 6 points) ○ Pain severity and suffering ○ Pain-related life interference ○ Dissatisfaction with level of functioning ○ Appraisal of support ○ Perceived life control ○ Affective distress • Part II (0 – 6 points): patients evaluated 21 behavioral items of how others responded to displays of pain and suffering • Part III (0 – 6 points): patients evaluated how often they performed 30 common domestic activities	1 – 364 points	Higher score = greater impact of chronic pain	

*MCIDs were only looked for if an outcome was significant in any of the results of this report, those for which we could not locate a MCID in the literature are reported as NR; all others are left blank.
†Study administered to patients for self-assessment but original citation indicates assessment should be done by clinician.
‡Measurements taken by study authors do not appear to be consistent with original outcome measure.

1.4 Washington State Utilization and Cost Data

Treatment of chronic migraine and chronic tension-type headache

Populations

The *Chronic Migraine and Chronic Tension-type Headache* (migraine) analysis includes member utilization and cost data from the following agencies: PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan); PEBB Medicare, the Department of Labor and Industries (LNI) workers' compensation plan; and the HCA Medicaid (formerly Fee-for-Service) and the Managed Care (MCO) Medicaid program.

The analysis period was five (5) calendar years, 2012 - 2016. Primary population inclusion criteria included age greater than 17 years old at time of service AND experiencing at least one of the CPT/HCPCS codes from Table I. Denied claims were excluded from the analysis.

Methods

Migraine and tension headache treatments were calculated based on an individual experiencing a paid provider-patient face-to-face, on a specific date *and* including at least one of the CPT codes from Table I. Data evaluation included examining utilization by member; by treatment modality (Table I, Modality), and by total claims' cost incurred by a member on the date of their migraine/tension headache treatment (Total Claims).

Analyzing total claims for the date of service provided an enhanced view of the cost of a migraine/tension headache treatment (e.g., facility costs, labs, etc.). "Dollars" refers to paid dollars.

Table I. CPT Descriptions

CPT		Modality
64612	Chemo denervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (e.g., for blepharospasm,	Botox
64613	Deleted 1.1.2015	Botox
61615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine)	Botox
J0585	Injection, onabotulinumtoxina, 1 unit	Botox
20553	Injection(s); single or multiple trigger point(s), 3 or more muscles	Trigger Point Injections
20552	Injection(s); single or multiple trigger point(s), 1 or 2 muscle(s)	Trigger Point Injections
90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management	Transcranial Magnetic Stimulation

CPT		Modality
90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session	Transcranial Magnetic Stimulation
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management	Transcranial Magnetic Stimulation
97140	Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)	Manual Manipulation
97124	Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)	Manual Manipulation
97799	Unlisted physical medicine/rehabilitation service or procedure Per American Physical Therapy Assoc 2014	Dry needling at trigger points
20999	Unlisted procedure, musculoskeletal system , general Regence BlueShield State of Washington	Dry needling at trigger points
S8930	Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient	Acupuncture
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient	Acupuncture
97813	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient	Acupuncture
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)	Acupuncture
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)	Acupuncture

Table II. Definitions for Utilization Tables

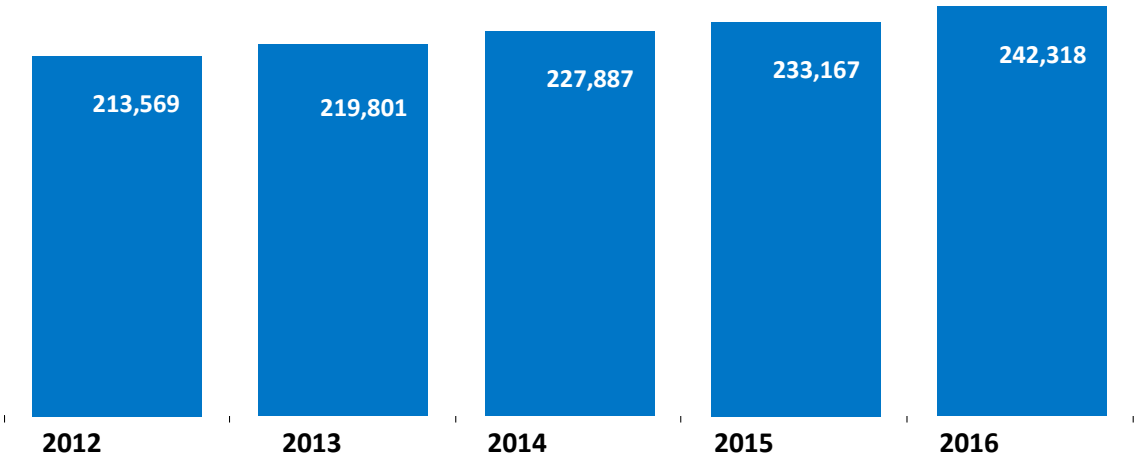
Unique patients	Non-duplicated patient by year, reported by agency
Total treatments	Treatment defined as a single patient-provider face-to-face on a specific date.
Average treatment/patient	Total treatments/total unique patients
Dollars paid by total treatments	Paid dollars for all migraine and tension headaches treatments
Average dollars/patient	Total paid dollars for services received on the date of the treatment
Average dollars/treatment	Dollars paid on date of treatment/ Total treatments -- annual
Treatments/1,000 members	Dollars paid on date of treatment/ Total treatments -- annual

Demographics

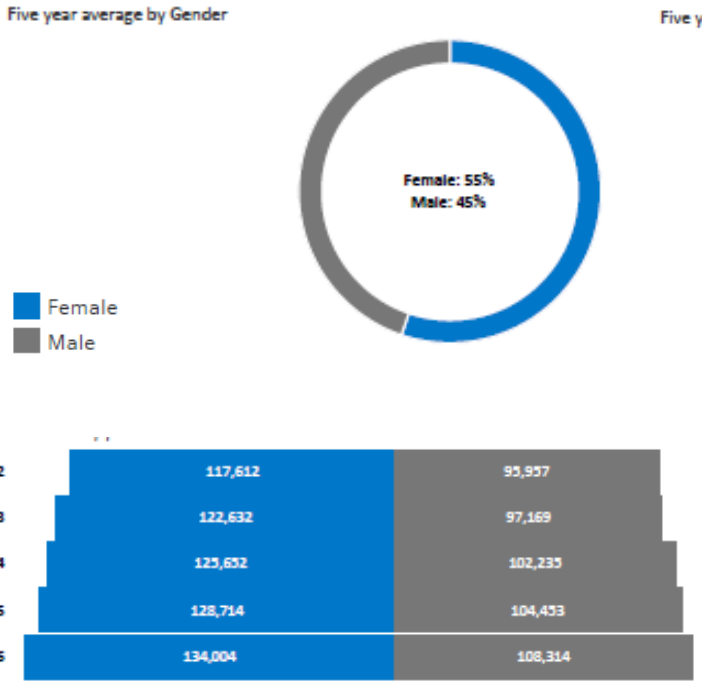
The following graphs and charts depict the populations of study, PEBB and HCA Medicaid, and Managed Care Medicaid. Each agency population is analyzed over a five (5) year period.

PEBB demographics 2012 – 2016
PEBB/UMP and Medicare/PEBB

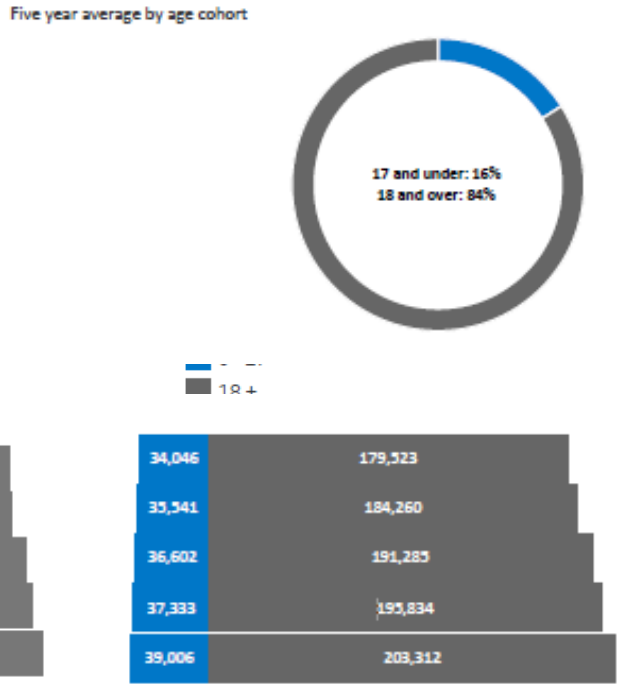
PEBB population growth over time



PEBB distribution by year: Gender and age cohorts with 5-year average



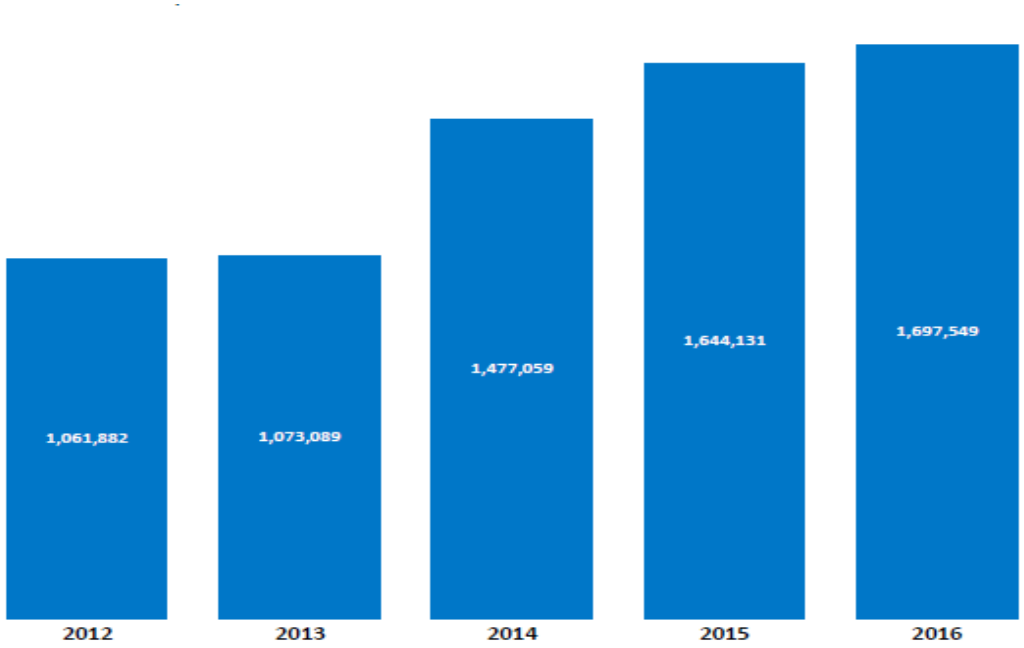
Distribution by Gender

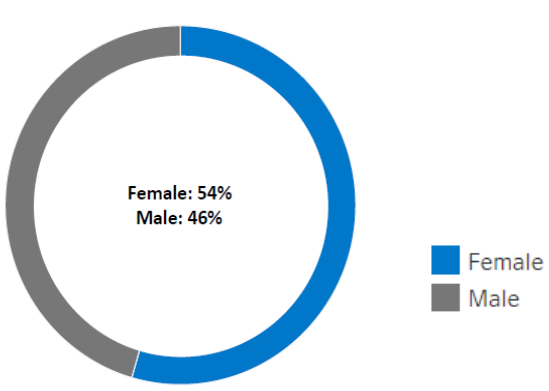


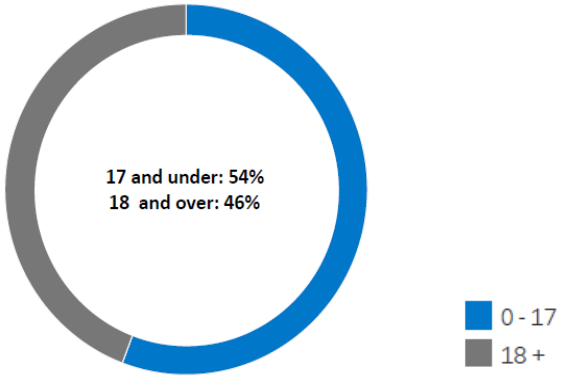
Distribution by Age

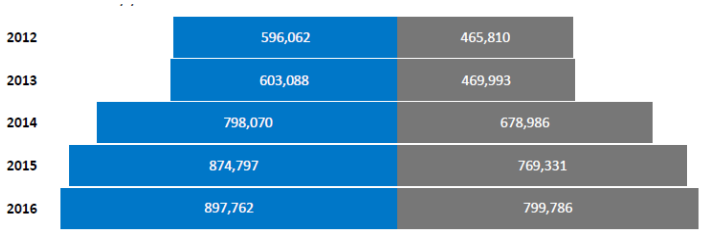
Medicaid demographics 2012 – 2016

Managed and HCA Medicaid Population Growth over Time

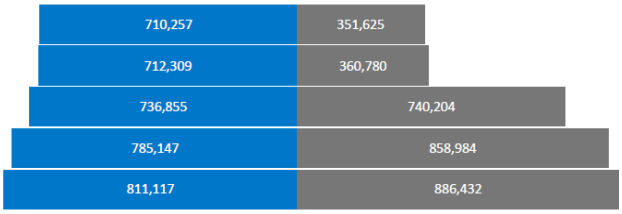








Distribution by Gender



Distribution by Age

PEBB/UMP, Medicare/PEBB, HCA Medicaid, MCO Medicaid, LNI

Utilization and Costs: Chronic Migraines and Tension Headaches

Medicaid MCO	2012	2013	2014	2015	2016
Unique Patients	**67**	**105**	**263**	**551**	**811**
Total Treatments	**187**	**485**	**1061**	**1061**	**1859**
Average Treatments/Patient	**2.8**	**4.6**	**4.0**	**1.9**	**2.3**
Dollars Paid by Total Treatment	**$24,510**	**$49,766**	**$134,084**	**$363,277**	**$589,351**
Average Dollars/Patient	**$366**	**$474**	**$510**	**$659**	**$727**
Average Dollars/Treatment	**$131**	**$103**	**$126**	**$342**	**$317**

Medicaid HCA	2012	2013	2014	2015	2016
Unique Patients	**37**	**21**	**33**	**50**	**43**
Total Treatments	**122**	**29**	**48**	**76**	**76**
Average Treatments/Patient	**3.3**	**1.4**	**1.5**	**1.5**	**1.8**
Dollars Paid by Total Treatment	**$18,129**	**$4,598**	**$12,934**	**$23,383**	**$10,813**
Average Dollars/Patient	**490**	**219**	**392**	**468**	**251**
Average Dollars/Treatment	**149**	**159**	**269**	**308**	**142**

Medicaid MCO and HCA (Combined)	2012	2013	2014	2015	2016
Treatments/1,000	**0.88**	**1.42**	**1.50**	**1.32**	**2.18**

LNI	2012	2013	2014	2015	2016
Unique Patients	4	7	10	19	34
Total Treatments	7	8	15	41	64
Average Treatments/Patient	1.8	1.1	1.5	2.2	1.9
Dollars Paid by Total Treatment	$5,886	$7,490	$21,811	$23,341	$40,399
Average Dollars/Patient	$1,472	$1,070	$2,181	$1,228	$1,188
Average Dollars/Treatment	$841	$936	$1,454	$569	$631

PEBB/UMP	2012	2013	2014	2015	2016
Unique Patients	118	168	201	262	285
Total Treatments	653	707	896	1247	1257
Average Treatments/Patient	5.5	4.2	4.5	4.8	4.4
Dollars Paid by Total Treatment	$263,431	$387,153	$499,225	$664,586	$691,698
Average Dollars/Patient	$2,232	$2,304	$2,484	$2,537	$2,427
Average Dollars/Treatment	$403	$548	$557	$533	$550

Medicare/PEB	2012	2013	2014	2015	2016
Unique Patients	17	34	45	55	62
Total Treatments	91	122	188	224	225
Average Treatments/Patient	5.4	3.6	4.2	4.1	3.6
Dollars Paid by Total Treatment	$9,859	$9,860	$9,861	$9,862	$9,863
Average Dollars/Patient	$580	$290	$219	$179	$159
Average Dollars/Treatment	$108	$81	$52	$44	$44

PEBB pays secondary to Medicare; numbers do not reflect true costs.

PEBB/UMP & Medicare/PEBB (Combined)	2012	2013	2014	2015	2016
Treatments/1,000**	4.1	4.5	5.7	7.5	7.3

Figure 1

2012 - 2016

Chronic Migraines and Chronic Tension Headaches

Utilization All Modalities: Average Treatments/Patient by Agency

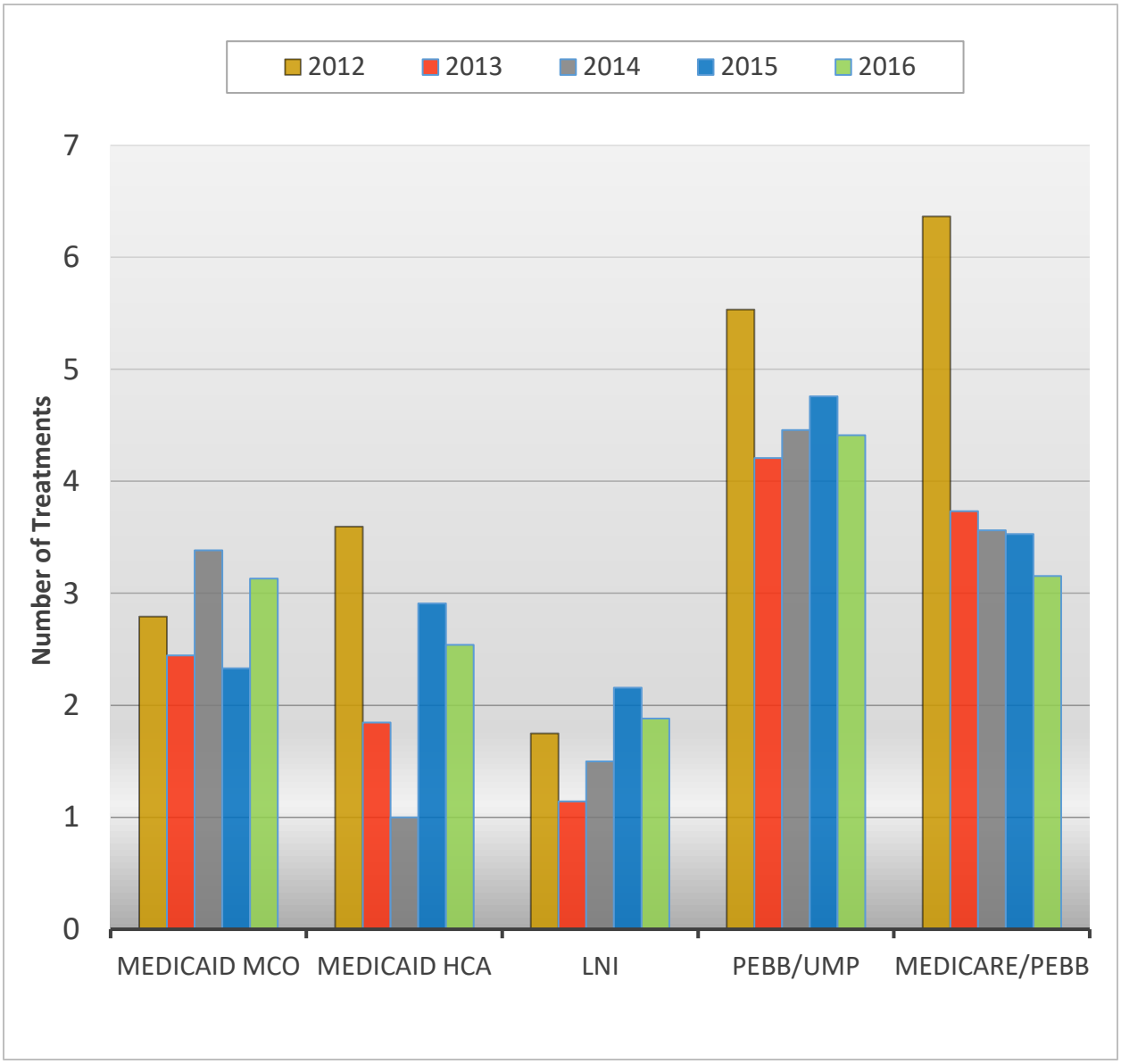


Figure 2

Medicaid MCO

Chronic Migraines and Chronic Tension Headaches Utilization: All Modalities

Total treatments and average dollars/patient

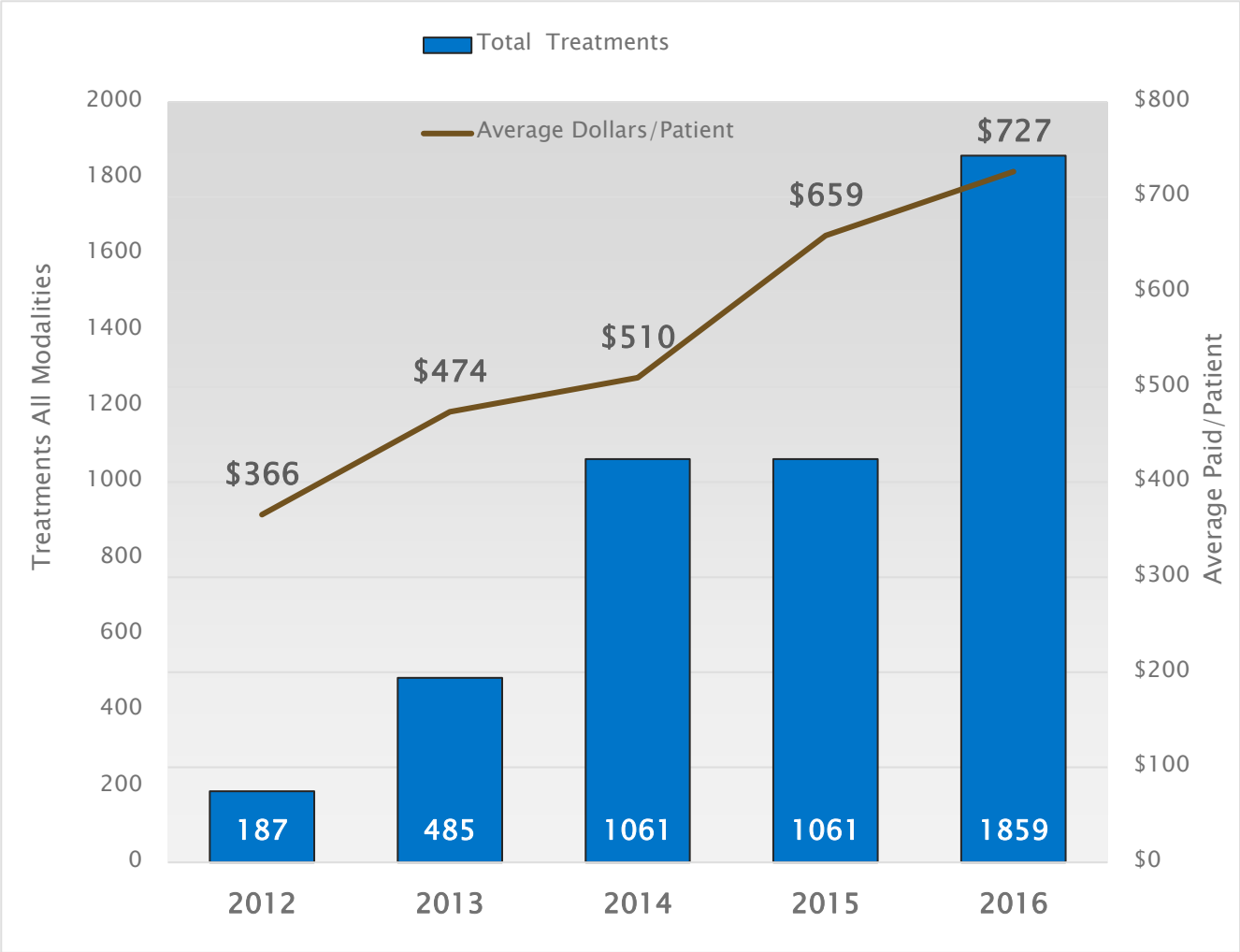
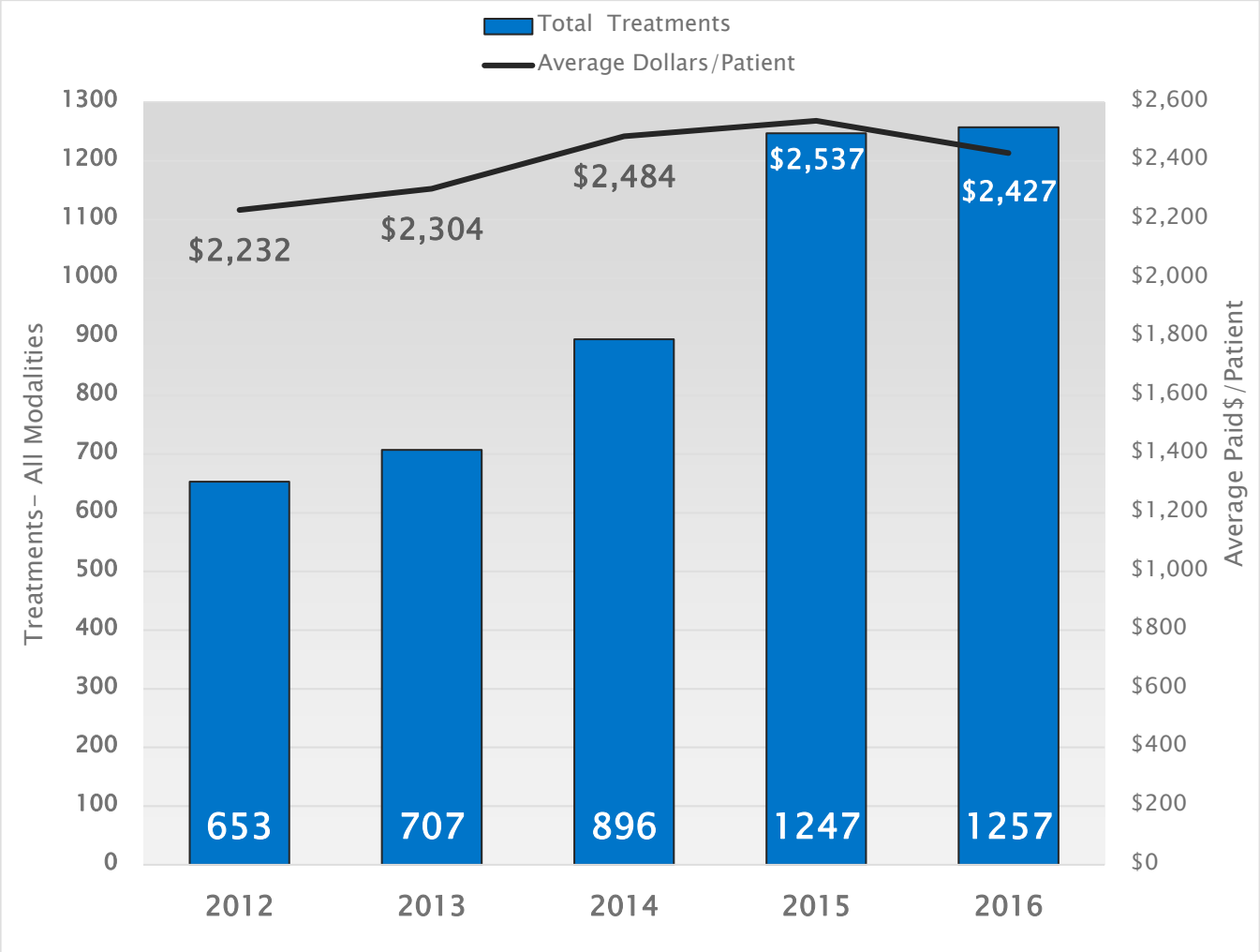


Figure 3

PEBB/UMP

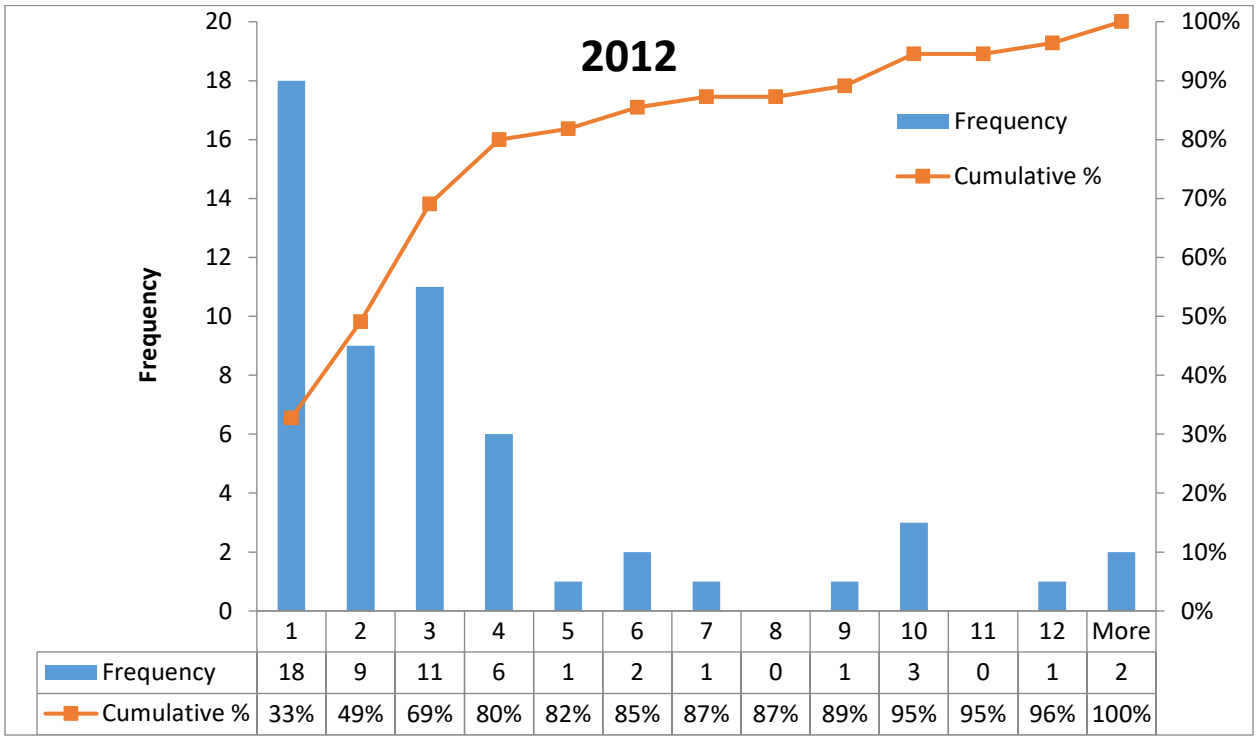
Chronic Migraines and Chronic Tension Headaches Utilization: All Modalities
Total treatments and average dollars/patient
N =1,034



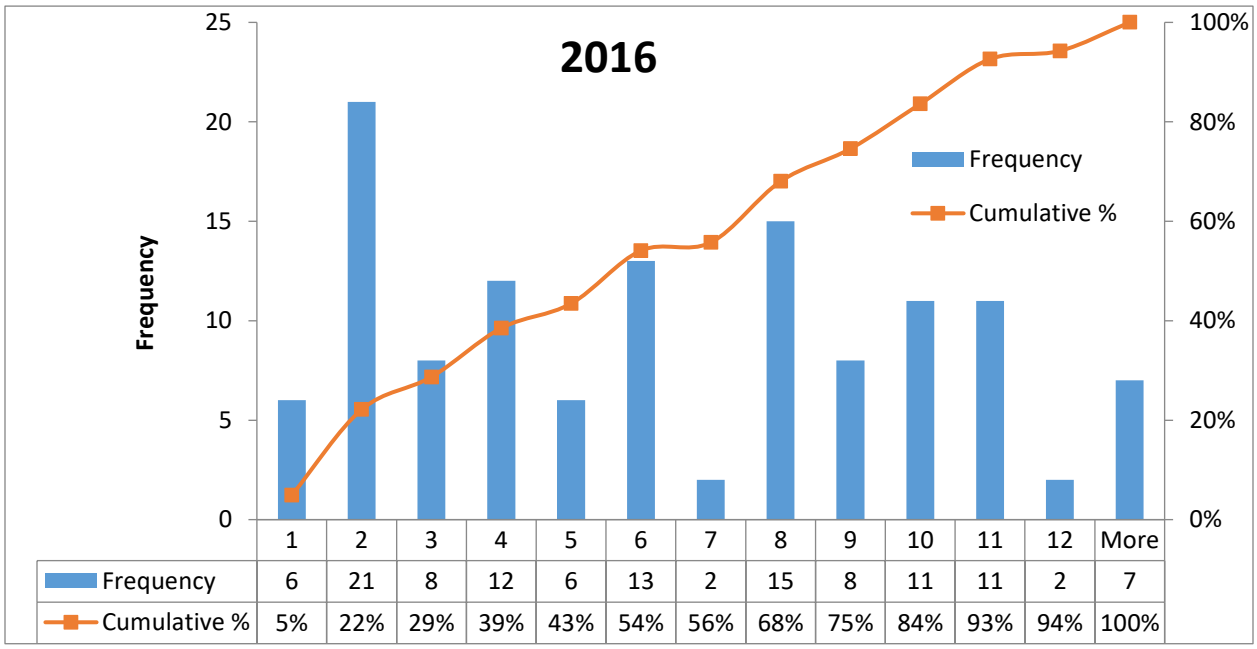
Figures 4 and 5

PEBB/UMP

2012 and 2016
Distribution of the Number of Treatments per Patient
Members with Multiple Years of services
N = 1,034



	1	2	3	4	5	6	7	8	9	10	11	12	More
Frequency	18	9	11	6	1	2	1	0	1	3	0	1	2
Cumulative %	33%	49%	69%	80%	82%	85%	87%	87%	89%	95%	95%	96%	100%

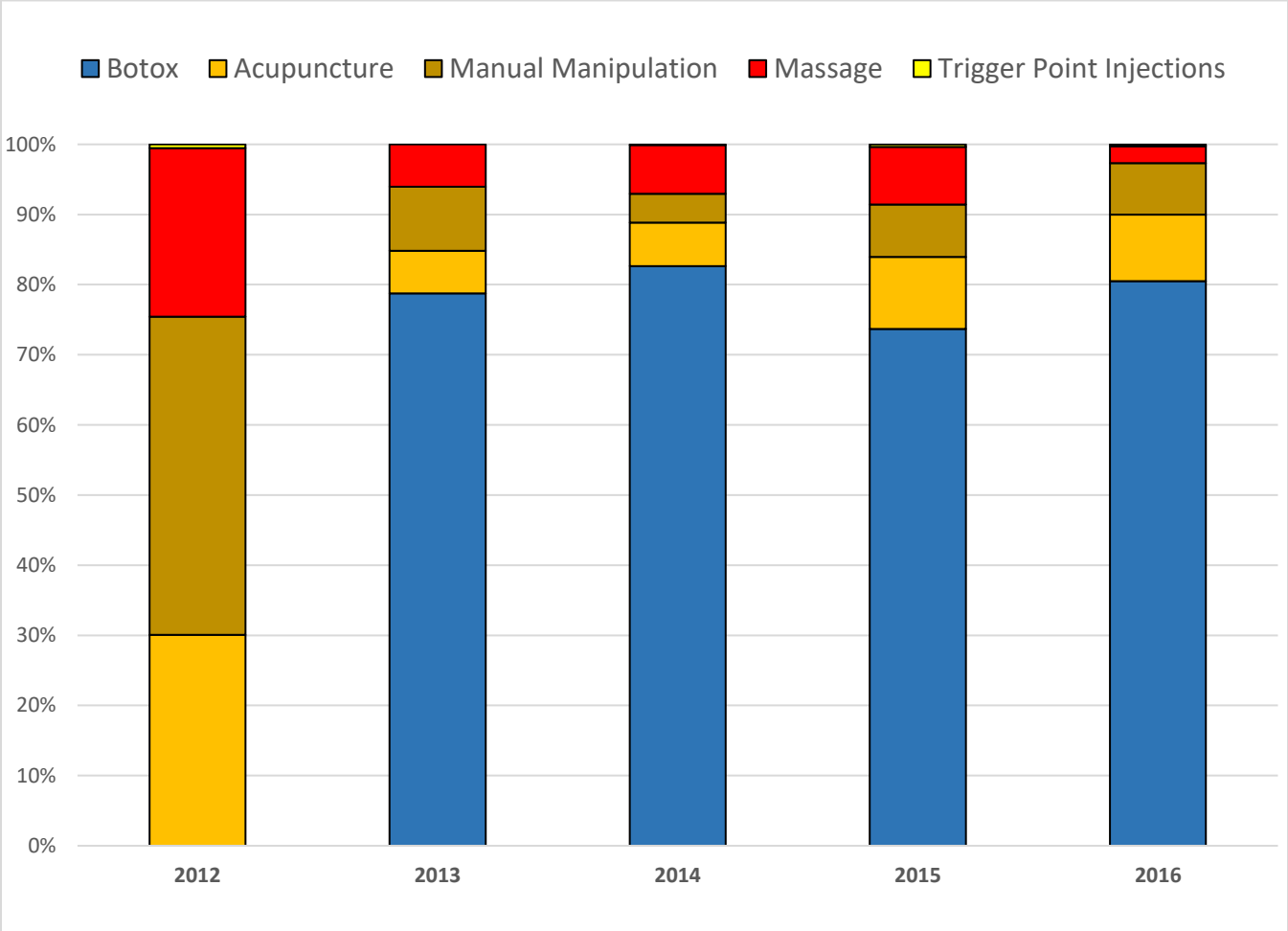


	1	2	3	4	5	6	7	8	9	10	11	12	More
Frequency	6	21	8	12	6	13	2	15	8	11	11	2	7
Cumulative %	5%	22%	29%	39%	43%	54%	56%	68%	75%	84%	93%	94%	100%

Figure 6
2012 – 2016

PEBB UMP

Distribution of Treatment Modalities by Year



2. Background

2.1. Epidemiology and Burden of Disease

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

In an analysis of the 2013 Global Burden of Disease report, headache disorders combined were the third highest cause of years of life lost to disability (YLD).[162] The 2012 National Health Interview Survey (NHIS) reported 17.1% of people had migraine or severe headache in the past 3 months.[46] In 2015, 17.9% of adults had migraine or severe headache in the past three months, nearly a 1% increase from 2012.[3] The 2009 National Ambulatory Medical Care Survey ranked headache/pain in the head as the 20th most common patient-reported reason for outpatient visits, causing 1.2% of total visits.[46] The survey recorded 7.7 billion emergency department (ED) visits due to headache, making it the 4th most common reason for ED visits.[46] 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 in the span of 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.[75,173] The 2015 Global Burden of Disease Study ranked TTH as the second most prevalent disease out of the 310 examined, and reported a 15.3% increase of prevalence TTH from 2005 to 2015.[79] TTH is associated with considerable disability, with a reported 60% of afflicted individuals citing negative impacts on work and social engagement.[19] Prevalence of the chronic form of TTH range from 0.9% to 2.2%.[19] 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.[133]

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. Migraine ranked as the 6th highest cause of YLD worldwide[79] and 1 out of every 7 Americans are affected by migraine annually.[46] Prevalence estimates of chronic migraine (CM) range from 1.4% to 2.2% of the world population.[128] CM is more prevalent in females than males, with both genders experiencing peak prevalence in their 40's.[48] Estimates of annual US costs from emergency department visits to treat migraine range from $646 million to $1.94 billion.[28] Estimates of indirect costs of migraines, which are primarily due to reduced work productivity and missed workdays,[94] range from $5.6 to $17.2 billion worldwide,[61] with a 1999 study from the US estimating indirect costs of migraine to be $13.3 billion.[90]

The public health and economic burdens of chronic primary headache are high. Treatment and prevention of them is of public health importance. Usual management of tension-type headache and migraine include pharmacotherapy, psychological therapy, and physical therapy. In chronic headache disorders, including chronic tension-type headache (CTTH) and chronic migraine (CM), the focus of treatment is on preventative measures. The interventions evaluated in this report are

OnabotulinumtoxinA (BoNTA) injections, acupuncture, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), and trigger point injections (TPIs).

2.1.1. Headache Classification and Types

This report focuses on patients with chronic migraine (CM) and chronic tension-type headache (CTTH) as well as those who have coexistence of migraine and tension-type headache. Although CM and CTTH are explicitly classified in the 2013 International Classification of Headache Disorders, 3rd edition (ICHD-3)[9] the terminology, definitions and criteria have evolved over the past two decades.[100,177] The terminology related to chronic migraine in particular and coexistent migraine and tension type headache appears to vary substantially in clinical practice, in the literature,[19] and in 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"[177] while other sources suggest that combined tension-type and migraine headaches have been referred to as mixed tension migraine,[13] mixed headache syndrome, transformed migraine, chronic migraine and chronic daily headache as well as co-existent migraine and tension headache.[6,105] In addition, the pathophysiology of migraine and tension-type headaches is not well understood and some have suggested that they exist along a continuum. Context with regard to 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 for the purpose of ensuring coherent patient populations for research in headache disorders,[177] but also provide a basis for clinical diagnosis.

The (ICHD-3) classifies headaches as primary or secondary.[9] 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).[9] TTH and migraines are the disorders included in this report and are two of the most common primary headaches.[143] Common causes of secondary headache are cerebrovascular disease, infection, musculoskeletal disorders, and intracranial space-occupying lesions.[76] Medication overuse headache are another common type of secondary headache. Secondary headaches are not evaluated in this report.

Headaches are also classified with respect to frequency in the ICHD-3. Individuals with episodic headaches experience 0 to 14 headache days per month[100] 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.

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. As a consequence, the terminology used in clinical studies has also varied. For purposes of this report, we have generally followed the classifications of headache as specified by study authors.

For the purposes of this 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 (CDH). This is not listed as an official classification.

2.1.2. 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 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[9]:

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[5] resulting in visual, sensory, speech and/or language, motor, brainstem, or retinal symptoms. About 20% of migraine patients are estimated to experience aura.[177] The diagnostic criteria from ICHD-3 for migraine with aura are as follows[9]:

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. 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.[100] It is estimated that EM may progress to CM at a rate of 2.5% per year[39] with CM remitting to EM at an estimated 2-year transition rate of 26%.[117] Certain classes of medication used to treat episodic migraine appear to increase the risk of developing CM including barituates 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.[39,100] The American Migraine Prevalence and Prevention study suggest 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 int hose with fewer than 10 headache days per month but increased risk of CM in those with ≥10 headaches per month.[113]

Factors associated with CM include female sex, lower household income and lower socioeconomic status (SES),[48,178] in addition to potentially modifiable risk factors such as overuse of acute headache medication,[153] depression,[37] obesity,[36] anxiety, caffeine consumption, and snoring.[111] 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.

Chronic Migraine Usual Care/Comparators

In general, lifestyle and trigger management, acute treatments to mitigate attacks, and preventative treatments are the three main approaches used to treat CM.

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[177] is an important part of the lifestyle change component of management. Usual management of chronic migraine includes psychological therapy as well as pharmacological treatment.[131]

Management of acute episodes for chronic migraine generally focus on pharmaceutical agents. Acute treatment starts with non-steroidal anti-inflammatory drugs (NSAIDs) or mixed analgesics,[10] drugs that have either one or more type of analgesics or an analgesic combined with another medicine. If migraines are unresponsive to this first line defense, migraine-specific agents such as triptans or ergotamine are used.[10] Triptans are serotonin receptor agonists that act to relieve swelling and narrow blood vessels.[14] Ergotamine is also a vasoconstrictor and serotonin agonist,[2] but it targets different receptors.[10]

Common prophylactic treatments for CM are also largely based in pharmaceutical agents, including beta blockers, tricyclic antidepressants, calcium channel blockers, angiotensin blockers, anticonvulsants, vitamins, and minerals.[70,177] 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. Similar to 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 is an anticonvulsant used for preventative treatment and is one of the most commonly used drugs. It 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.[43] Vitamin B2 has been used to address mitochondrial dysfunction, an issue associated with some types of migraine,[148] while magnesium is a mineral that has been used to target CSD.[70]

Prophylactic treatment is administered when acute treatments have not been effective and the frequency of migraine attacks interferes with day to day life.[177] Choosing the appropriate preventative agent is based on contraindications, precautions, side effects, compliance issues, and cost. Once an agent is chosen, a 2 to 3 month trial period is used to assess the efficacy of the regime.

2.1.3. Chronic Tension-Type Headache

Clinical history and patient presentation form the basis of diagnosing CTTH. Similar to 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.[123] The ICHD-3 diagnostic criteria for chronic tension-type headache are summarized as follows[9]:

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.[38] Stress is widely accepted to be a contributing factor to TTH,[97] with CTTH patients presenting higher reported levels of stress and a decreased ability to cope with stress.[55] Population studies have reported correlations between TTHC and anxiety, depression, and mood disorders[89,161] 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. [89,162]

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 utilize pharmaceutical agents while prophylactic tactics include both pharmacological and non-pharmacological approaches.

Pharmacologicalreatments 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.[65]

The most common pharmacological prophylactic treatment of CTTH are tricylic antidepressants, with amitriptyline as the most frequently prescribed.[33] 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.[53] Other selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, venlafaxine, and fluoxetine[123] have also been used as prophylactically but their efficacy is still debated.[75]

Of nonpharmacological treatments used preventatively, physical therapy may be used,[32] focusing on muscles and joints of the peripheral nervous system.[11,160]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.[118] Physical therapy often includes exercise and physical training. Psycho-behavioral treatments, including EMG biofeedback, cognitive-behavioral therapy, and relaxation training,[33] 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.[78] Cognitive behavioral therapy teaches patients to identify thoughts that increase stress and trigger headaches.[33] Relaxation training is based on recognizing and controlling tension that occurs during daily activities.[33]

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.[177]

2.1.4. 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 a 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 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.[19]

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.[105] The pathophysiology of combination headache is not well understood but it is believed that typically, patients initially have episodic migraine that causes tension, triggering tension-type headache.

Medication overuse may contribute to 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[19] and is frequently described with them although the pathophysiology is not clear. The terminology and criteria for medication overuse has also evolved over time as had recognition of its potential impact on patients. Prior to the ICHD-2, there was no agreed upon definition of medication overuse and related headache.[74,120] Thus, medication overuse and related headache are variably described in the literature included in this report.

Chronic Daily Headache Usual Care

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 include the medications used to treat CM or CTTH.

2.2. Technologies/Interventions

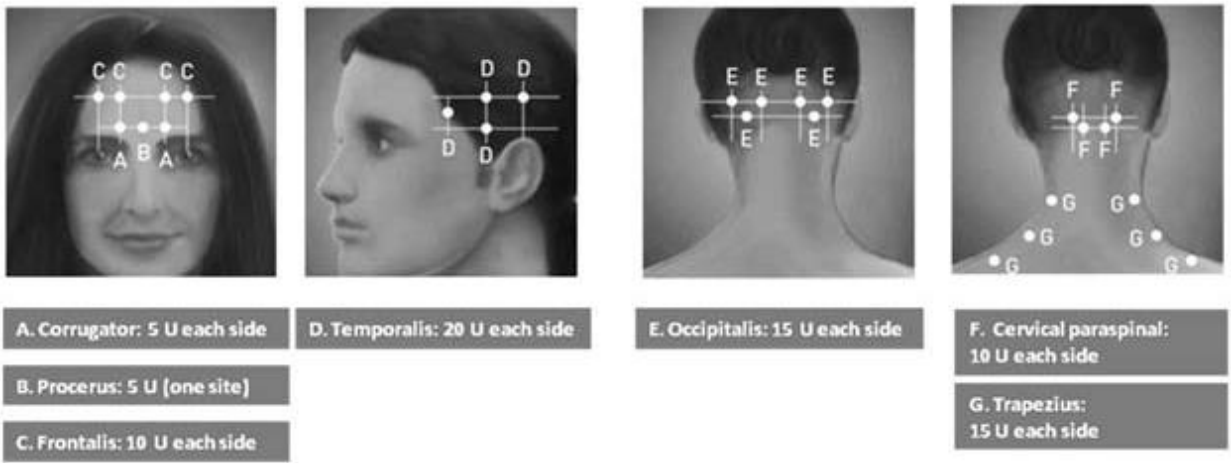
2.2.1. OnabotulinumtoxinA

Botulinum toxins are neurotoxic proteins produced by *Clostridium botulinum.* There are seven known botulinum toxins (A-G) but only OnabotulinumtoxinA (BoNT-A) has FDA approval for treatment of a headache disorder and is exclusively approved for the treatment of CM. The FDA approved form of BoNTA is marketed as BOTOX or BOTOX Cosmetic, which consist of the same components and can be used to treat the same disorders, but BOTOX is administered in larger quantities than BOTOX cosmetic and is therefore packaged differently. BOTOX cosmetic is approved for the treatment of CM, but BOTOX is the most common used form clinically.[16]

The mechanism of BoNTA is thought to therapeutically target central sensitization,[77] a condition associated with the development and maintenance of chronic pain in CM patients. Central sensitization of central trigeminovascular neurons is considered to be a potential mechanism for chronic headache disorders. Research has indicated BoNTA may potentially inhibit this peripheral mechanism of sensitization.[66]

Recommended dosing for BOTOX on patients with chronic migraine is a total of 155 Units injected as 0.1 mL (5 units) into 31 individual sites spread across seven head and neck muscles.[18] The doses are distributed bilaterally and target the frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, and cervical paraspinal muscle group muscles. Recommended injection sites are described in Figure 2.

Figure 2. FDA Recommended injection sites for BOTOX in chronic migraine patients[17]



Two different injection approaches have been described in the literature, the 'follow-the-pain' approach and the 'fixed-site' method. The fixed-site method is used most commonly for patients with migraine headache and consists of the BoNTA administered to the FDA approved injection sites (Figure 2). In contrast, the 'follow-the-pain' method is used most often with patients presenting with tension-type headache. In this approach, the sites and doses of the BoNTA injections are adjusted based on the patient's symptom profile and their specific locations of pain and tenderness. The examiner determines the injection sites by evaluating palpable muscle tenderness and through assessing the head and neck position, muscle bulk, tender spots, and temporomandibular joint function.[42] Common muscle areas assessed for muscle tenderness are the frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, and cervical paraspinal muscle groups. [41]

From two distinct placebo-controlled clinical trials, adverse events that occurred in Botox patients at a frequency of greater than 1% compared to the control group include nervous system disorders, eyelid ptosis, bronchitis, musculoskeletal and connective tissue disorders, injection site pain, and hypertension (Table 2). Additional adverse events that were reported to occur more frequently but at less than 1% were vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain.

Table 2. FDA reported adverse events occurring more frequently in ≥1% of BOTOX patients compared to placebo patients in two placebo-controlled clinical trials evaluating chronic migraine patients[18]

Adverse Events	BOTOX (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	5%	3%
Migraine	4%	3%
Facial paresis	2%	0%
Eye disorders		
Eyelid ptosis	4%	<1%
Infections and Infestations		
Bronchitis	3%	2%
Musculoskeletal and connective tissue disorders		
Neck pain	9%	3%
Musculoskeletal stiffness	4%	1%
Muscular weakness	4%	<1%
Myalgia	3%	1%
Musculoskeletal pain	3%	1%
Muscle spasms	2%	1%
General disorders and administration site conditions		
Injection site pain	3%	2%
Vascular disorders		
Hypertension	2%	1%

Dysphagia, a condition that causes impairment of swallowing, is considered one of the most serious adverse events associated with BOTOX. It results from the diffusion of BoNTA toxin through tissues, inducing paralysis on nerve terminals used for swallowing.[106] The FDA black box warning states[17]:

> "WARNING: DISTANT SPREAD OF TOXIN EFFECT. *See full prescribing information for complete boxed warning*. The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms"

Two studies identified from clinicaltrials.gov reported safety information for BoNTA treatment in chronic migraine patients, but no corresponding publications were found. One trial was completed in May 2015, enrolled 1168 subjects, and performed BoNTA injections every 3 months for a year. The second trial was completed February 2015, enrolled 280 subjects, and administered one BoNTA injection and completed

a follow-up after 4 weeks. Additional information and reported adverse events can be found in the appendices.

Indications and Contraindications of BOTOX

Indications for BOTOX used in chronic migraine patients can be summarized by the following[17]:

- Chronic migraine
  - 15 or more days a month with migraine, each lasting 4 or more hours each day
- 18 years or older

Contraindications for BOTOX in chronic migraine patients can be summarized by the following

- Migraine causing 14 or fewer headache days per month
- Allergy to any ingredients in BOTOX or BOTOX Cosmetic, MYOBLOC, DYSPORT, or XEOMIN
- Skin infection at the planned injection site
- Under 18 years old

2.2.2. Acupuncture

Acupuncture has been used for thousands of years and is based in the Eastern philosophy of activating or correcting qi, the believed vital energy source in humans. Research and patient response have led to expanded use of acupuncture in a Western medicine setting,[151] with the WHO reporting that acupuncture is effective in treating 28 conditions.[60]

Acupuncture uses solid, filiform needles that are 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. 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.[47] The literature reports slightly different acupuncture techniques between migraine and TTH patients. Although there is variation, acupuncture for 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.[110] A Cochrane review of acupuncture for TTH prophylaxis found that studies consisted of 6 to 15 sessions, using primarily individualized or semi-standardized methods.[110] There is no FDA guidance for acupuncture as an intervention, but several different types of needles have received 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.

The mechanism of action for acupuncture for 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.[174] The theory suggests that vasodilation caused by migraine activates receptors on the temporal artery, causing stimulation of trigeminal nerves, resulting in neurogenic inflammation.[174] The influence of acupuncture on cerebral hemodynamics is another possible mechanism. A systematic review that found that acupuncture positively affected the cerebrovascular dysfunction in migraine patients.[115]

Although acupuncture is commonly prescribed for treatment of TTH, the mechanisms of pain relief are unclear. One possible mechanism that has been suggested is that acupuncture influences the central nervous system. As a result, the intervention may possibly reverse central sensitization and aid in the coping of stress.[75]

Although the mechanisms of acupuncture for prophylaxis of both migraine and TTH remain unclear, studies generally agree that acupuncture causes physiological changes in an organism.[49]

2.2.3. Manual Therapies

Manual therapy consists of skilled passive movement of joints and soft tissues. The intervention covers a range of techniques which may be used by physiotherapists, chiropractors, osteopathic physicians and others. For the purposes of this report, included manual therapies are chiropractic and osteopathic manipulation.

Although the mechanism of spinal manipulation for relief of migraine is not known, muscular tightness and mechanical abnormalities of head and neck muscles have been reported in migraine patients.[40,118] Manual therapy may serve to decrease tightness and correct these irregularities, helping to alleviate symptoms. Another theory is that sensory nerve cells in the upper cervical spine cause hypersensitivity of the trigeminal pathway, causing migraine. Is has been suggested that spinal manipulation may activate neural inhibitory systems, possibly stimulating inhibitory pathways that counteract the hypersensitivity.[57]

In TTH, subjects have also demonstrated muscular tightness and mechanical abnormalities in the head and neck region that manual therapy may target.[40,118] Additionally, pericranial myofascial tenderness has been linked to TTH.[72] Evidence suggests that the tenderness results from sensitization of pain pathways of the central nervous system (CNS).[34] Manual therapy techniques have been developed that seek to reset the connection between the CNS and the muscle,[91,96] targeting the sensitization. A chiropractic perspective often views TTH as a result of abnormal tone or tension (subluxations) in the neck and upper back due to misaligned vertebrae.

Reported adverse events of manual therapy include stiffness, increased pain, neurological deficits, dissection of carotid or vertebral arteries, and even death as a result of vascular accidents.[71] When done correctly, nearly half of potential adverse events can be avoided, but there may a 10% or greater chance of an adverse event occurring.[71]

2.2.4. Massage Therapy

Massage therapy (MT) is based in Chinese medicine and dates back thousands of years. It consists of manual manipulation of soft body tissues and is performed by massage therapists. . Massage is often

classified as a manual therapy and involves systematic and methodical manipulation of body tissues, including trigger points, usually with the hands.

CTTH may be caused in part from contraction of head and neck muscles, generating areas of tightness called trigger points. Massage therapy may serve to increase blood flow to tissues, potentially reducing the activity of the trigger points and pain caused by the muscle contractions.[140] Research has also shown that massage on cervical trigger points in patients with CTTH improved autonomic nervous system regulation.[166] In the case of migraines, the mechanisms of massage therapy are less studied. There is evidence, however, that migraine headaches are linked to low levels of serotonin[83] and massage therapy has been shown to increase serotonin levels.[73]

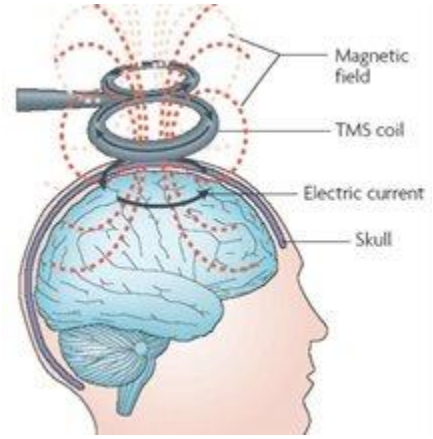
Massage therapy sessions for headache disorders may vary by patient but tend to range from eight to twelve treatments, lasting between thirty minutes and an hour. Serious adverse events of massage therapy are rare but have been reported, usually in the format of case reports or case series.[69] Despite the rarity, one systematic review found that the most common site for adverse events was in the neck,[139] a site targeted when using massage therapy for headache disorders. Examples of adverse events in the neck included neck pain, vertebral arterial dissecting aneurysm, and cervical disc herniation.[181]

2.2.5. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a newer method for headache treatment. It was first developed in 1985 to both evaluate and treat depression, anxiety, and other psychological disorders. With headache disorders, TMS has been used both diagnostically and therapeutically, with research mostly focusing on migraine with aura.

A TMS device consists of a copper wire coil attached to an electrical source. Current is run through the coil, generating a magnetic field that is sent in pulses through the scalp. The extracorporeal magnetic pulses produced penetrate into the brain to stimulate nerve cells, altering the pattern of neuronal firing. TMS electrically excites neural tissue in either single or paired pulses, with each pulse described as a stimuli.[103] Single pulses can be administered independently, called single-pulse TMS (sTMS), or delivered repetitively, called repetitive TMS (rTMS). Paired pulse TMS administers two pulses of different frequencies nearly simultaneously. The treatment procedure for migraine lasts between 30 to 60 minutes and consists of the patient seated, the electromagnetic coil placed on the head, and pulses administered by a clinician.[8,130] Figure 3 shows a schematic of TMS.

Figure 3. Transcranial Magnetic Stimulation[12]



For migraine prophylaxis, one hypothesis is that TMS attenuates cortical spreading depression (CSD), a proposed cause of migraine with aura that causes electrical changes in neurons.[27] The electromagnetic properties of TMS may potentially reverse or disrupt these electrical changes due to CSD.[112] Another related mechanism is based in dysfunction of cortical excitability, which has been proposed to be an important factor in spontaneous CSD.[136] In migraine with aura patients, cortical excitability has been shown to be negatively impacted and rTMS has been researched as a potential therapeutical agent[107] to reverse this dysfunction. The FDA has approved three devices for the acute treatment of pain associated with migraine with aura, which are the Cerena TMS device, the Spring TMS device, and the eNeura sTMS mini device. All three are single-pulse devices and are classified as class II, indicating that the devices have elevated risks compared to class I devices and require increased regulatory controls. The specific controls for using the single pulse TMS for migraine with aura using the aforementioned devices are as follows[15]:

I. Appropriate analysis/testing must demonstrate electromagnetic compatibility (EMC), electrical safety, and thermal safety.
II. Appropriate verification, validation, and hazard analysis must be performed on the device software and firmware.
III. The elements of the device that contact the patient must be assessed to be biocompatible.
IV. Non-clinical testing data must demonstrate that the device performs as intended under anticipated conditions of use. This includes full characterization of the magnetic pulse output and resulting magnetic field map. This also includes characterization of the sound level of the device during use.
V. Clinical testing must demonstrate that the device is safe and effective for treating headache in the indicated patient population.
VI. The physician and patient labeling must include the following:
    a. A summary of the clinical performance testing, including any adverse events and complications
    b. The intended use population in terms of the types of headaches appropriate for use with the device.
    c. Information on how to report adverse events and device malfunctions.
    d. A diagram of picture depicting the proper placement of the device on the user

For diagnostic uses, TMS is used to induce electrical current flows in brain tissues and subsequently, electrical signals elicited are recorded and measured.[108] One example are motor evoked potentials (MEPs), which are electrical signals produced from neural tissue or muscle after central motor pathways are activated.[108] TMS used for diagnostic purposes typically emit a single pulse. In contrast, multiple pulses are used for therapeutic purposes.[145]

Although TMS utilizes magnetic fields, its mechanism is electrically based; the magnetic field produced by TMS devices serve as a way of inducing electrical current in neural tissue.[80] As a result, many TMS devices are labeled as electrical stimulators. A series of devices developed by MagVenture, (previously Dantec), have received FDA approval as electrical stimulators for diagnostic purposes. The MagPro device was included in this series, approved in 1993. The FDA has also approved several devices for the use of repetitive TMS therapy for major depressive disorder (MDD). The NeuroStar TMS system was the first device to receive FDA approval for the treatment of MDD using rTMS. The MagStim Rapid 2 was approved with 510(k) classification, indicating it was found to be substantially equivalent to the NeuroStar unit.

The largest safety concern with TMS is the risk of seizure. Some suggest that, given the rarity of reported seizures, it is possible that the observations may be coincidental.[144] Other adverse reactions reported for TMS include scalp discomfort or burn, dizziness, nausea, adverse tissue reaction, electrical shock or burn, interference with other electrical equipment, noise irritation, and hearing loss.[15]

2.2.6. Trigger Point Injections

Trigger points injections (TPIs) involve the injection of local anesthetic or other injectate into small areas of contracted muscles called trigger points. Trigger points are irritable and tight, and when pressed, produce a twitch within the muscle area. Pain may not be confined to the affected muscle but may spread to distant areas such as the head and neck, a characteristic called referred pain.[20] TPIs are distinct from peripheral nerve blocks (PNBs), targeting contracted muscle areas rather than specific nerves.[23] TPIs and PNBs may be used in conjunction, but PNBs are not included in this review. Dry needling at trigger points is the process involving the insertion of very fine single filament needles into trigger points without injection of medication and is another form of treatment that will be included in this report if data is available.[68]

Injectates used for TPIs are often local anesthetics such as lidocaine or bupivacaine.[142] The procedure is performed while the patient is seated or laying down while a health care provider palpates muscles to determine the trigger points. Once noted, one or more injections are be made into the trigger point. For headache, common injection sites are in the trapezius, sternocleidomastoid, and temporalis muscles. Trigger points causing referred pain have commonly been found in the cervical paraspinal muscles, masseter, levator scapulae, frontalis, and occipitalis muscles[142] and are also possible areas for injections. A variety of doses of agents have been used to treat headaches,[142] hindering the establishment of standardized protocols for this intervention.

The pathophysiological mechanism relating trigger points and pain is not well understood. With tension-type headache, some research has suggested that trigger points may cause referred muscle pain to the head.[72] TPIs may serve to decrease the tightness of the trigger points, decreasing the intensity of the referred pain. In regards to migraine, muscle tenderness and referred pain stemming from trigger points have also been reported in migraineurs.[51] Local anesthetics are generally the recommended agent for TPIs in headache disorders

Adverse events associated with TPIs include fainting, temporary numbness at site of injection, skin infection, hematoma, direct nerve or muscle injury, and needle breakage.[142]

2.3. Clinical Guidelines

The National Guideline Clearinghouse (NGC), PubMed, Google and Google Scholar, references in other papers, the American Academy of Neurology webpage, the American Academy of Family Practice webpage, the American Academy of Pain Physicians webpage, and the American College of Physicians webpage were searched for guidelines related to the use of botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation (TMS), manipulation/manual therapy, and massage for the treatment of chronic headache in adults.

Key word searches were performed: (“tension headache” OR “migraine” OR migrain* OR tension* OR “chronic daily headache*”) AND (“Botulinum Toxins, Type A” OR “botulinum toxin type a” OR onabotulinumtoxinA OR “botox” OR “botulinum” OR botox* OR botulinum*); OR (trigger* OR “trigger

point*" OR "trigger" OR "trigger point" OR "trigger points" OR "dry needling" OR "dry needle" OR "Anesthetics, local"); OR ("transcranial magnetic stimulation" OR "magnetic stimulation" OR "magnetic stimulation therapy" OR "magnetic therapy" OR "transcranial stimulation therapy" OR "transcranial stimulation" OR "transcranial therapy" OR "magnetic stimulation*" OR "transcranial stimulation*"); OR ("acupuncture" OR "acupuncture therapy" OR "manual acupuncture" OR "electroacupuncture" OR "auricular acupuncture" OR "eye acupuncture" or "scalp acupuncture" OR acupunct* OR acupuncture* OR electroacupunct* OR electro-acupunct*); OR ("chiropractic" OR "osteopathic manipulation" OR "chiropractic manipulation" OR "cervical manipulation" OR "spinal manipulation" OR "manual therapy" OR chiropract* OR osteopath*); OR("massage" OR "massage therapy" OR massage* OR massage therapy*)

Guidelines from the following sources are summarized:

- The American Academy of Neurosurgeons (AAN) 2016
- The European Headache Federation 2013
- Towards Optimized Practice (TOP) 2012
- Institute for Clinical Systems Improvement (ISCI) 2013
- Bryans et al. 2011
- European Academy of Neurology (EFNS) 2013
- Scottish Intercollegiate Guidelines Network (SIGN) 2008
- National Institute for Health and Care Excellence (NICE) 2012
- The Japanese Society for Neurology 2013

Details of each included recommendation for the use of botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation (TMS), manipulation/manual therapy, and massage for the treatment of chronic headache in adults can be found in Table 3.

Table 3. Summary of Clinical Guidelines

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
American Academy of Neurosurgeons (AAN) 2016[156] *Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache* United States	Botox vs. placebo for chronic migraine (CM): 2 RCT; Botox vs. topiramate for chronic migraine (CM): 1 Class III study; Botox for tension-type headaches: 2 RCTs*	Botox **should be offered** as a treatment option to patients with CM to increase the number of headache-free days. Botox **should be considered** to reduce chronic migraine impact on health-related quality of life. Botox injection **is probably ineffective** for treating chronic tension-type headaches.	Level A Effective: should be offered Level B Effective: should be considered Level B Ineffective: should not be considered
European Headache Federation 2013[119]	1 sham-controlled study, 1 RCT, 1 study type NR	For repetitive transcranial magnetic stimulation in patients with chronic primary headache‡:	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Neuromodulation of chronic headaches: position statement from the European Headache Federation European Union		1) The application of a neurostimulator, either in a trial or on the basis of a CE mark treatment should be considered only once all alternative drug and behavioral therapies as recommended by international guidelines have failed and medication overuse headache is excluded. 2) This involves that the patient is considered chronic, following the current IHS definition and have been evaluated at a tertiary care headache center. 3) This involves that the patient is considered medically intractable as defined by international consensus. 4) Non-invasive medical technologies should be considered prior to implantation of a neurostimulator and the least invasive and most effective treatment should always be first line therapy. Application of repetitive transcranial magnetic stimulation in chronic headaches **is not yet evidence based**, given the poor amount of controlled data. However, the device is relatively harmless when compared to more invasive and costly neurostimulation devices and may be tried before using more invasive neurostimulation devices.	
Towards Optimized Practice (TOP) 2016[167] *Guideline for Primary Care Management of Headache in Adults* Canada	SR from a clinical guideline 1 RCT from a clinical guideline, 1 SR from a clinical guideline 1 SR from a clinical guideline	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 (2 or more) months, with each treatment lasting approximately 30 minutes. There is **insufficient evidence** to make a recommendation for or against the use of the massage or spinal manipulation for migraine† management. Physical therapy/exercise and acupuncture **may be considered** for patients with frequent TTH†.	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
	1 SR from a clinical guideline	There is **insufficient evidence** to make a recommendation for or against the use of massage or trigger point injections for the treatment of patients with TTH†.	
Institute for Clinical Systems Improvement (ISCI) 2013[31] *Diagnosis and Treatment of Headache* United States	1 meta-analysis	There is **insufficient evidence** supporting significant benefit of cervical manipulation for the treatment of migraine†.	NR
Bryans 2011[45] *Evidence-Based Guidelines for the Chiropractic Treatment of Adults with Headache* Canada	One high-quality RCT, 1 low-quality RCT, and 1 high-quality SR One high-quality RCT One high quality RCT	Spinal manipulation **is recommended** for the management of patients with chronic migraine with or without aura. This recommendation is based on studies that used a treatment frequency 1 to 2 times per week for 8 weeks (evidence level, moderate). Multimodal multidisciplinary care (exercise, relaxation, stress and nutritional counseling, massage therapy) **is recommended** for the management of patients with chronic migraine (evidence level, moderate). A **recommendation cannot be made** for or against the use of spinal manipulation (2 times per week for 6 weeks) for patients with chronic tension-type headache.	NR
European Academy of Neurology (EFNS) 2010[33] *EFNS guideline on the treatment of tension-type headache – Report of an EFNS task force* Denmark	Physical therapy: 13 studies, type NR; Acupuncture: 17 studies, type NR	Physical therapy or acupuncture **may be valuable** options for patients with frequent TTH†, although there is no robust scientific evidence for efficacy.	NR
Scottish Intercollegiate Guidelines Network (SIGN) 2008[149] *Diagnosis and management of headache in adults: A national clinical guideline*	1 RCT 1 RCT, 1 study type NR	Botox is **not recommended** for the prophylactic treatment of migraine†. Botox is **not recommended** for the preventive treatment of chronic tension-type headache.	Level C

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Scotland			
National Institute for Health and Care Excellence (NICE) 2012[127] *Diagnosis and management of headaches in young people and adults* United Kingdom	*Acupuncture*: CM: 4 RCT‡ CTTH: 4 RCTs‡ *Manual therapies*§: CM, 1 RCT CTTH, 2 RCTs *Relaxation for CM*§: 1 RCT *Exercise for CM*§: 1 RCT	A course of up to 10 sessions of acupuncture over 5 to 8 weeks **can be considered** for the prophylactic treatment of chronic migraine with or without aura (if both topiramate and propranolol are unsuitable or ineffective) and chronic tension-type headache. There is **not enough evidence to make a recommendation** for or against the use of the following as prophylactic treatment: • Manual therapies for chronic migraine (with or without aura) or chronic tension type headache. • Relaxation therapy for chronic migraine with or without aura (two CTTH studies were identified but did not meet our inclusion criteria) • Exercise therapy for chronic migraine with or without aura (no studies were identified for CTTH)	NR
National Institute for Health and Care Excellence (NICE) 2012[126] *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine* United Kingdom	2 RCTs (PREEMPT 1 & 2)**	BoNTA **is recommended** as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on ≥15 days per month of which ≥8 days are with migraine) if (1) they have not responded to at least three prior pharmacological prophylaxis therapies **AND** (2) their condition is appropriately managed for medication overuse BoNTA **should be stopped** in people whose condition (1) is not adequately responding to treatment (defined as <30% reduction in headache days per month after two treatment cycles) **OR** (2) has changed to episodic migraine (defined as <15 headache days per month) for three consecutive months).	NR
Japanese Society for Neurology (2013)[125]	12 studies, study type NR	Botox **may be considered** for chronic migraine where other treatments have failed.	Grade A†† Grade C††

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Clinical Practice Guidelines for Chronic Headache Japan	8 studies, study type NR NR NR	Botox **may be considered** for chronic tension-type headache where other treatments have failed. There is **no clear evidence** to support the use physical therapy (massage, neck acupressure, electrical stimulation) for tension-type† headache. There is **no clear evidence** to support the use of acupuncture for tension-type† headache.	Grade C†† Grade C††

AAN: American Academy of Neurology; EFNS: European Academy of Neurology; EM: Episodic Migraine; IHS: International Headache Society; NR: Not Reported; RCT: Randomized Controlled Trial; SR: Systematic Review; TTH: Tension-Type Headache
* Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
† Chronic or episodic was not specified.
‡ Unclear if all trials met our inclusion criteria regarding "chronic" headache.
§ Only the numbers of trials meeting our inclusion criteria are listed.
**The PREEMPT trials are included in this report. A total of 7 trials were identified by NICE committee, 5 of which were excluded (4 because they were versus an active comparator, and one due to concerns regarding quality and relevance to the decision problem)
††Japanese Society for Neurology Grades of Recommendation:
Grade A: Use strongly recommended.
Grade B: Use recommended.
Grade C: No clear evidence to support recommendation for use.

2.4. Previous Systematic Review/Technology Assessments

The HTAs, comparative effectiveness reviews and systematic reviews summarized below all include a large number of studies which did not meet the inclusion criteria for this HTA. In general, these reviews did not distinguish between episodic headache types and chronic forms of headache.

2.4.1. Previous Health Technology Assessments and Comparative Effectiveness Reviews

Health technology assessments (HTAs) were found by searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse from inception to 10/23/2016. Reference lists of relevant studies and the bibliographies of systematic reviews were hand searched. See Appendix B for search terms and full search strategy. A total of two HTAs were identified; both HTAs report on OnabotulinumtoxinA (BoNTA) as a prophylactic treatment for episodic and/or chronic migraine. These HTAs are summarized in Table 4. None of the included HTAs provided levels of recommendations for their evidence base.

2.4.2. AHRQ Report

A 2013 AHRQ review examined preventive pharmacological treatments for migraine in adults.[150] The review included evaluation of preventive treatments, including BoNTA, for both episodic and chronic migraine. The bibliography for this report and data abstractions for relevant included studies were carefully reviewed to assure that the present report captured all relevant studies. The AHRQ report included studies of Dysport (abobotulinumtoxinA), which is not FDA approved for use headache and were therefore excluded in this HTA or compared it to medications that are not FDA approved, which were also grounds for exclusion from this HTA. For many of the BoNTA studies in the AHRQ report, chronic migraine and episodic migraine could not be distinguished and/or baseline characteristics of included studies were most consistent with episodic migraine. Such studies thus did not meet inclusion criteria for this HTA.

With the above in mind, the primary results for use of BoNTA for the prevention of chronic migraine from the 2013 AHRQ report are summarized in Table 4. With regard to efficacy, they report that BoNTA was more effective than placebo for reduction of migraine attacks by ≥50% (low strength of evidence) across 3 RCTs (n=459); per 1000 treated adults, 170 (95% CI 82, 258) would experience such a reduction. Data on safety included studies of both episodic and chronic migraine. Across studies, per 1000 treated adults, 155 (95% CI 90, 220) would experiences adverse effects with 26 (95%ICI 10, 43) choosing to discontinue treatments due to the bothersome adverse effects. The authors note that the risk of adverse events was lower in trials which had higher rates of placebo adverse effects. They also report that adverse effects were dose dependent: Eyelid edema was more common with 50 units of BoNTA that with 25 units and doses of 150U to 225U had a greater risk of blepharoptosis, muscle weakness, and neck rigidity.

The AHRQ review also included studies that included persons with coexistent chronic migraine and chronic tension headache that we've classified under chronic daily headache. Their analysis was of placebo responders; they report that BoNTA was better than placebo in preventing migraine attacks/month by ≥50 percent, regardless of placebo response in one study[120] and that the magnitude of

effect was slightly larger in placebo non-responders (RR 2.2, 95% CI 1.4, 3.4). With regard to dose, in a European study of patients primarily with episodic migraine, there was no benefit of increased dose regardless of placebo response and number of migraine days did not differ by dose.[141]

2.4.3. Previous Systematic Reviews

Systematic reviews (SRs) were identified using the same search strategy developed to find HTAs. Nine SRs assessing prophylactic treatments of chronic migraine and/or chronic tension-type headache were identified; one evaluated on BoNTA, three reported on acupuncture, and five assessed manual therapy. Table 5 summarizes these SRs.

Table 4. Previous Health Technology Assessments and Comparative Effectiveness Reviews

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
OnabotulinimtoxinA (BoNTA)						
AHRQ (2013) Effective Health Care Program CER[150] Agency for Healthcare Research Quality *Migraine in Adults: Preventative Pharmacologic Treatments*	Database inception to May 20, 2012	Migraine (Episodic or Chronic)*	Drug treatment (including topiramate, propranolol, BoNTA and others) vs. inactive controls, pharmacologic or non-pharmacologic interventions	20 RCTs (n = 4237)†	**Efficacy:** BoNTA compared to placebo for treatment of CM was examined in 20 RCTs (n = 4237) and was found to be more effective at creating a ≥50% reduction in migraine frequency for patients receiving BoNTA • Reduced migraine attacks but increased risk of AEs and treatment discontinuation • Long-term (>3 months) preventative benefits of drug adherence could not be determined • Low-strength evidence from individual RCTs suggests dose-responsive increase in prevention with higher doses of BoNTA • 5 RCTs indicate low-strength evidence about CM prevention effectiveness of BoNTA compared to other drugs **Safety:** Among CM patients, treatment with BoNTA resulted in more AEs and treatment discontinuations compared to treatment with placebo: • AEs includes risk of blepharoptosis, muscle weakness, neck rigidity, back or neck pain, dysphagia, and hypertonia • Per 1000 patients treated with BoNTA, 170 experienced ≥50% reduction, 155 experienced AEs, and 26 discontinued treatment due to AE • Increase in risk of AEs was dose-dependent, individual RCTs demonstrated less frequent treatment discontinuation due to AEs than topiramate or amitriptyline **Economic:** NR **Future Research:** • Future studies should focus on impact of patient characteristics on drug benefits and safety	Yes

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					• More examination of comparative effectiveness of approved drugs and the most effective off-label options is needed • Further examination of the potential impact of treatment-modifying effects of patient age, sex, race, migraine family history, comorbidities, and prior treatment with migraine preventative drugs should be done • Future observational studies should focus on analyzing off-label drug use, comparative effectiveness, and safety	
CADTH (2015) Canadian Agency for Drugs and Technologies in Health CDR *Clinical Review Report for OnabotulinumtoxinA*	Database inception to March 2014	Chronic Migraine	BotulinumtoxinA as migraine prophylactic	2 RCT (N = 1384)	**Efficacy:** The two included trials were identical in design. Results suggest that BoNTA was superior to placebo in improving patient-reported outcomes measured by MSQ and HIT-6. • The mean changes from baseline from baseline for MSQ domains demonstrated clinically important and consistent results in both trials through until the end of the double blind phase. • Mean total of HIT-6 score changes from baseline were statistically significant in favor of BoNTA versus placebo (P<0.001) in both studies. • Statistically significant between-group difference in the frequency of HA days and migraine days in favor of BoNTA patients (one to two fewer HA days per month than placebo). However, these results are unlikely to be clinically significant. **Safety:** In the double blind phase, the OnabotulinimtoxinA group saw a higher proportion of patients who experienced at least one AE compared to placebo and. • The proportion of patients with at least one serious AE was higher in BoNTA group (5.3% and 4.3%) than the placebo group) • AEs included neck pain, muscular weakness, headache, eyelid ptosis, injection site pain, musculoskeletal pain, muscle spasms, myalgia and more.	Yes

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					Economic: The manufacturer's (Allergan, Inc.) economic evaluation was reviewed and critiqued and CADTH did their own analyses based on limitations of the submitted evaluation. Limitations cited include inclusion of patients who no longer had chronic migraine, short time horizon (3 years) and likely underestimation of cost association with clinician visits, drug acquisition and administration. They concluded that the manufacturer's (Allergan, Inc.) modelling of health state utilities creates uncertainty regarding the likely cost-effectiveness of BoNTA. Specifically, the use of different utility values between treatment groups within the same health state. • When accounting for more likely cost inputs, this report calculated incremental cost-utility ratios in the range of $42,000 to $47,000 per quality-adjusted life-year • Cost per 12-week course was estimated as $714 based on evaluated prices. • Administration of BoNTA is a complicated procedure which requires proper training and possibly requires patients to access specialized treatment centers. **Future Research:** Evidence has limitations arising from lack of trials to assess comparative efficacy and safety of BoNTA against standard prophylactic CM treatments, the difficulty in maintaining blinding. • Long term efficacy and safety of BoNTA have yet to be determined • Trials were limited by short duration, lack of active comparator, patient characteristic imbalance in one study	
Kim (2014) Sweden, Regional Health Technology	Database inception to October 2013	Chronic migraine	BotulinumtoxinA as migraine prophylactic vs.	3 RCTs (N = 1444)‡	**Efficacy:** Three RCTs comparing BoNTA vs. saline (placebo). Two were identical in design (n = 679, n= 705). The third RCT included only 60 patients	Yes

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
Assessment Center (HTA-centrum)[102] *Botulinum toxin type A for Prophylactic Treatment of Chronic Migraine*			Placebo (saline injections)		• One trial found no difference in frequency of HA episodes between study groups. Another reported a difference of 0.7 episodes per 28 days. In these two studies, the patient populations were possibly not representative of overall CM population. Medication overuse was found in two thirds of all patients at baseline. • Overall, BoNTA may result in little or no difference in the frequency of HA episodes compared to saline, and it is uncertain whether BoNTA reduces frequency of days with HA **Safety:** BoNTA for the treatment of CM is considered relatively safe. • Serious AEs are rare and mostly related to injection site. Symptoms can spread from injection areas to other parts of the body. • AEs can include muscle weakness, diplopia, ptosis, dysphagia, dysarthria and breathing difficulties. **Economic:** • Cost per patient can be difficult to estimate. Cost primarily comes from medication used and time spent with physician. • No cost for new equipment, and only one day of training in injection technique is needed. **Future Research:** Future research should focus on identifying optimal doses of BoNTA and exploring the long-term effects of treatment.	

AE: Adverse events; BoNTA: OnabotulinumtoxinA; CM: Chronic migraine; HA: Headache; HIT-6, Headache Impact Test-6; MSQ, Migraine-Specific Quality of Life Questionnaire;
* Primary conclusions reported only for chronic migraine
† Total evidence base assessed included 245 RCTs and 76 nonrandomized therapeutic studies, evidence base reported in table refers to trials comparing BoNTA.
‡ Studies required to be either SR, RCT of BoNTA, or case series of more than 100 patients (used only for analysis of adverse effects)

Table 5. Selected Previous Systematic Reviews

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
OnabotulinimtoxinA (BontA)								
Jackson (2012)[92] 1966 to March 2012 MEDLINE, EMBASE, bibliographies of published SRs, Cochrane trial registries (Database of Clinical Trials; Pain, Palliative, and Supportive Care Trials Register; CENTRAL), bibliographic review of all articles retrieved.	To assess BontA for the prophylactic treatment of migraine and tension-type headaches (TTHs) in adults.	Chronic migraine and/or chronic TTH	BontA vs. placebo or other interventions (amitriptyline, prednisone, topiramate, and valproate for) headaches among adults	Measures Headache frequency, number of HAs/month (mean change, % with ≥50% reduction); HA severity; HA index (frequency and severity); % patient experiencing ≥50% reduction in headache Adverse events Any reported adverse event; withdrawal from protocol treatment due to any cause	Episodic Migraine: 10 RCTs (n = 1938) CM: 5 RCTs (n = 1544) CDH: 3 RCTs (n = 1115) Mixed episodic and TTH: 1 RCT (n = 21) CTTH: 8 RCTs (n = 616)	Yes (Cochrane tool, Jadad scale)	Yes (moderate heterogeneity)	**Efficacy** Among 27 placebo-controlled RCTs BoNTA was associated with a reduction in number of HA/month for both CDH (-2.06 headaches per month; 95% CI, −3.56 to −0.56; P=.25) and CM (−2.30 headaches per month; 95% CI, P=.21) but was not associated with reduction in frequency of episodic migraine or episodic (95% CI, -0.26 to 0.36; P=.18) and chronic TTH (95% CI, -3.13 to 0.27; P=0.2). Eight studies reported that BoNTA was associated with greater likelihood of ≥ 50% improvement in CM (RR, 2.21; 95% CI, 1.30-3.78; P=.86) and that there was no improvement in CDH compared to placebo (RR, 1.15; 95% CI, 0.91-1.45). None of the comparative trials found differences between BoNTA and other meds, though all were

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								underpowered and unable to show modest differences. **Safety:** BoNTA recipients were more likely (RR, 1.25; 95% CI, 1.14-1.36) to report any AEs than placebo recipients, and some AEs were more common among BoNTA recipients (such as blepharoptosis, muscle weakness, etc.). **Overall**: BoNTA was associated with small to modest improvement in frequency of CM and CDH. BoNTA provided some clinical benefit, but it was limited to those with CM.
Acupuncture								
Linde (2009) [110] Database inception to January 2008 Cochrane Pain, Palliative & Supportive Care Trials Register, CENTRAL, MEDLINE, EMBASE and the Cochrane Complementary	To investigate whether acupuncture is more effective than no prophylactic treatment/routine care only or sham acupuncture and as effective as other interventions in	Migraine and TTH *†	Acupuncture vs. control (no prophylactic treatment or routine care only), sham acupuncture, prophylactic drug, or other treatments.‡	Measures Proportion of responders; frequency of migraine attacks per 4 weeks.; number of migraine days over 4 weeks.; HA frequency; pain intensity; frequency of analgesic use	22 RCTs (N = 4419)§	Yes	Yes	**Efficacy** Acupuncture was associated with higher response rates and fewer headaches up to 9 months follow-up. True acupuncture was not s superior compared to sham interventions in a pooled analysis. **Safety**

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Medicine Field Trials Register	reducing migraine frequency							Acupuncture was associated with slightly better outcomes and fewer AEs compared to prophylactic treatment. Severe AEs such as pneumothorax are very rare. Between 8% and 11% of patients reported minor adverse effects (such as fatigue or temporary aggravations). **Overall** Available studies suggest that acupuncture is at least as effective as, or possibly more effective than prophylactic drug treatment, but with fewer AEs.
Linde (2016)[109] Database inception to January 2016 CENTRAL, MEDLINE, EMBASE, AMED, and WHO International Clinical Trials Registry Platform for ongoing and	To investigate whether acupuncture is more effective than no prophylactic treatment/routine care only or sham (placebo) acupuncture and as effective as other interventions in reducing HA frequency in	Adults with episodic or chronic TTH (excluded studies involving various headache types unless they presented findings for TTH patients separately)	Acupuncture vs. control (acute HA treatment or routine care),sham acupuncture, or other prophylactic intervention	Measures Response (≥50% reduction in HA frequency) after treatment completion Adverse Events Number of participants reporting AEs or dropping out due to AE.	Acupuncture vs. routine care: 2 trials (n = 1472) Acupuncture vs. Sham: 7 RCTs (n = NR) Acupuncture vs. physiotherapy, massage or exercise: 4 RCTs (n = NR)	Yes	Yes	**Efficacy** 52% of acupuncture participants experienced at least 50% reduction in HA frequency compared to sham recipients. None of the four trials comparing acupuncture with physiotherapy, massage, or exercise found superiority for acupuncture, although those trials are older and of limited quality. **Safety**

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
unpublished trials.	adults with episodic or chronic TTH							0.002% (1/420) of acupuncture recipients dropped out due to AE compared to 0% (0/343) of sham recipients. None of the trials comparing acupuncture with other interventions reported number of participants reporting or dropping out due to AE. **Overall** Results suggest that acupuncture is effective towards reducing frequency of episodic or chronic TTH; further trials comparing with other treatment options needed

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Hao (2013)[86] Database inception to August 2010 4 Chinese databases (CNKI, CQVIP, Wangfang, and CBM), Pubmed, EMBASE, CINAHL, Proquest, Cochrane Library, Acubriefs, Science direct, SCOPUS, and Informit	Identify factors contributing to conflicting outcomes in efficacy of acupuncture for TTH (esp. through the use of subgroup analyses to explain heterogeneity source)	TTH	Acupuncture versus sham**	Measures: HA days at end of treatment and follow-up	5 RCTs (N=838)	Yes (Jadad scale, IVS, and OPVS)	Yes	**Efficacy** Meta-analysis results show no significant difference between real and sham acupuncture on HA days. Subgroup analyses indicated that stimulation mode, needle retention and treatment frequency could contribute to difference in treatment effect for TTH. **Overall:** Subgroup analyses indicate that adequacy of treatment is as important as methodological quality when assessing acupuncture efficacy, future studies should investigate effective treatment parameters to better translate RCT findings into patient outcomes.
Manual Therapy								
Chaibi (2011)[58] Database inception to NR CINAHL, Cochrane, Medline, Ovid and PubMed	Assessing the efficacy of manual therapies on migraine patients	Migraine (Chronic vs. episodic not specified)	Manual therapies to include massage therapy, physiotherapy, relaxation and chiropractic spinal	Measures: Pain intensity, frequency, or duration	Massage therapy: 2 RCTs (n = 74) Physiotherapy: 1 RCT (n = 118) Chiropractic manipulation:	Yes (PEDro scale)	No	**Efficacy** Statistically significant reduction in pain intensity (71%) in massage group(unchanged in control). 13% of physical therapy patients experienced >50% improvement in HA

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
			manipulative therapy vs. Propranolol and topiramate		5 RCTs (n = 514)			severity. Chiropractic treatment reduced HA frequency similarly to treatment with topiramate and propranolol. **Safety:** NR **Overall:** Evidence suggests that manual therapies might be equally effective compared to prophylactic medications; further evidence is needed from well-conducted RCTs with fewer methodological shortcomings.
Chaibi (2014)[56] Search dates NR CINHAL, Cochrane, Medline, Ovid, PubMed	To evaluate the efficacy of manual therapy in RCTs treating CTTH	CTTH diagnosed according to IHS guidelines	Manual therapy vs. No treatment control, Manual Therapy vs. other treatment.[††]	Measures: HA frequency, duration, and pain intensity.	Massage therapy: 1 RCT (n = 11) Physiotherapy: 5 RCTs (n = 266)	Yes (PEDro scale)	No	**Efficacy** 54%, 82% and 85% of participants in three physiotherapy RCTs had a ≥50% reduction in HA frequency, and effect was maintained up to 6 months post-treatment. One trial showed that physiotherapy made a statistically significant reduction in HA frequency and intensity compared to routine care. **Safety** Achieves similar reduction rates as tricyclic

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								antidepressants but with far fewer side effects. **Overall:** Massage and physiotherapy are effective treatment options for CTTH. Manual therapy equals prophylactic medications in efficacy.
Bronfort (2004)[44] Database inception to November 2002 MEDLINE, EMBASE, BIOSIS, CINAHL, Science Citation Index, Dissertation Abstracts, CENTRAL and Specialized Register of the Cochrane Pain, Palliative Care and Supportive Care review group	To quantify and compare short- and long-term effects of non-invasive treatments for chronic primary HA patients	Patients aged 12-78 with migraine, TTH, cervicogenic(n = 461), mix migraine and tension-type, and post-traumatic headache (n = 23) ‡‡	Non-invasive physical treatment vs. any control or other treatment (e.g., massage vs. acupuncture; SMT vs. amitriptyline, etc.)	Measures: 1) HA pain and/or HA index 2) Short term follow up (outcomes evaluated ≤3 months after therapy onset); 3) Long term follow up (outcomes evaluated >3 months after therapy onset)	22 RCTs/quasi-RCTs (N = 2628)	Yes	Yes§§	**Efficacy:** For prophylactic treatment of migraine, there is evidence that SMT may be comparable to amitriptyline in the short-term (up to 3 mos. post-treatment) For CTTH treatment, amitriptyline is more effective than SMT during treatment, but SMT was shown superior in short term after treatment. **Safety:** Non-invasive treatments appear to be associated with little risk of serious AE. Side-effects mostly addressed for spinal manipulation (serious or severe complications

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								considered very rare). **Overall:** Some non-invasive manual therapy may be effective treatment for chronic HA; however, this requires further high quality research to assess clinical- and cost-effectiveness.
Posadzki (2011)[137] Database inception to November 2010 Amed, EMBASE, Medline, CINAHL, Mantis, ICL and Cochrane Central Register of Controlled Trials	Assess the effectiveness of spinal manipulation therapy (SMT) as a treatment for migraine	Migraine Headache**	SMT vs. amitriptyline, SMT and amitriptyline; SMT vs. mobilization; SMT vs. placebo (detuned interferential therapy)***	Measures: HA index, migraine duration, VAS for pain, disability, frequency, intensity, use of medication	3 quasi-RCTs (N = 430)	Yes (Jadad scale)	No	**Efficacy:** One RCT showed SMT had significant improvements in migraine frequency, intensity, and duration compared to placebo; however, the other two RCTs showed no difference in outcome measures compared with mobilization, drug treatment, or SMT and drug treatment. All trials had major methodological flaws. None adhered to IHS guidelines for migraine prevention trials. **Safety:** One study reported that patients receiving SMT were more likely to complain of side effects (e.g., neck pain and soreness)

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								Overall: Current evidence does not support the use of spinal manipulation for migraine HA treatment, based on scant evidence and poor trial quality.
Posadzki (2012)[138] Database inception to May 2011 AMED, EMBASE, MEDLINE, CINAHL, MANTIS, PEDro, ICL and Cochrane Central Register of Controlled Trials	Assess the effectiveness of spinal manipulation therapy (SMT) as treatment for TTH	Adults diagnosed with TTH	SMT vs.amitriptyline; SMT and soft tissue therapy vs. soft tissue therapy and placebo laser treatment; Manual therapy vs. routine care; Osteopathic SMT vs. palpatory examination or no intervention; Cervical SMT and amitriptyline vs. cervical SMT and placebo vs. sham cervical SMT and amitriptyline vs. sham cervical SMT and placebo	Measures: Daily HA hours, HA pain intensity, HA frequency, and daily analgesic use	5 RCTs (N = 348) [†††]	Yes (Cochrane tool and Jadad scale)	No (meta-analysis deemed impossible due to statistical and clinical heterogeneity)	**Efficacy:** Results from 4 studies suggest SMT is more effective than drug therapy, SMT and placebo, sham SMT and drug therapy, sham SMT and placebo, usual care, or no intervention. One study showed no difference in outcomes compared to soft tissue therapy and placebo laser treatment. The two studies showing positive results included both CTTH and episodic TTH possibly indicating higher effectiveness in that regard. **Safety:** Three studies reported AEs, two did not provide information. AEs from SMT include minor aggravation of neck pain or HA, neck stiffness.

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								Overall: Evidence for SMT for the treatment of TTH is mostly positive and encouraging but far from conclusive because total sample size and methodological quality of included studies were too low for definitive judgment.

AE: Adverse events; BoNTA: OnabotulinumtoxinA; CDH: Chronic daily headache; CM: Chronic migraine; CTTH: Chronic tension-type headache; HA: Headache; IHS: International Headache Society; Meds: medications; SMT: Spinal manipulation therapy;
*Chronic or episodic not reported.
†Includes studies focused on migraine but including TTH, as well as those including various headache types that presented findings for migraine patients separately.
‡ Other treatment includes: drugs, relaxation, physical therapies, etc.
§ One study in TTH population included (Vickers 2004, n = 401) because 94% of patients were primarily diagnosed with migraine; two other TTH studies included because subgroup data was available for migraine patients (data of the remaining n excluded).
** This study aimed to identify factors contributing to inconsistency of results between real and sham acupuncture. To focus on this all sham acupuncture trials were included without including trials comparing real with no acupuncture or another active treatment.
††Other treatment includes: biofeedback, detuned ultrasound at head and neck area, soft tissue work with ultrasound and transcutaneous electrical nerve stimulation (TENS), cervical mobilization, postural correction, etc.
‡‡ Proportion of participants <18 NR
§§ Effect sizes calculated, and subgroup analyses planned but they were unable to pool data because of study heterogeneity
*** SMT performed either by chiropractor or by medical practitioner and physiotherapist
††† Three RCTs each with 2 parallel groups (n = 150, n = 75, and n = 82); 1 RCT with 3 parallel groups (n= 22); 1 4x4 balanced factorial design (n = 19)

2.5. Medicare and Representative Private Insurer Coverage Policies

Coverage decisions are summarized briefly below and policy details are provided in Table 6. In general, information specific to the chronic forms of migraine, tension-type headache or the combination of these two headache types was not well delineated by payers.

Bellwether payer websites (e.g., Cigna, Humana, Anthem, CMS, United Health Care, Blue Cross Blue Shield), the Centers for Medicare and Medicaid Services (CMS) website, and Google were searched for coverage decisions on the use of botulinum toxin A injections, trigger point injections, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), and acupuncture for management of chronic migraine and/or headache. Seven policies were found for botulinum toxin a injections, zero were found for trigger point injections, two were found for manipulation/manual therapy, zero were found for massage, three were found for TMS, and four were found for acupuncture.

The following terms were searched: “headache” OR “migraine”, “trigger point injection*”; ("osteopathic manipulative medicine" OR "OMM" OR "osteopathic manipulative therapy" OR "OMT") AND (headache* OR migraine*); “massage*”; “acupuncture”; and “transcranial magnetic stimulation”.

Table 6. Overview of payer policies

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
Botulinum Toxin A				
Centers for Medicare Medicaid Services (CMS) National Coverage Decision (NCD)	NR	NR	There is no NCD from CMS for the use of botulinum toxin A for headache or chronic migraine.	NR
Aetna Botulinum Toxin Policy #: 0113 Effective: 07/29/1996 Last review: 09/15/2016 Next review: 01/26/2017	NR	5 randomized controlled trials, 2 systematic reviews/secondary analyses/meta-analyses, 1 clinical guideline	Continuing botulinum toxin type A injections are considered medically necessary for the ongoing prevention of chronic migraine when: - Migraine headache frequency was reduced by at least 7 days per month (when compared to pre-treatment average) by the end of the initial botulinum toxin a treatment trial; or - Migraine headache duration was reduced by at least 100 total hours per month. Botulinum toxin type A is considered medically necessary for the prevention of chronic (more than 14 days/month with headaches lasting 4 hours a day or longer) migraine headaches in adults who have tried and failed trials of at least 3 medications from at least two classes of migraine headache prophylaxis medications of at least 2 months/60 days duration for each medication:	CPT: J0585 ICD-10: G43.001- G43.919

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
			- Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers - Antidepressants - Anti-epileptic drugs - Beta blockers - Calcium channel blockers Botulinum Toxin A is considered experimental and investigational for migraines that do not meet this criteria. Botulinum toxin A is also considered not medically necessary for the treatment of non-chronic migraine. Botulinum Toxin A is not considered medically necessary for the treatment of chronic daily headache is not considered medically necessary)	
Anthem Botulinum Toxin Policy #: DRUG.00006 Effective: 06/28/2018 Last review date: 05/05/2016	NR	14 studies, study type NR	An initial 6 month trial of botulinum toxin A is considered medically necessary when all the following criteria are met: - Adult individual diagnosed with chronic migraine headache; and - Fifteen (15) or more headache-days/month with headache last 4 hours or longer; and - First episode at least 6 months ago; and	HCPCS: J0585 ICD-10: G43.001- G43.919

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
			- Symptoms persist despite trials of at least 1 agent in any 2 of the following classes of medications used to prevent migraines or reduce migraine frequency: anti-depresseants, anti-hypertensives, or anti-epileptics. Continuing treatment with botulinum toxin injection for ongoing prevention of chronic migraine headache is considered medically necessary for individuals who have previously met criteria above and completed an initial 6 month trial when: - Migraine headache frequency was reduced by at least 7 days/month (when compared to pre-treatment average) by the end of the initial trial; OR - Migraine headache duration was reduced by at least 100 total hours per month (when compared to the pre-treatment average) by the end of the initial trial. Botulinum toxin injection is not considered medically necessary for the treatment of headache other than chronic migraine meeting the criteria listed above, including tension, episodic migraine (14 migraine days per	

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
			month or less), or chronic daily headaches.	
Trigger Point Injections				
Centers for Medicare Medicaid Services (CMS) National Coverage Decision (NCD)	NR	NR	There is no NCD from CMS for the use of trigger point injections for headache or chronic migraine.	NR
Manipulation/Manual Therapy (Osteopathic, Chiropractic)				
CMS (Noridian) Local Coverage Decision (LCD): Chiropractic Services Policy #: L34009 Last Revised: 10/01/2016	NR	NR	Chiropractic services are considered medically necessary for short-term treatment of headache (both chronic and tension-type).	CPT/HCPCS Codes: 98940 – 98943 ICD-10 Codes: G44.209, G44.219, G44.229
Aetna *Chiropractic Services* Policy #: 0107 Effective: 03/25/1995 Last review: 06/30/2016 Next review: 01/26/2017	NR	NR	Chiropractic services are covered for migraine, tension and other headaches if selection criteria are met for adults and children (aged 4 years or older). Selection criteria include: The member has a neuromusculoskeletal disorder; the medical necessity for treatment is clearly documented; *and* improvement is documented within the initial 2 weeks of chiropractic care.	CPT/HCPCS Codes: 98940 – 98943 ICD-10 Codes: G43.001- G43.919, G44.001- G44.89, R51
Massage				
Centers for Medicare Medicaid Services (CMS) National Coverage Decision (NCD)	NR	NR	There is no NCD from CMS for massage therapy for treatment of chronic migraine or headache.	NR

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
Acupuncture				
Centers for Medicare and Medicaid Services (CMS) National Coverage Decision for Acupuncture (30.3) Publication #: 100-3	NR	NR	Medicare reimbursement for acupuncture, as an anesthetic or as an analgesic or for other therapeutic purposes, may not be made. Accordingly, acupuncture is not considered reasonable and necessary.	NR
Cigna Acupuncture Coverage policy #: 0024 Effective date: 03/15/2016 Next review date: 03/15/2017	NR	10 RCTs, case reports/series, systematic reviews	Cigna considers acupuncture medically necessary when all the criteria have been met: - Treatment is expected to result in significant therapeutic improvement over a clearly defined period of time; - An individualized treatment plan has been developed with identification of treatment goals, frequency, and duration of treatment; Acupuncture is used for treatment of pain for chronic migraine or tension headache.	CPT: 97810, 97811, 97813, 97814 ICD-9-CM: 307.81, 339.10-339.12, 346.00-346.93 ICD-10-CM: G43.001-G43.919, G44.221-G44.229
Anthem Acupuncture Guideline #: CG-ANC-03 Effective date: 01/05/2016 Last review date: 11/05/2015	NR	5 RCTs, 3 meta-analyses, 2 Cochrane reviews, 1 study type NR	Although studies are promising, acupuncture is not considered medically necessary for migraine and tension-type headache, as studies have been small and of limited quality.	NR
Transcranial Magnetic Stimulation				
Centers for Medicare Medicaid Services (CMS)	NR	NR	There is no NCD for the use of transcranial magnetic stimulation	NR

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale / comments
National Coverage Decision (NCD)			for the treatment of headache or chronic migraine.	
Anthem Transcranial Magnetic Stimulation Policy #: BEH.00002 Effective: 08/18/2016 Last review date: 08/04/2016	NR	1 RCT, 1 HTA	Transcranial magnetic stimulation of the brain is considered investigational and not medically necessary for migraine headache	NR
UnitedHealthCare Transcranial Magnetic Stimulation Policy #: 2016T0536H Effective: 03/01/2016	NR	3 RCTs, 1 professional society position statement	Unproven and not medically necessary for treatment of headache due to limited number of studies and small sample sizes.	CPT: 90876, 90868, 90869 ICD-10: NR

CMS: Centers of Medicare and Medicaid Services; CM: Clinical Modification; CPT: Current Procedural Terminology; HCPS: Healthcare Common Procedure Coding; HTA: Health Technology Assessment; ICD: International Classification of Diseases; NCD: National Coverage Decision; NR: Not Reported; RCT: Randomized Controlled Trial

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1. Objectives

The primary aim of this assessment is to systematically review and synthesis published evidence on the efficacy, safety, and cost-effectiveness of botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, or no treatment for the prevention of chronic migraine and chronic tension-type headache in adults.

3.1.2. Key Questions

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 botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

2. What is the evidence regarding short- and long-term harms and complications of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

3. Is there evidence of differential efficacy, effectiveness, or safety of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo sham, waitlist or no treatment? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation.

4. What is the evidence of cost-effectiveness of botulinum toxin injection, trigger point injection or dry needling, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

3.1.3. Inclusion/exclusion criteria

Inclusion and exclusion criteria are summarized in Table 7. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with chronic migraine (with or without aura) or chronic tension-type headache or co-existent chronic migraine and tension-type headache. While chronic headache is currently defined by the International Classification of Headache Disorders, 3rd edition as 15 or more days each month for at least 3 months or more than 180 days a year, older studies may have used varied definitions. 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.
- **Interventions:** Botulinum toxin injection, acupuncture, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), trigger point injection (TPI) or dry needling
- **Comparators:** Usual (standard) treatment(s), sham, placebo, waitlist or no treatment
- **Outcomes:** Primary/critical outcomes are 1) the proportion of treatment responders, 2) cessation/prevention of headache (including reduction in mean number of episodes and/or headache days), 3) function/disability (based on validated outcomes measures), 4) treatment related adverse events/harms, 5) quality of life. 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.
- **Studies:** Studies must report at least one of the primary outcomes. Focus will be on studies with the least potential for bias such as high quality systematic reviews of randomized controlled trials and randomized controlled trials and full economic studies.
- **Timing:** Focus will be on intermediate (>6 months) and long term (> 12months) for efficacy outcomes, particularly cessation/prevention; any time frame for harms.

Table 7. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Adults with the following 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 (migraine 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 cephaglias including cluster headache) • Secondary headache types as defined in The International Classification of Headache Disorders, 3rd edition • Acute trauma-related headache • 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	• Botulinum toxin injection (Botox, OnabotulinumtoxinA, BoNTA) • Trigger point injection or dry needling • Acupuncture • Transcranial magnetic stimulation (TMS) • Manipulation/manual therapy (e.g. osteopathic, chiropractic) • Massage	• 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) • 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.)

Study Component	Inclusion	Exclusion
		• Pharmacological treatment (including oral agents such as opioids, NSAIDS, beta blockers, antiepileptics, calcium channel blockers, calcium channel antagonists, antidepressants, 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	• Non-clinical outcomes • Intermediate outcomes • Imaging outcomes

Study Component	Inclusion	Exclusion
	Index (Inventory); HDQ, Headache Disability 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

Study Component	Inclusion	Exclusion
Publication	• Studies published in English in peer reviewed journals or publically available FDA reports	• Abstracts, editorials, letters • 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 (>6 months) and long term (> 12months) 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.[122,152,168]

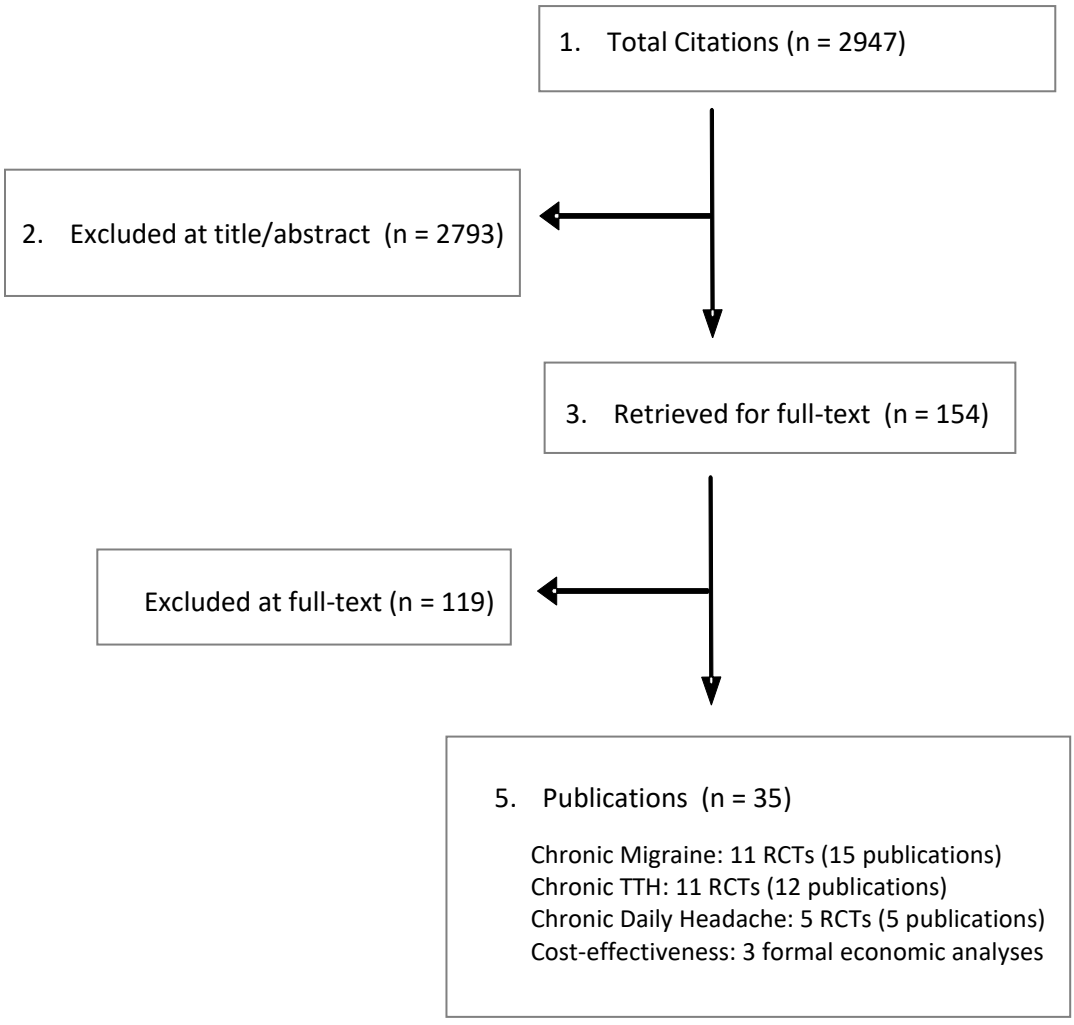
3.1.4. Data sources and search strategy

We searched electronic databases from inception to November 10, 2016 to identify publications assessing treatments for chronic migraine and/or chronic tension-type headache. Electronic databases searched include PubMed, EMBASE the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse (see Appendix B for full search strategy). We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography check. 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. Articles were selected for full-text review if they included a comparison of an intervention and a control of interest for the treatment of chronic migraine, chronic tension-type headache, or chronic daily headache. We excluded conference abstracts, non-English-language articles, and studies of nonhuman subjects. 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 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 4.

Figure 4. Flow chart of literature search results



3.1.5. Data extraction

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. Detailed study and patient characteristics is available in Appendix F, all results are available in the results section of this document and in Appendices G and H.

3.1.6. Quality assessment: Overall Strength of evidence (SoE), Risk of Bias, and QHES evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SoE) for each primary outcome from RCTs are based on criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions*, [88] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, and recommendations made by the Agency for Healthcare Research and Quality (AHRQ). Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. Based on these quality criteria, each study chosen for inclusion for a Key Question was given a RoB (or QHES) rating; details of each rating are available in Appendix E. Standardized, pre-defined abstraction guidelines were used to determine the RoB (or QHES) rating for each study included in this assessment.

The SoE for all primary health outcomes was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) 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 a given outcome. In determining the strength of 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. Comparisons of interventions with sham or placebo treatments are considered indirect comparisons.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing or selective reporting.

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.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the observational studies could be upgraded if the study had large magnitude of effect (strength of association) if there are no downgrades for the primary domains listed above. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs. Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. 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 no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Similar 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

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. When more than one follow-up time was reported within a category, we used data from the longest duration available within that category.

Meta-analyses were considered when there were two or more studies with similar patient populations, indications, interventions, control groups and outcomes. We grouped control treatments according to whether the control was a sham treatment active comparator (e.g., pharmacological agent, physical therapy). For all dichotomous outcomes, risk ratios (RR) or risk differences and their respective 95% confidence intervals (CI) were calculated to compare the rate of occurrence or relative risk between treatments. For those dichotomous outcomes (e.g proportion of responders) that could be pooled, risk ratios or risk differences and figures were produced using Review Manager v5.2.6 and the difference within each study was weighted and pooled using the Mantel-Haenszel and Dersimmonian-Laird methods. For those dichotomous outcomes that could not be pooled, RDs were calculated using the Rothman Episheet (www.krothman.org/episheet.xls*).*

For all continuous outcomes, mean differences (MD) and their respective 95% confidence intervals were calculated. For outcomes that could be pooled, mean differences were weighted according to the inverse of their variance; results and figures were produced using Review Manager v5.2.6. The more conservative random effects model was assumed to account for inter-study variability. In some instances, when a study did not report the standard deviation, it was imputed by taking the average from other studies within respective subgroups. If outcome measures with different scales were reported, the standard deviation (SD) was first scaled before being averaged, and standardized mean differences (SMD) were calculated by dividing the MD by the SD. In some studies, standard errors (SE) or 95% confidence intervals were reported in lieu 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 = $[-1.6B \pm \sqrt{[(-1.6B)^2 - 4(B^2-C^2)]}] \div 2$. 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. 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. For some comparisons, mean difference was calculated using the change between the follow-up and baseline scores. These methods are consistent with those outlined in the *Cochrane Handbook*.[88]

Silberstein 2006 presented results for different dosage groups. The study concluded no significant difference in headache severity between dosages at any time point. The baseline sample sizes were used to create a single weighted average 'Any Dosage' group to be compared with the placebo group. Padberg 2004 gave pain scores on a 0-100 scale while others used 0-10. Therefore, to be consistent it was necessary to convert all to a 0-10 scale. This was done by applying a constant multiplying factor of 0.1 to the original mean and SD values before differencing.

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.[87] When statistical heterogeneity was present, we performed sensitivity analyses first by omitting obvious outliers if sufficient data and trials were available. In cases where there were no obvious outliers, we repeated the analysis excluding poor quality studies, again if sufficient trials were available. A sensitivity analysis of different doses based on number of injections was done to assess their impact on headache severity but these data only apply to patients receiving BoNTA. All meta-analysis results and figures were produced using Review Manager v5.2.6.

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 and Overall Quality of Studies

Overall, 27 randomized trials (in 32 publications) were included. The comparisons evaluated and their respective studies are listed in Table 8; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. Three additional economic studies were included.

Table 8. Number of studies for each comparison of efficacy for included conditions.

Comparisons	Studies
CHRONIC MIGRAINE	
OnabotulinumtoxinA vs. Placebo	4 RCTs (8 publications)[24-26,64,67,114]
OnabotulinumtoxinA vs. Amitriptyline	1 RCT[116]
OnabotulinumtoxinA vs. Topiramate	1 RCT[121]
Acupuncture vs. Usual Care	1 RCT[170]
Acupuncture vs. Topiramate	1 RCT[180]
Spinal Manipulation Therapy vs. Amitriptyline	1 RCT[129]
Transcranial Magnetic Stimulation vs. Sham	2 RCTs[124,165]
CHRONIC TENSION-TYPE HEADACHE	
OnabotulinumtoxinA vs. Placebo	5 RCTs[82,104,135,147,154]
Acupuncture vs. Sham	2 RCT[99,164]
Acupuncture vs. Physical Training*	1 RCT (2 publications)[158,159]
Acupuncture vs. Physiotherapy	1 RCT[52]
Acupuncture vs. Relaxation Training*	1 RCT (2 publications)[158,159]
Manual Therapy vs. Usual Care	1 RCT[54]
Trigger Point Injection vs. Placebo	1 RCT[98]
CHRONIC DAILY HEADACHE	
OnabotulinumtoxinA vs. Placebo	3 RCTs[120,134,155]
OnabotulinumtoxinA vs. Topiramate	1 RCT[50]
Massage vs. Sham	1 RCT[59]

*This study (Soderberg 2006, 2011) had 3 arms: an acupuncture, a physical training, and a relaxation training group.

With regard to the overall quality of retained studies, only the PREEMPT 1 and 2 trials comparing BoNTA and placebo and one trial evaluating massage were considered to be at low risk of bias (good quality RCTs). The majority of trials (n= 15) were considered to be at moderately high risk of bias (poor quality

RCTs); nine were considered to be at moderately low risk of bias (moderate quality RCTs). Two economic studies were considered to be at poor to moderate quality and one was very poor quality. Detailed descriptions of study quality are provided below for each headache type and comparator set and in Appendix E.

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 has 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. For the purposes of this 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 (CDH), which is generally consistent with the terminology used by authors.

Across studies, headache types and comparators, the majority of patients were female, with a mean age in most trials of 40 to 45 years old. In general a large proportion of study participants reported previous use of prophylactic medications and a few trials permitted concurrent use of them. 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 employed placebo or 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 alternative treatments. Few trials compared interventions to active alternative treatments that might be used to treat headache conditions.

4.2. Key Question 1: Efficacy

The number of studies retained and result regarding efficacy are provided below.

Primary outcomes considered for evaluation of efficacy were:

1. Responders (proportion of patients meeting a pre-specified threshold of success for treatment; definition may vary across studies)
2. Reduction in number of episodes (specify HA type)
3. Reduction in number if HA days
4. Function/Disability Measures

Secondary outcomes considered for evaluation of efficacy were:

5. Quality of life
6. Change in frequency of medication/analgesic use
7. Emergency department visits

8. Loss of working days
9. Patient satisfaction (or self-reported improvement)
10. Headache intensity
11. Headache scores

Not all studies reported on all outcomes.

4.2.1. Chronic Migraine

Summary of results

The general findings for chronic migraine (CM) treatment for the primary outcomes are briefly summarized below by treatment and comparator. Detailed findings (including results for secondary outcomes) are then presented. We report following primary outcomes:

- The proportion of treatment responders is a primary outcome of interest; it was variable defined across trials.
- Reduction in mean frequency of headache. This may include frequency of attacks/episodes (e.g. migraine episodes), overall headache days or headache days for a specific headache type (e.g. migraine days)
- Function as measured by validated measures

For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Most trials were at moderately high risk of bias; assessment details are provided in Appendix E.

OnabotulinumtoxinA (BoNTA) versus Placebo

Two large Phase III trials and one small trial reported on the primary outcomes of interest.

No studies reported outcomes of interest in the short term (≤8 weeks) or intermediate term (>8 to 12 weeks).

In the longer-term (>12 weeks), findings include the following:

- At 24 weeks, across 2 large RCTs, a ≥ 50 % reduction in number of *migraine days* and overall number of *headache days* per month was achieved by more BoNTA recipients compared with placebo (RD 12%, moderate evidence).
- With regard to mean headache days (3 trials) and migraine days (2 trials) per month a small difference between groups (<2 days) favoring BoNTA was observed through 24 weeks (moderate evidence for all outcomes)

- When migraine episodes and headache episodes were considered, there was not a difference between groups in the percent of patients who achieved ≥ 50 % reduction in the number of *migraine episodes* per month across 2 large trials or in one small trial over 4 months (moderate evidence). Similarly, there were no statistically significant differences in the reduction of mean number of *headache episodes* or *migraine episodes* per month through 24 weeks (3 trials). (moderate evidence for all outcomes)
- At 24 weeks BoNTA was associated with improved function based in Headache Impact Test-6 Scores and significantly fewer BoNTA recipients had severe HIT-6 scores compared with placebo across two trials (moderate evidence for both outcomes). One small trial reported greater reduction in Migraine Disability Assessment Scale (MIDAS) scores following BoNTA versus placebo, suggesting better function by 16 weeks, but the result was not statistically significant (insufficient evidence), in part due to inadequate sample size.Over 60% of participants in the two largest trials reported medication overuse at baseline; the other small trial excluded those with medication overuse

OnabotulinumtoxinA (BoNTA) versus Active Control

- BoNTA versus Topiramate: one small RCT provided data on primary outcomes
  - No data on short- or intermediate-term outcomes were available
  - Longer-term outcomes were as follows:
  - At 12, 24, and 36 weeks, more BoNTA recipients achieved ≥ 50% reduction overall number of *headache days* compared with placebo, however the differences did not reach statistical significance in one small RCT. Differential attrition between treatment groups and substantial loss to follow-up may be contributing factors. Data available for the BoNTA and topiramate groups respectively: 80% versus 70% at 12 weeks, 70% versus 60% at 24 weeks and 63% versus 57% at 36 weeks.(low level of evidence at 12 weeks, insufficient at 24 and 36 weeks).
  - There were no differences at any time points up for the functional measures reported including MIDAS, HIT-6 and MIQ (low level of evidence at 12 weeks, insufficient at 24 and 36 weeks).
- BoNTA versus Amitriptyline: one small RCT provided data on primary outcomes
  - No data on short- or intermediate term outcomes were available
  - At long-term follow-up (12 weeks), there were no differences between groups with regard to the percent of patients with ≥ 50% reduction in the frequency of pain days or the percent of patients with ≥3 point reduction in pain intensity in one small RCT (low evidence for both outcomes)

Acupuncture versus Sham

- No trials were identified that met the inclusion criteria.

Acupuncture versus Active Control

- Acupuncture versus Usual Care: one RCT provided data on primary outcomes
    - No data on short- or intermediate term outcomes were available.
    - In the longer term (36 weeks), acupuncture resulted in a statistically greater improvement in all outcomes measured compared with usual care: proportion of patients achieving ≥50% reduction in any, mild, and moderate/severe headache days; proportion of patients achieving ≥35% reduction in headache days; mean reduction from baseline in any, mild or moderate/severe headache days per month (low quality evidence for all outcomes).
- Acupuncture versus Topiramate: one small RCT provided data on primary outcomes
    - In the short-term (4 weeks), acupuncture resulted in a statistically greater improvement in all outcomes measured compared with topiramate (low quality evidence for all): proportion of patients achieving ≥50% reduction headache days (any and moderate/severe); and mean reduction from baseline in headache days (any and moderate/severe) per month and in the Migraine Disability Assessment (MIDAS); for the latter outcome, it is unclear if the difference is clinically meaningful.
    - No data on intermediate- or long-term outcomes were available

Spinal Manipulation Therapy versus Sham

- No trials were identified that met the inclusion criteria.

Spinal Manipulation Therapy versus Active Control

- Spinal Manipulation Therapy versus Amitriptyline: one small RCT provided data on primary outocmes
    - In the short-term (4 weeks), SMT resulted in a statistically greater proportion of patients achieving >20% and >40%, but not >60%, reduction in Headache Index scores from baseline compared with amitriptyline. There was no statistical difference between groups in the mean reduction in the percentage of days per month with headache. The strength of evidence was low for all outcomes.
    - No data on intermediate- or long-term outcomes were available.

Massage versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham

Two small RCTs provided data on primary outcomes over the short-term only for this comparison:

- At 4 weeks in one RCT, transcranial magnetic stimulation (TMS) resulted in a statistically greater improvement in all outcomes measured compared with sham (low quality evidence for all):

proportion of patients achieving a >50% reduction in migraine attacks and in headache severity; reduction in the mean number of migraine attacks per month; and the proportion of patients improving to a functional disability rating of normal or mild.

- At 8 weeks in a second RCT, no statistical differences were seen between low-frequency TMS and sham for reduction in migraine attacks and reduction in migraine days during the 8 week period following treatment; however, all data is of insufficient quality to draw conclusions.
- No data on intermediate- or long-term outcomes were available.

Transcranial Magnetic Stimulation versus Active Control

- No trials were identified that met the inclusion criteria.

Trigger Point Injection versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

4.2.1.1. OnabotulinumtoxinA (BoNTA) versus Placebo for Chronic Migraine

Studies included

Four RCTs[25,64,74,172] were identified that met our inclusion criteria and randomized as few as 49 and as many as 705 participants (Tables 9 and 11). Brief overviews of the trials are included below. Detailed information on participant and study characteristics is available in Appendix Table F1.

The largest of the RCTs were the PREEMPT 1 (N=679)[25] and 2 (N=705)[64] trials which were part of the Phase III REsearch Evaluating Migraine Prophylaxis Therapy clinical program sponsored by Allergen, Inc. and were operated in tandem: PREEMPT 1 was conducted from January 2006 to July 2008 at 56 sites (all North American) and PREEMPT 2 was conducted from February 2006 to August 2008 at 66 sites (50 North American and 16 European). The design of both trials was identical, consisting of a 28-day baseline screening period followed by a 24-week, double-blind, placebo-controlled phase wherein participants were randomized to receive BoNTA 155 U or placebo (i.e. saline) at 31 fixed injection sites across seven specific head/neck muscle areas (additionally, 40 U could be administered into the temporalis occipitalis and/or trapezius muscles using a follow-the-pain strategy at the investigator's discretion), Table 9. Thus, the maximum dose per treatment cycle was 195 U. Injections were administered at baseline and 12 weeks with the primary follow-up time point at 24 weeks (12 weeks after the second injection). Authors do not provide data on the proportion of placebo responders in each group during the baseline phase, but suggest that the proportion may have been large in their discussion. All participants who completed the double-blind phase of the trial were eligible to receive BoNTA treatment at weeks 24, 36 and 48 in an open-label phase of the study. Details of this open label phase, which was un-blinded and non-randomized, and related results are described in more detail following the efficacy section below.

The mean age and proportion of females was similar across the PREEMPT 1 and 2 trials, 41.6 versus 40.9 years and 87.5% versus 85.4%, respectively; the majority of patients in both trials (~90%) were Caucasian. Regarding headache characteristics (Table 9), the mean duration of migraine symptoms

ranged from 18.0 to 20.4 years across the trials. Patients in both trials reported a mean of 19 days per month with migraine at baseline (and a mean 20/days per month with *headache*) and over 90% reported severe disability as a result (i.e., score of ≥60 on the Headache Impact Test which measures pain; social, work and cognitive function; vitality; and psychological distress). The proportion of patients reporting prior use of one or more prophylactic medications was substantial in both the PREEMPT 1 (59.5% of BoNTA, 64.2% placebo)[25] and PREEMPT 2 trials (64.0% and 66.2%, respectively).[64] A total of 68% of PREEMPT 1 and 63% of PREEMPT 2 reported medication overuse at baseline defined as intake of simple analgesics on ≥15 days, or other medication types or combination of types for ≥10 days, with intake ≥2 days/week from the category of overuse.[25] Both trials stratified randomization based on overuse (yes/no) and the proportion was balanced across treatment groups at baseline.

The PREEMPT 1 and 2 trials, reported in six included publications,[24-26,64,67,114] were at LOW risk of bias meeting all the criteria for a good quality trial (risk of bias assessment for all studies is found in Appendix Table E1). An overview of the various PREEMPT publications is provided in Table 10. The results presented in this report focus on data from the two index trials when possible; for some outcomes only pooled data across both PREEMPT trials were available.

Table 9. Summary of Patient, Baseline and Procedural Characteristics from the Double-Blind, Randomized Phase of the PREEMPT trials, BoNTA versus Placebo in CM

Patient demographics	Study					
	PREEMPT 1 (Aurora 2010)		PREEMPT 2 (Diener 2010)		PREEMPT 1 & 2 (Aurora 2011, Lipton 2011, Dodick 2010)*	
Population	N = 679		N = 705		N = 1384	
	BoNTA	Placebo	BoNTA	Placebo	BoNTA	Placebo
Randomized	n=341	n=338	n=347	n=358	n=688	n=696
Treated	n=296	n=295	n=311	n=334	n=607	n=629
Age, years; mean ± SD	41.2	42.1	41.0	40.9	41.1 (10.4)	42.3 (10.7)
% Female	89.1%	85.8%	86.2%	84.6%	87.6%	85.2%
Mean Chronicity of Headache (years)	20.3	20.6	18.5	17.6	19.4	19.0
Mean # HA days/month	20.0 (3.7)	19.8 (3.7)	19.9 (3.6)	19.7 (3.7)	19.9 (3.7)	19.8 (3.7)
Mean # Migraine days/month	19.1 (4.0)	19.1 (4.1)	19.2 (3.9)	18.7 (4.1)	19.1 (4.0)	18.9 (4.1)
Mean # HA attacks/month	12.3 (5.2)	13.4 (5.7)	12.0 (5.3)	12.7 (5.3)	12.2 (5.3)	13.2 (5.5)
Mean # Migraine attacks/month	11.5 (5.1)	12.7 (5.7)	NR	NR	11.4 (5.0)	12.2 (5.5)
Percent with medication overuse	66.3%	69.8%	63.4%	62.6%	64.8	66.1
Patients who had prior preventative treatments	59.5%	64.2%	64.0%	66.2%	NR†	NR†
Procedural characteristics						
Doses of Botox, placebo (saline), units (U)	155–195	155–195	155–195	155–195	155–195	155–195

Patient demographics	Study					
	PREEMPT 1 (Aurora 2010)		PREEMPT 2 (Diener 2010)		PREEMPT 1 & 2 (Aurora 2011, Lipton 2011, Dodick 2010)*	
Number of Treatments‡	2	2	2	2	2	2
Number of Muscle Areas	7	7	7	7	7	7
Number of Injection sites	31-39	31-39	31-39	31-39	31-39	31-39
Length of double-blind phase	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks
% F/U (at end of 24 week randomized phase)	86.8%	87.3%	89.6%	93.3%	88.2%	90.4%
Co-interventions	NR	NR	NR	NR	NR	NR
Country	Canada, U.S. (56 sites)		50 sites in North America, 16 sites in Europe (66 sites)		Canada, U.S. Croatia, Germany, Switzerland, UK (multicenter)	
Funding	Allergan, Inc.		Allergan, Inc.		Allergan, Inc.	

BoNTA: OnabotulinumtoxinA; CM: chronic migraine; COI: conflict of interest; F/U: follow-up; HA: headache; NA: not applicable; NR: not reported; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; SD: standard deviation; U: units
*These publications pooled results from the PREEMPT 1 and PREEMPT 2 trials; see Table 9 for details.
†Authors report that "two-thirds had previously failed to respond to HA prophylactic medications"
‡ Injections were received at beginning of treatment and at 12 weeks into 24 week treatment phase.

Table 10. Overview of PREEMPT Trial Publications

	Publication	Randomized Phase	Open-label Phase*	Comments
PREEMPT 1	Aurora 2010	N=679	N=607	• Index report
PREEMPT 2	Diener 2010	N=705	N=629	• Index report
POOLED ANALYSES of PREEMPT 1 and 2†	Dodick 2010	N=1384	NR	• Pooled results at 24-week follow-up (end of randomized, placebo-controlled phases) • All prespecified primary and secondary endpoints were evaluated
	Lipton 2011	N=1384	NR	• Pooled results at 24 week follow-up (end of randomized, placebo-controlled phases) • Only the HIT-6 (disability) and MSQ v2.1 (HRQoL) measures were evaluated; provided 12 week data not reported in Dodick 2010
	Aurora 2011	N=1384	N=1236	• Pooled results through 56 weeks of follow-up (end of open-label phase); patients in placebo groups crossed over to receive BoNTA after 24 weeks. During the open label phase, participants received 3 BoNTA injections. Thus a total of 5 BoNTA injections were received by those who had orginially been randomized to BoNTA (2 during randomized phase, 3 during open label) and those originally assigned to placebo placebo received 3

	Publication	Randomized Phase	Open-label Phase*	Comments
				BoNTA injections during the open label phase in addition to the saline placebo injections.† • All prespecified primary and secondary endpoints were evaluated
	Aurora 2014	N=1384	N=1005‡	• Pooled results through 56 weeks of follow-up (end of open-label phase); similar to Aurora 2011, however, this analysis only includes subjects that received all 5 treatment cycles‡

HIT-6: Headache Impact Test (6 items); HRQoL: Health-Related Quality of LifeMSQ: Migraine-Specific Quality of Life Questionnaire version 2.1; NR: not reported; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy.
*At the end of the 24-week randomized phase, patients from both treatment groups were allowed to participate in a 32 week open-label phase (nonrandomized), wherein all patients received three injection cycles of BoNTA.
†Authors state that pooling of the PREEMPT 1 and 2 studies was "performed for regulatory submissions and because the studies were of essentially the same design and were run almost simultaneously. Also, pooling provided additional statistical power to identify safety and tolerability results that could be missed if each study were only reported individually".
‡Two treatment cycles were performed during the randomized, placebo-controlled phase and were either BoNTA injections or placebo. Three treatment cycles were performed during the Open-label Phase and all patients received BoNTA injections. This study thus compares those who received 5 treatment cycles of BoNTA (i.e., originally randomized to BoNTA) to those who received 3 cycles of BoNTA (i.e., originally randomized to placebo).

Two smaller, single-site trials (N=49 and 60)[74,172] were also included (Table 11). The mean age of the patients in both trials was 42.3 years and the majority were female (73.2% and 84.4%). Both trials employed a double-blind, placebo-controlled design using a fixed dose and fixed site approach. Following a 28-day baseline period, patients were randomized to receive BoNTA – 100 U at 22 injection sites across five specific head/neck muscle areas in one trial[74] and 135 to 205 U (based on weight) at 22 injection sites across six specific head/neck muscle areas in the other[172] – or placebo which consisted of sterile saline delivered in a manner identical to that of the BoNTA groups. Patients were followed for a total of 16 weeks after baseline in one trial[74] and 12 weeks in the other[172]; in both trials, patients were assessed every 4 weeks until the end of the study period. These trials did not include an open-label phase.

Regarding headache characteristics (Table 11), the mean duration of migraine was 19.5 years (BoNTA 20.5 years vs. Placebo 18.6 years) in one trial[172]; mean chronicity was not reported by the other trial.[74] At baseline, the mean number of days per month with migraine was 19.4 (BoNTA 20.6 days vs. Placebo 18.4 days) in one trial[172]; the second trial reported a mean of 23 days with headache in both groups (unclear from article whether this refers specifically to migraine headache) and a mean of 14.2 migraine attacks/episodes per month (BoNTA 13.8 and Placebo 14.6).[74] Freitag et al. 2008 specifically excluded patients with medication overuse at baseline and provided detailed criteria used to diagnoses this condition (criteria varied based on the type of medication: simple and combination analgesics, narcotics, ergotamine/dihydroergotamine, triptans, and caffeine); acute medication use in this population averaged 20 doses/month (BoNTA 19 and Placebo 21) at baseline (no further details provided).[74] This same trial allowed patients to continue taking preventive medications throughout the duration of the trial as long as they had been on stable doses of the medication for 60 days prior to enrollment. The second trial, Vo et al. 2007, did not specifically exclude patients with medication overuse and indicated that the majority of subjects (75%) used sumatriptan to control their headaches (the remaining patients used various other triptans and NSAIDs).[172] Prior prophylactic medications utilized in this population

included primarily rofecoxib, naproxen, and hydroxychloroquine sulfate; the authors of this trial did not indicate whether or not patients were required to stop current prophylactic treatments upon study entry.

Both of the smaller RCTs were considered to be at MODERATELY HIGH risk of bias. Limitations included lack of information regarding random sequence generation,[74] , concealment of allocation,[74,172] and intention-to-treat.[172] Both trials also suffered from significant loss to follow-up: 35% by 12 weeks in the trial by Vo et al. 2007 and 40% by 16 weeks in the trial by Freitag et al. 2008. Of note, in the latter trial, a total of 19 patients were excluded after randomization but before treatment due to medication overuse (one of the authors' exclusion criteria) and not accounted for in any analysis. Risk of bias assessment for all studies is found in Appendix Table E1.

Table 11. Summary of Patient, Baseline and Procedural Characteristics from Additional RCTs Evaluating BoNTA versus Placebo in CM

	Freitag 2008		Vo 2007	
Population	N = 60		N = 49	
	BoNTA	**Placebo**	**BoNTA**	**Placebo**
Randomized	n=30	n=30	NR†	NR†
Treated	n=20	n=21	n=15†	n=17†
Age, years; mean ± SD	42.2	42.4	44.3 (11.3)	40.7 (4.2)
% Female	75%	71.4%	86.7%	82.4%
Mean Chronicity of Headache (years)	NR	NR	20.5 (11.2)	18.6 (10.1)
Mean # HA days/month	23	23	NR	NR
Mean # Migraine days/month	NR	NR	20.6 (5.7)	18.4 (8.4)
Mean # HA attacks/month	NR	NR	NR	NR
Mean # Migraine attacks/month	NR	NR	NR	NR
Percent with medication overuse	0%*	0%*	NR	NR
Patients who had prior preventative treatments	NR	NR	75%‡	
Procedural characteristics				
Doses of Botox, placebo	100 U	100 U	135 or 205 U§	135 or 205 U§
Number of Treatments	1	1	NR	NR
Number of Muscle Areas	5	5	6	6
Number of Injection sites	22	22	22	22
Length of F/U past treatment	16 weeks	16 weeks	12 weeks	12 weeks
% F/U at Last F/U	70%	70%	65.3%**	
Co-interventions	NR		NR	
Country	United States		United States	
Funding	Allergan, Inc.		Comprehensive Neuroscience Program and The Uniformed Services University of the Health Science Award	

BoNTA, onabotulinumtoxinA; CM, chronic migraine; COI, conflict of interest; F/U, follow-up; HA, headache; NA, not applicable; NR, not reported; SD, standard deviation; U, units
*19 were excludedin Freitag after randomization due to medication overuse.
†17 patients dropped out immediately following treatment. The study did not report the number patients randomized into each group before the drop-outs, only the number that were treated in total.
‡Vo reported that 75% used sumatriptan and the rest used a variety of other pharmacological medications, but did not give a specific overall value. Will this suffice?
§ Patients less than 65 kg received 135 U while patients 65 kg or greater received 205 U
**The follow-up percentage is based on the overall percentage of the population because exact data on group size before drop-outs was not reported.

Efficacy (RCT) Results

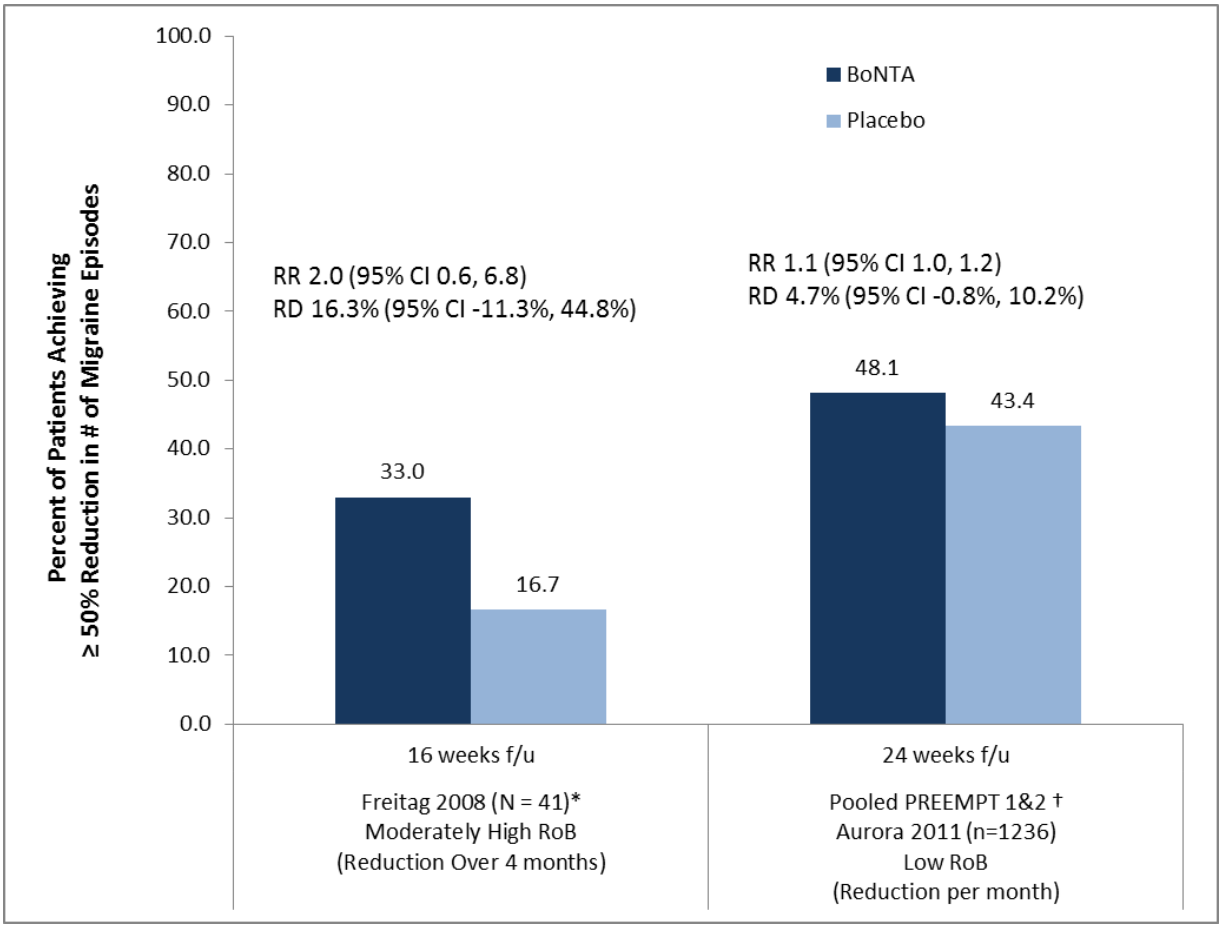
Findings from the double-blinded phases of the PREEMPT 1 and 2 trials provided the bulk of the evidence comparing BoNTA with placebo. Two injections were given, one at day 0 and the second at 12 weeks, with 12 weeks of follow-up after the second injections for a total of 24 weeks for the double-blind placebo controlled phase. Data from the unblinded, non-randomized, open label phase of the PREEMPT trials are presented at the end of the section.

Treatment Responders

Treatment responders were defined as those who experienced ≥50% reduction in *migraine* episodes *migraine* days and/or *headache* days. Data from PREEMPT 1 and 2 trials[25,26,64] and one small trial[74] were available.

<u>*Longer term (16-24 weeks):*</u> The proportion of participants who experienced ≥50% reduction in *number of <u>migraine</u> episodes* per month from baseline was higher following BoNTA compared to placebo, but statistical significance was not reached in three trials.[25,64,74] Differences in time frames for evaluating the reduction in the number of migraines precluded pooling across all the three trials. The difference between BoNTA and placebo was not statistically significant base on pooled data across PREEMPT 1 and 2 trials with regard to 50% reduction in *number migraine episodes*, (RR 1.1, 95% CI 1.0, 1.2),[26] Figure 5. Over 60% of participants in the PREEMPT trials reported medication overuse at baseline. Results did not reach statistical significance in the one small moderately high risk of bias trial at 16 weeks (RR 2.0, 95% CI 0.6, 6.8).[74] Although this trial excluded patients with medication overuse, an unknown proportion of them were taking other prophylactic medications concurrently. Alternatively, when the number of migraine days and overall headache days are considered, the proportion of participants who experienced ≥50% reduction in number of *migraine days* (RR 1.3 95% CI 1.1, 1.5) and *overall headache days* (RR 1.3 (95% CI 1.2, 1.5) favored BoNTA over placebo based on pooled estimates from the PREEMPT 1 and 2 trials[26] (Figure 6), with a risk difference of 12% between treatments; medication overuse at baseline was reported in 64.8% of BoNTA and 66.1% of placebo recipients. Over 60% of patients had used one or more prophylactic medications prior to the trial.

Figure 5. Percent of Patients Experiencing ≥ 50% Reduction in Number of Migraine Episodes Longer Term (≥ 12 weeks): BoNTA versus Placebo in CM

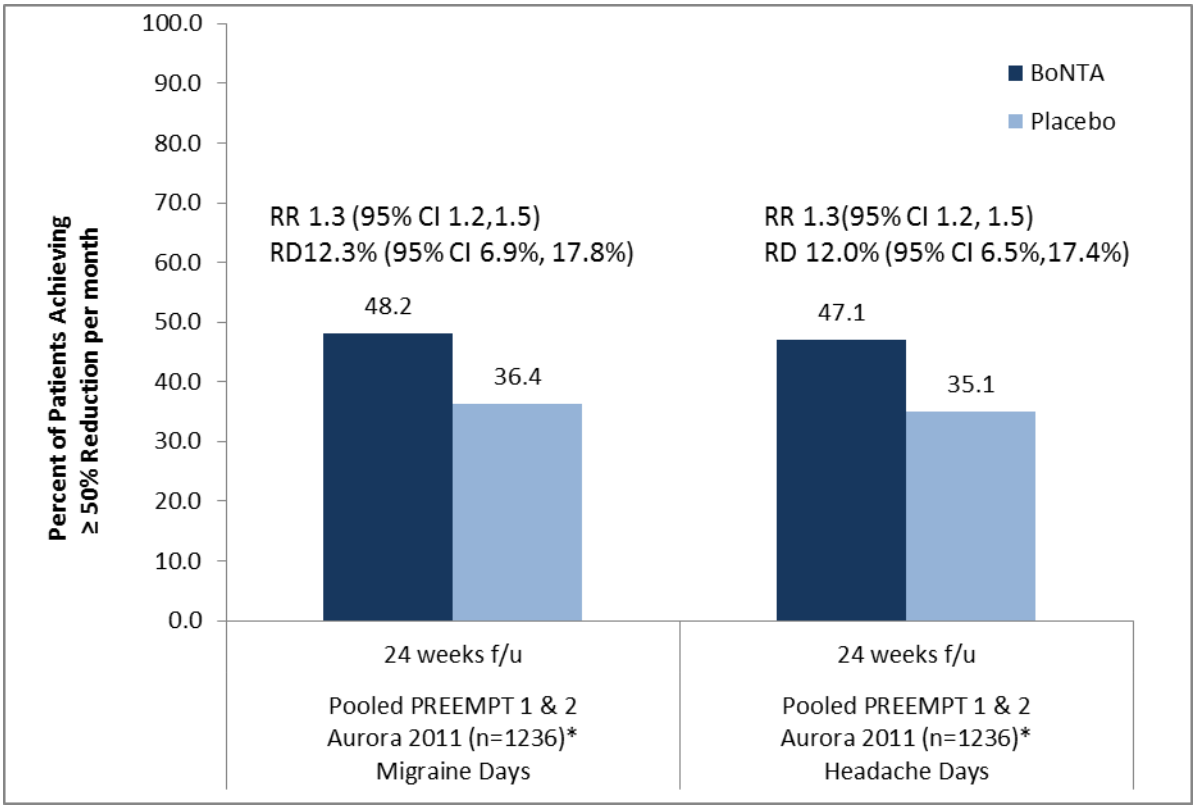


BoNTA: OnabotulinumtoxinA; CM: chronic migraine; f/u: follow-up; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; RD: risk difference; RoB: risk of bias; RR: risk ratio.

*Freitag 2008 excluded patients with medication overuse but included patients with concomitant use of other prophylactic medications.

†Only pooled PREEMPT 1 and 2 data were available for this outcome; data used are "observed data" (without imputation for missing values). Medication overuse was present in 64.8% of BoNTA and 66.1% of placebo participants at baseline.

Figure 6. Percent of Patients Experiencing ≥ 50% Reduction in Migraine Days and Headache Days at Long-term Follow-up (24 weeks): BoNTA versus Placebo in CM

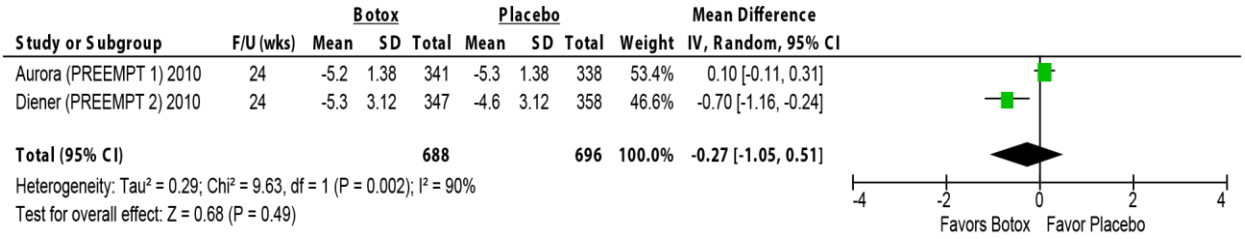


BoNTA: OnabotulinumtoxinA; CM: chronic migraine; f/u: follow-up; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; RD: risk difference; RR: risk ratio.
*Only pooled PREEMPT 1 and 2 data were available for these outcome; data used are "observed data" (without imputation for missing values). Medication overuse was present in 64.8% of BoNTA and 66.1% of placebo participants at baseline.

Reduction in Mean Frequency of Headache Episodes and Days

Longer-term (12-24 weeks): The reduction in number of headache episodes per month at 24 weeks after initiation of treatment was reported in the two PREEMPT trialswith low risk of bias.[25,64] Reductions were similar across groups in the pooled analysis comparing BoNTA to placebo, mean difference -0.27 (95% CI -1.05, 0.51), I^2= 90%Figure 7. Substantial heterogeneity is noted, however the cause is not clear; the methods for both trials were similar, >60% of patients in both trials had medication overuse at baseline.

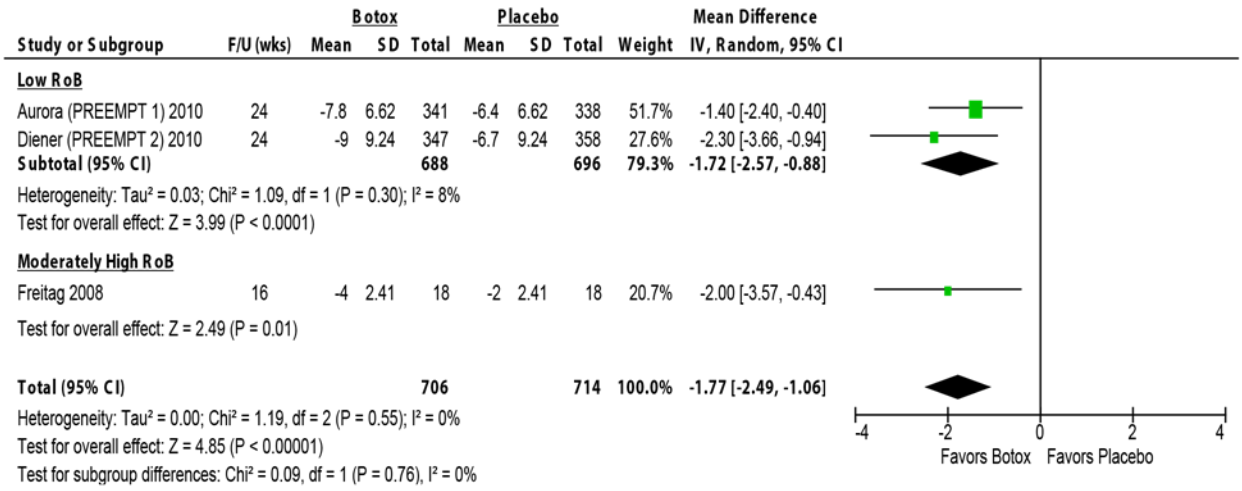
Figure 7. Pooled Analysis of Reduction in Frequency of Headache Episodes per Month at Long-term Follow-up (24 weeks): BoNTA versus Placebo in CM



A third small trial (Vo et al. 2007) with a moderately high risk of bias reported no significant differences between groups in the frequency of headache episodes per month (no data available); this trial experienced a large loss to follow-up (35%) at 12 weeks.[172]

Reduction in frequency of headache days per month at 16 to 24 weeks after initiation of treatment was reported in three studies.[25,64,74] The reduction was statistically greater in the BoNTA group compared to placebo in a pooled analysis, mean difference -1.77 (95% CI -2.49, -1.06), I^2= 0% Figure 8. It is not clear if a difference of 1.7 days is clinically meaningful. As previously noted, over 60% of participants in the PREEMPT trials reported medication overuse at baseline and the Freitag trial excluded patients with medication overuse.

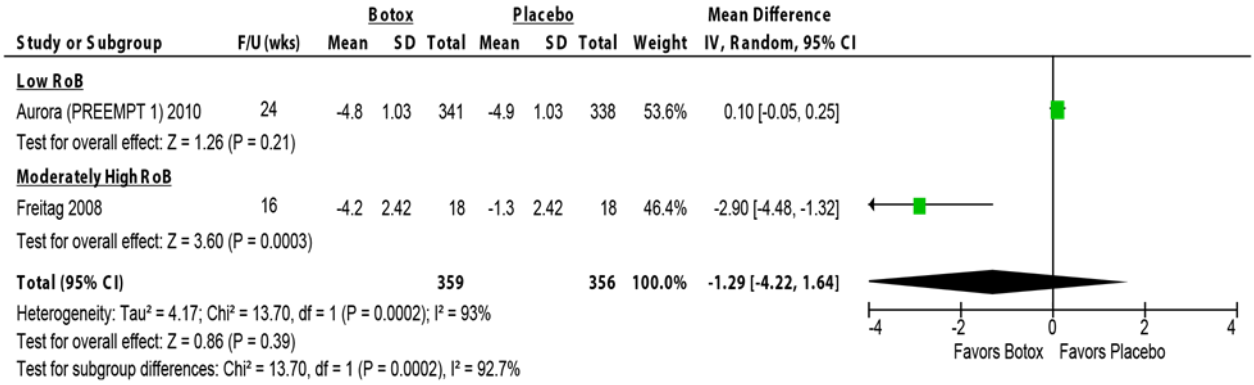
Figure 8. Pooled Analysis of Reduction in Frequency of Headache Days per Month over the Longer term (≥ 12 weeks): BoNTA versus Placebo in CM*



*Medication overuse was present in 68% of PREEMPT 1 and 63% of PREEMPT 2 participants at baseline; Freitag 2008 excluded patients with medication overuse.

The reduction in the frequency of migraine *episodes* per month varied across the two trials reporting this outcome and was not statistically different in a pooled analysis of two studies at low to moderately low risk of bias, mean difference -1.29 (95% CI -4.22, 1.64),) I^2= 93%,[25,74] Figure 9. It is not clear if this difference is clinically meaningful. The reason for the large amount of heterogeneity is unclear; it may be due to a variety of factors; the PREEMPT trial, which was at low risk of bias included >60% of patients with medication overuse whereas the smaller Freitag 2008, which was at moderately high risk of bias excluded those with medication overuse and baseline frequency of migraine episodes were similar (estimated from graph, p = 0.255).

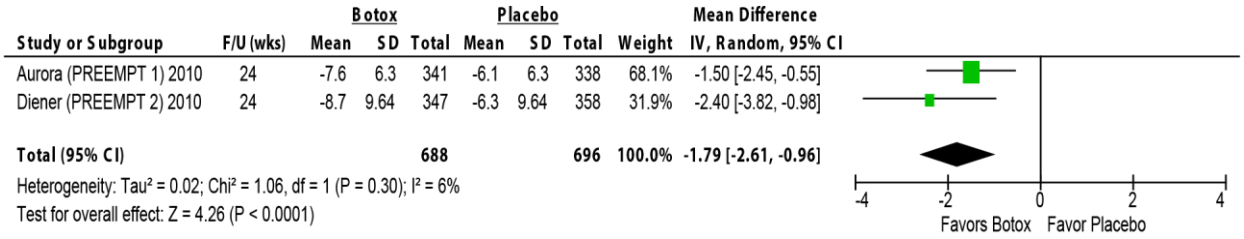
Figure 9. Pooled Analysis of Reduction in Frequency of Migraine Episodes per Month over the Longer-term (≥ 12 weeks): BoNTA versus Placebo in CM*



*Medication overuse was present in 68% of PREEMPT 1 participants at baseline; Freitag 2008 excluded patients with medication overuse;

The reduction in number of *migraine days* per month at 24 weeks after initiation of treatment was reported in the two PREEMPT trials with low risk of bias.[25,64] In a pooled analysis, there was a significantly greater reduction in the BoNTA group compared to placebo, mean difference -1.79 (95% CI -2.61, -0.96),) I^2= 6%, Figure 10. It is not clear that a difference of 1.8 days is clinically meaningful. As previously noted, >60% of participants reported medication overuse at baseline.

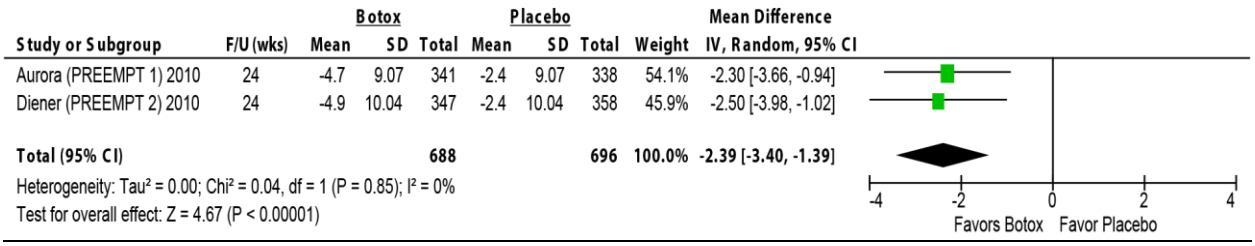
Figure 10. Pooled Analysis of Reduction in Frequency of Migraine Days per Month at Long-term Follow-up (24 weeks): BoNTA versus Placebo in CM



Function and Disability

Longer-term (16-24 weeks): The two PREEMPT trials at LOW risk of bias reported the reduction in Headache Impact Test-6 (HIT-6) scores at 24 weeks after initiation of treatment.[25,64] In a pooled analysis, there was a significantly greater reduction in the BoNTA group compared to placebo, mean difference -2.39 (95% CI -3.40, -1.39) I^2= 0%. The change from baseline in the BoNTA group was -4.7 and -2.4 in the placebo group. For patients with chronic daily headache (≥ 15 headache days/month), one study suggests that a between group difference in change scores of 2.3 units over time may be considered clinically significant[62] (Figure 11).

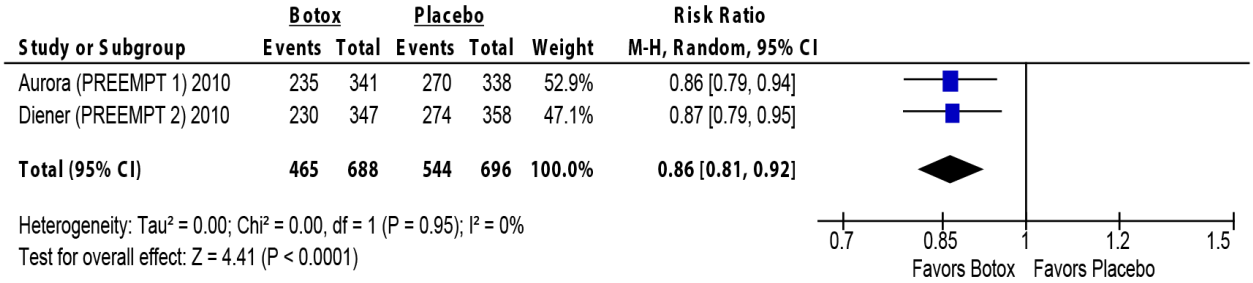
Figure 11. Pooled Analysis of Reduction in HIT-6 Scores at Long-term Follow-up (24 Weeks): BoNTA versus Placebo in CM



*Headache Impact Test-6 (HIT) measures the impact headache has on function. Higher scores = higher impact on activities of daily living; a between-group difference in change scores of 2.3 units may be considered clinically significant in patients with ≥ 15 headache days/month.

In a pooled analysis, the percentage of participants with a severe (≥ 60) HIT-6 score at 24 weeks after initiation of treatment was significantly less in the BoNTA group compared to placebo, risk ratio (RR) 0.86 (95% CI 0.81, 0.92) I^2= 0%,[25,64] Figure 12.

Figure 12. Pooled Analysis of Percentage of Participants with a Severe HIT-6 Score (≥60)* at Long-term Follow-up (24 Weeks), BoNTA versus Placebo in CM



*Headache Impact Test-6 (HIT) measures the impact headache has on function. Higher scores = higher impact on activities of daily living; Scoring interpretation- Little or no impact: <46, Some impact: 50 – 55, Substantial impact: 56 – 59, Severe impact: 60 –78; a between-group difference in change scores of 2.3 units may be considered clinically significant in patients with ≥ 15 headache days/month.

One small trial (Freitag 2008)[74] with a moderately high risk of bias reported a greater reduction in the Migraine Disability Assessment Scale (MIDAS) score (0-27 [worst]) changes between baseline with the BoNTA group (-11 points) compared with the placebo group whose scores worsened (+2 points); authors describe this as not statistically significant.

Secondary Outcomes (RCTs)

Health Related Quality of Life (HRQoL): HRQoL was measured with the Migraine Specific Quality of Life Questionnaire (MSQ) in three RCTs,[25,64,172] all at longer-term follow-up. In a pooled analysis of the PREEMPT 1 AND 2 trials, there was a statistically significant improvement in HRQoL in the BoNTA group compared to placebo for all three domains of the MSQ at 24 weeks (Aurora 2011; restrictive: MD 8.4, 95% CI 10.8, 6.0; preventive: MD 6.7, 95% CI: 9.0, 4.4; emotional: MD 8.4, 95% CI: 11.4, 5.6). One trial with a moderately high risk of bias reported no significant differences between treatment groups for the three MSQ domains at 12 weeks (data not provided).[172] In one trial with a moderately low risk of bias, there were no significant differences between treatment groups in the Headache Pain Specific QoL at 16 weeks (BoNTA: 14±53.9, placebo: 22±48.2; MD: -8.0, 95% CI: -42.6, 26.6),[74] Table 12.

Table 12. Summary of Quality of Life Measures: BoNTA versus Placebo Chronic Migraine

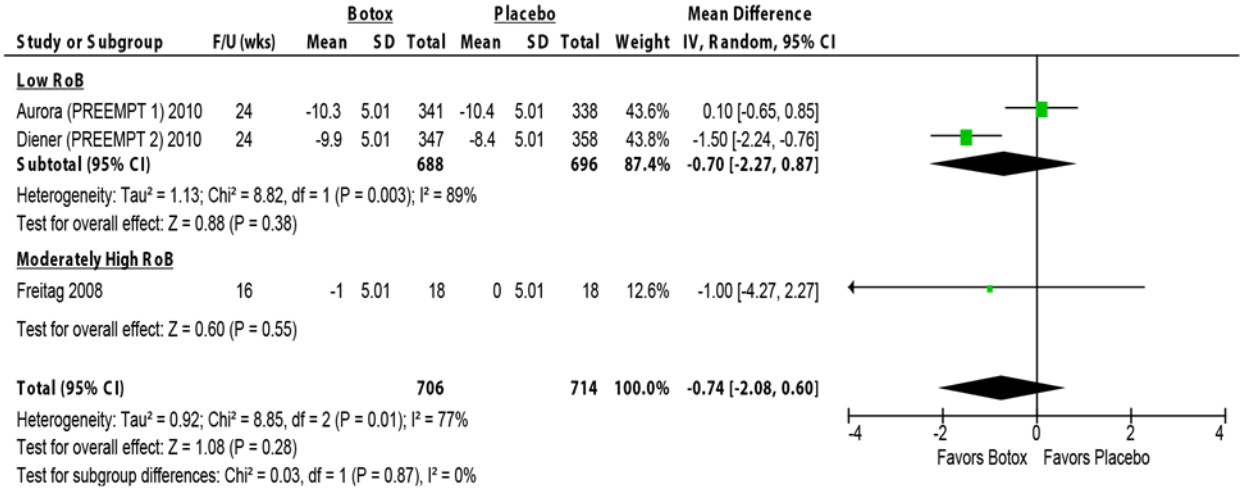
Risk of Bias	Study	F/U	BoNTA Mean ± SD or Mean (95% CI)	Comparator Mean Δ	MD (95% CI)	p-value
Headache Pain Specific QoL, Δ from baseline (higher score proportional to greater disability)						
Mod High	Freitag 2008*	16	14 ± 53.9	22 ± 48.2	-8.0 (-42.6, 26.6)	P=0.642
Headache related QoL restrictive, Δ from baseline (higher score proportion to higher quality of life)						
Low	Aurora 2011, Dodick 2010 *(Pooled across PREEMPT 1 and 2)*	24	17 (18.7, 15.2)	8.6 (10.2, 7.0)	8.4 (10.76, 6.01)	P<0.001
Headache related QoL preventive, Δ from baseline (higher score proportion to higher quality of life)						
Low	Aurora 2011 *(Pooled across PREEMPT 1 and 2)*	24	13.1 (14.8, 11.4)	6.4 (8.0, 4.9)	6.7 (9.01, 4.35)	P<0.001
Headache related QoL emotional, Δ from baseline (higher score proportion to higher quality of life)						
Low	Aurora 2011 *(Pooled across PREEMPT 1 and 2)*	24	17.9 (20.1, 15.8)	9.5 (11.4, 7.5)	8.4 (11.37, 5.56)	P<0.001

BoNTA, OnabotulinumtoxinA; CI, confidence interval; F/U, follow-up; MD, mean difference; Mod, moderately; QoL, quality of life; SD, standard deviation

* Only 41 of 60 individuals randomized received treatment.

Medication use: Reduction in frequency of acute headache medication intake per month was reported in three studies, two with a low (PREEMPT trials) risk of bias, the other (Freitag) with a moderately high risk of bias, reporting outcomes after 16 to 24 weeks of follow-up (long-term).[25,64,74] A pooled analysis reported nonsignificant differences between the BoNTA and placebo groups, mean difference -0.74 (95% CI -2.08, 0.60), Figure 13.

Figure 13. Pooled Analysis of Reduction in Frequency of Acute Headache Medication Intake per Month over Longer-term Follow-up (≥ 12 Weeks), BoNTA versus Placebo for CM*



*Medication overuse was present in 68% of PREEMPT 1 and 63% of PREEMPT 2 participants at baseline; Freitag 2008 excluded patients with medication overuse but permitted concomitant use of other prophylactic medications.

Headache Intensity: One small trial (Freitag 2008) with a moderately high risk of bias reported a significantly greater reduction in headache severity in the BoNTA compared to placebo group at long-term follow-up (i.e., 16 weeks), measured with the Headache Index (HAI) (BoNTA: -6.1 ± 2.2, placebo: -3.8 ±).[74]

Open label (BoNTA only, case series) phase of PREEMPT 1 and 2

All participants who completed the 24 week double-blind phase of the PREEMPT 1 and 2 trials[25,64] were eligible to receive BoNTA treatment at weeks 24, 36 and 48 in an open-label, uncontrolled phase of these studies. Two treatment cycles were performed during the randomized, placebo-controlled phase and were either BoNTA injections or placebo. Three treatment cycles were then performed during the open-label phase and all patients received BoNTA injections at weeks 24, 36 and 48 then followed to 56 weeks. Thus a total of five BoNTA injection cycles were received by those who had originally been randomized to BoNTA (2 during randomized phase, 3 during open label) and those originally assigned to placebo received three BoNTA injection cycles during the open label phase. Across the PREEMPT 1 and 2 trials, of those originally randomized to receive BoNTA, 513 patients continued to the open label phase and 492 patients who were originally randomized to placebo continued to the open label phase in addition to the two placebo (saline) injection cycles given during the double-blind randomized phase; thus patients could receive a total of five treatment cycles.

The Aurora 2014 publication[24] compares results for patients who received a total of five BoNTA injections to those receiving three total BoNTA injections/two placebo injections. Pooled results from the open label phases of both PREEMPT 1 and 2 for patients who had completed five treatment cycles (n = 1005) were reported in one publication (Aurora 2014)[24]. The mean age (42 years old) and proportion

of females (86%) reflects those of the index trials as does the mean number of headache days (19.9) and mean number of migraine days per month (19) and were similar between those receiving five BoNTA injections and those receiving three BoNTA injections (Table 13). The mean number of migraine episodes and headache episodes was statistically different between the two groups, however. As noted during the double-blind phase of the trial, >60% of participants reported overuse of acute headache medication at baseline.

The open label phase was considered as a case series for the purposes of this report and thus, considered at high risk of bias. Findings from this phase were not considered in the overall strength of evidence. Data on this phase are reported for context and completeness.

Table 13. Summary of Patient, Baseline and Study Characteristics for Subanalysis of PREEMPT 1 and 2 Open-Label Phase.

Patient demographics	Study	
	PREEMPT 1 & 2, Open-Label Completers (Aurora 2014)	
Population	N = 1005	
Comparators	**O/O***	**P/O***
Treated	n=513	n=492
Age, years; mean ± SD	41.4 (10.2)	42.3 (10.7)
% Female	87.7%	86.4%
Mean Chronicity of Headache (years)	19.6 (12.4)	19.3 (12.6)
Mean # HA days/month	19.9 (3.7)	19.8 (3.7)
Mean # Migraine days/month	19.1 (4.0)	19.0 (4.0)
Mean # HA attacks/month	12.4 (5.3)	13.2 (5.6)
Mean # Migraine attacks/month	11.6 (5.1)	12.4 (5.5)
Percent with medication overuse	64.9	68.5
Patients who had prior preventative treatments	NR	NR
Procedural characteristics		
Doses of Botox	155 U-195 U	155 U-195 U
Number of BoNTA Treatments	5 (O/O)*	3 (P/O)*
Number of Muscle Areas	7	7
Number of Injection sites	31	31
Length of open-label phase past end of 24 week double-blind phase	32 weeks	32 weeks
% F/U	N/A†	N/A†
Co-interventions	NR	
Country	North America and Europe‡	
Funding	Allergan, Inc.	

BoNTA: OnabotulinumtoxinA; CM: chronic migraine; COI: conflict of interest; F/U: follow-up; HA: headache; NA: not applicable; NR: not reported; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; SD: standard deviation; U: units
* The O/O treatment arm includes patients who received 5 cycles of OnabotulinimtoxinA, 2 cycles in randomized portion and 3 cycles in open-label. The P/O treatment arm represents those who received 2 cycles of placebo in the blind portion of the trial and who continued on to receive 3 cycles of OnabotulinimtoxinA in the open-label portion.
† F/U percentage is based on the percentage of the original study population (N=1384) who completed all five cycles in each treatment arm.
‡ Authors report the sites in the double-blind phase occurred across 56 sites in North America (PREEMPT 1) and 66 sites across North America and Europe (PREEMPT 2). Authors do not report the number of sites represented in this sub-analysis.

Results (Open label phase)

Authors report results to 56 weeks after the initial randomization treatments; thus the time frame includes both the time spent by patients in the randomized phase and in the open label phase for individuals who participated in both phases.

Treatment Responders:

At 56 weeks, in a pooled analysis of the open-label phase (n= 1005 participants) there was small but a statistically significant reduction in the proportion of participants who achieved a ≥ 50% reduction in headache days per month and migraine days per month in the five BoNTA injection group compared to the three BoNTA injection group (HA days: RR 1.1, 95% CI 1.0, 1.2; migraine days: RR 1.1, 95% CI 1.0, 1.2). The proportion of participants who achieved a ≥ 50% reduction in headache episodes per month and migraine episodes per month were similar across the two groups (HA episodes: RR 1.0, 95% CI 0.9, 1.1; migraine episodes: RR 1.0, 95% CI 0.9, 1.1),[24] Table 14 . Authors only report medication over use at baseline for the groups as randomized. At baseline >60% participants reported medication overuse; authors do not report the proportion of participants in the open-label phase who had previously used prophylactic medications or who had medication over use.

Table 14. Proportion of Patients Achieving ≥50% Treatment Response at 56 weeks: Pooled Data from PREEMPT 1 and 2 Open Label Phases.

Outcome	BoNTA 5 Treatments (n=513)	BoNTA 3 Treatments (n=492)	RR (95% CI)
≥ 50% Reduction in Frequency of Headache Days/month	69.6%	62.8%	1.1 (1.0, 1.2)
≥ 50% Reduction in Frequency of Migraine Days/month	69.0%	60.8%	1.1 (1.0, 1.2)
≥ 50% Reduction in Frequency of Headache Episodes/month	72.5%	71.3%	1.0 (0.9, 1.1)
≥ 50% Reduction in Frequency of Migraine Episodes/month	72.1%	70.3%	1.0 (0.9, 1.1)

BoNTA: OnabotulinumtoxinA; F/U: follow-up; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; RR: risk ratio.
*These data are for the open-label phase of the study. Patient initially randomized to receive BoNTA received 5 BoNTA treatments; those origininally randomized to placebo received 3 BoNTA treatments during the open label phase.

Reduction in Mean Frequency of Headache Episodes and Days

At 56 weeks, there was a statistically significant reduction in the frequency of headache days per month and migraine days per month in the five BoNTA injection group compared to the three BoNTAinjection group (HA days: MD -0.9, 95% CI: -1.7, -0.1; migraine days: MD -0.9, 95% CI: -1.7, -0.1), however, the difference likely does not constitute a clinically meaningful difference. There were no significant differences between groups in the reduction in frequency of headache episodes per month or migraine episodes per month (HA episodes: MD -0.6, 95% CI: -1.3, 0.1; migraine episodes: MD -0.5, 95% CI: -1.2, 0.2),[24] Table 15.

Table 15. Summary of Changes in Headache Frequency, Medication Days, and Functional and QoL Measures at 56 weeks: Pooled Data from the PREEMPT 1 & 2 Open Label Phases

Outcome	BoNTA 5 Treatments* (n=513)	BoNTA 3 Treatments* (n=492)	Effect Size
Headache frequency and medication use outcomes	**Mean (95% CI) change from baseline**	**Mean (95% CI) change from baseline**	**MD (95% CI)**
Reduction in Frequency of Headache Days	-12.0 (-12.6, -11.5)	-11.1 (-11.8, -10.5)	-0.9 (-1.7, -0.1)
Reduction in Frequency of Headache Episodes	-8.1 (-8.3, -7.4)	-7.5 (-8.3, -7.3)	-0.6 (-1.3, 0.1)
Reduction in Frequency of Migraine Days	-11.6 (-12.2, -11.0)	-10.7 (-11.3, -10.0)	-0.9 (-1.8, -0.1)
Reduction in Frequency of Migraine Episodes	-7.5 (-7.7, -6.8)	-7.0 (-7.8, -6.8)	-0.5 (-1.2, 0.2)

Outcome	BoNTA 5 Treatments* (n=513)	BoNTA 3 Treatments* (n=492)	Effect Size
Reduction in Frequency of Acute Headache Medication Intake (Days/ Month)	-8.1 (-8.9, -7.4)	-7.5 (-8.2, -6.7)	-0.6, (-1.7, 0.5)
Functional Measures	**Mean (95% CI) change from baseline**	**Mean (95% CI) change from baseline**	**MD (95% CI)**
MSQ: Restrictive†	26.5 (24.3, 28.7)	24.5 (22.3, 26.8)	2.0 (-1.1, 5.1)
MSQ: Preventative†	20.3 (18.2, 22.4)	19.7 (17.5, 21.9)	0.6 (-2.4, 3.6)
MSQ: Emotional†	26.2 (23.7, 28.8)	24.6 (21.9, 27.3)	1.6 (-2.1, 5.3)
HIT-6 score‡	-8.1 (- 8.9, -7.4)	-7.5 (-8.2, -6.7)	-0.6 (-1.7, 0.5)
	% (95% CI)	**% (95% CI)**	**RD (95% CI)**
Proportion with Severe (≥ 60) HIT-6 score‡	47.8% (43.4%, 52.1%)	49.4% (45.0%, 53.8%)	-1.6% (-7.8%, 4.6%)
Proportion with ≥5-point reduction in HIT-6 score‡§	59.1% (54.8%, 63.3%)	57.7% (53.4%, 62.1%)	1.4% (-4.8%, 7.4%)

BoNTA: OnabotulinumtoxinA; CI: confidence interval; F/U: follow-up; HIT-6: Headache Impact Test-6; MD: mean difference; MSQ: Migrain-Specific Quality of Life Questionnaire; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy; RD: risk difference.
*These data are for the open-label phase of the study. Patient initially randomized to receive BoNTA received 5 BoNTA treatments; those origininally randomized to placebo received 3 BoNTA treatments during the open label phase.
†MSQ scores range from 0 (poor HRQoL) to 100 (good HRQoL).
‡HIT-6 scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; and 60–78, severe impact.
§A ≥5-point reduction is considered a clinically meaningful individual response.

Other outcomes: Reduction in medication use, HIT scores and MSQ

At 56 weeks, the reduction in frequency of acute headache medication intake days month was similar between the 5 treatment and 3 treatment BoNTA groups (5 treatments: -16.1 (-17.4, -14.1); 3 treatments: -16.1 (-18.2, -14.8); MD: 0.0, 95% CI -2.4, 2.4), Table 15.[24]

There were no significant differences in the three domains of the Migraine Specific Quality of Life Questionnaire (MSQ) between the 5 treatment and 3 treatment BoNTA groups at 56 weeks (restrictive: MD 2.0, 95% CI -1.1, 5.1; preventive: MD 0.6, 95% CI: -2.4, 3.6; emotional: MD 1.6, 95% CI: -2.1, 5.3), Table 15.[24]

There were no significant differences in reduction of HIT-6 scores between the 5 treatment BoNTA and 3 treatment BoNTA groups at 56 weeks (5 treatments: -8.1 (-8.9, -7.4); 3 treatments: -7.5 (-8.2, -6.7); MD: -0.6, 95% CI -1.7, 0.5), Table 15. The percentage of patients with a severe (≥ 60) HIT-6 score at 56 weeks was similar across groups (5 treatments: 47.8% (43.4%, 52.1%); 3 treatments: 49.4% (45.0%, 53.8%); RD: -1.6%, 95% CI: -7.8%, 4.6%), as was the proportion of patients with at least a 5-point reduction in HIT-6

scores (5 treatments: 59.1% (54.8%, 63.3%); 3 treatments: 57.7% (53.4%, 62.1%); RD: 1.4%, 95% CI: -4.8%, 7.4%).[24]

4.2.1.2. OnabotunlinumtoxinA versus Active control for Chronic Migraine

Studies included

Two RCTs, both at moderately high risk of bias, were identified that evaluated the efficacy of BoNTA versus active comparators which included topiramate in one trial[116,121] and amitriptyline in the other[116,121]. Brief overviews of each trial are provided below and in Table 16, and detailed information on patient and study characteristics is available in Appendix Table F1; for risk of bias ratings, see Appendix Table E1.

BoNTA vs. Topiramate for Chronic Migraine

In one, small double-blind trial (Mathew et al. 2009),[121] 60 participants suffering from chronic migraine were randomized to receive either a maximum dose of 200U of BoNTA (100U via fixed site approach and 100U via follow-the-pain approach) along with an oral placebo (n=30), or topiramate 25 mg titrated to 100mg/day (with the option for titration to 200mg) along with placebo (i.e., saline) injections (n=30). The population was 90% female, with a mean age of 36.8 years (Table 16). The authors state that other than mean age at onset (BoNTA 14.9 years vs. topiramate 20.0 years; p=0.015) the groups were similar in demographic characteristics at baseline; however, details were not provided. The number of injection sites and the total number of muscle areas that received injections were not reported. Follow-up occurred at 36 weeks with only 60% of BoNTA patients and 50% of topiramate patients completing the trial; reasons for discontinuation in each group, respectively, included adverse events in three (10%) and eight (27%) patients; lost to follow-up in eight (27%) and five (17%) patients; and other reason in one (3%) and two (7%) patients.

Regarding headache characteristics, mean symptom chronicity was not reported but inclusion criteria required a diagnoses of CM for >3 months. The mean frequency of HA/migraine days at baseline was similar between the BoNTA (15.6 days) and the topiramate group (15.5 days). The proportion of patients who had prior preventative treatments was not reported but all patients considered for inclusion were required to discontinue any prohibited medication such as nonstudy migraine prophylaxis medications (e.g. propranolol, amitriptyline, divalproex sodium) and nonstudy anticonvulsant or antiepileptic medications, agents that might interfere with neuromuscular function (e.g. aminoglycoside antibiotics, curare-like agents), along with others. Patients with evidence of recent alcohol/drug abuse or acute medication overuse (verified based on patient history) were excluded. Patients were permitted to continue their usual acute HA medications for acute attacks during the study period; a majority of patients were taking triptans, nonsteroidal anti-inflammatory drugs, or nasal dihydroergotamine. At baseline, the number of days on HA medication was 13.2 ± 6.3 in the BoNTA group and 10.8 ± 6.0 in the topiramate group.

This trial was considered to be at MODERATELY HIGH risk of bias due to limitations in reporting randomization and allocation approach, and intent-to-treat analysis; and a large loss-to-follow-up

(including a ≥10% difference between groups in follow-up) as described above. Risk of bias assessment is available in Appendix Table E1.

BoNTA vs. Amitriptyline for Chronic Migraine

One RCT was identified that compared BoNTA (n=35) with amitriptyline (n=37) for the treatment of chronic migraine (Magalhaes 2010).[116] Participants were randomized to receive either 250U of BoNTA across 15 injection sites (number of muscle areas injected was not reported), or 25-50 mg of amitriptyline daily (Table 16). In both groups, 97% of patients were female; those in the BoNTA group were somewhat younger than those who received amitriptyline (30 ± 10 vs. 38 ± 10 years). No other baseline demographics were provided. Follow-up assessments were performed at 4, 8 and 12 weeks and loss-to-follow-up was unclear.

Regarding headache characteristics, the mean symptom chronicity and the percentage of participants who had prior preventative treatments were not reported; however, the trial did list as an exclusion criteria the use of any antidepressant or other drug with potential preventative effects on headache within 3 months prior to enrollment. The mean frequency of headache days at baseline was similar between the treatment groups (~24 days for both). The number of drug doses taken at baseline for headache control (i.e., rescue medication) was greater in those who received BoNTA compared with amitriptyline, mean 39.7 ± 54 versus 29.3 ± 34 doses; the authors report this difference to be not statistically significant (p=0.5). The authors explicitly state that they did not control for the overuse of analgesics, therefore it is unclear what proportion, if any, of the population had medication overuse headache and how that may have affected the results of the trial.

This trial was considered to be at MODERATELY HIGH risk of bias due to limitations in reporting allocation concealment and intent-to-treat analysis; lack of information provided regarding loss-to-follow-up; and failure to provide a robust description of baseline characteristics and to control for any that were unequally distributed (such as age and medication use at baseline). Risk of bias assessment is available in Appendix Table E1.

Table 16. Summary of Patient, Baseline and Procedural Characteristics, BoNTA versus Active Comparators in CM

	Mathew 2009		Magalhaes 2010	
Population	N = 60		N = 72	
Comparators	**BoNTA**	**Topiramate**	**BoNTA**	**Amitriptyline**
Randomized	n=30	n=30	n=35	n=37
Treated	n=30	n=30	n=35	n=37
Age, years; mean ± SD	36.8 (10.3)		30 (10)	38(10)
% Female	90.0%		97.1%	97.2%
Mean Chronicity of Headache (years)	NR	NR	NR	NR
Mean # HA days/month	15.6 (7.0)*	15.5 (7.2)*	23.7 (6.1)	24.3 (6.9)
Mean # Migraine days/month	NR	NR	NR	NR
Mean # HA attacks/month	NR	NR	NR	NR
Mean # Migraine attacks/month	NR	NR	NR	NR
Percent with medication overuse	NR	NR	NR	NR
Patients who had prior preventative treatments	NR	NR	NR	NR
Procedural characteristics				
Doses of BoNTA, active comparator	200 U maximum plus placebo tablets	4-week titration to 100 mg/day with option for additional 4 week titration up to 200 mg/day	250 U	25-50 mg
Number of Treatments	1		1	Daily
Number of Muscle Areas	NR		NR	NA
Number of Injection sites	NR		15	NA
Length of F/U past treatment	36 weeks	36 weeks	12 weeks	12 weeks
% F/U at Last F/U	60.0%	50.0%	NR	NR
Co-interventions	The BoNTA group also received placebo tablets, the topiramate group received placebo saline injections		NR	
Country	United States		Brazil	
Funding	Comprehensive Neuroscience Program and The Uniformed Services University of the Health Science Award		Brazilian government grant by CAPES and a CNPq research grant	

BoNTA, onabotulinumtoxinA; CM, chronic migraine; COI, conflict of interest; F/U, follow-up; HA, headache; mg, milligrams; NA, not applicable; NR, not reported; SD, standard deviation; U, units.

Efficacy Results

BoNTA vs. Topiramate

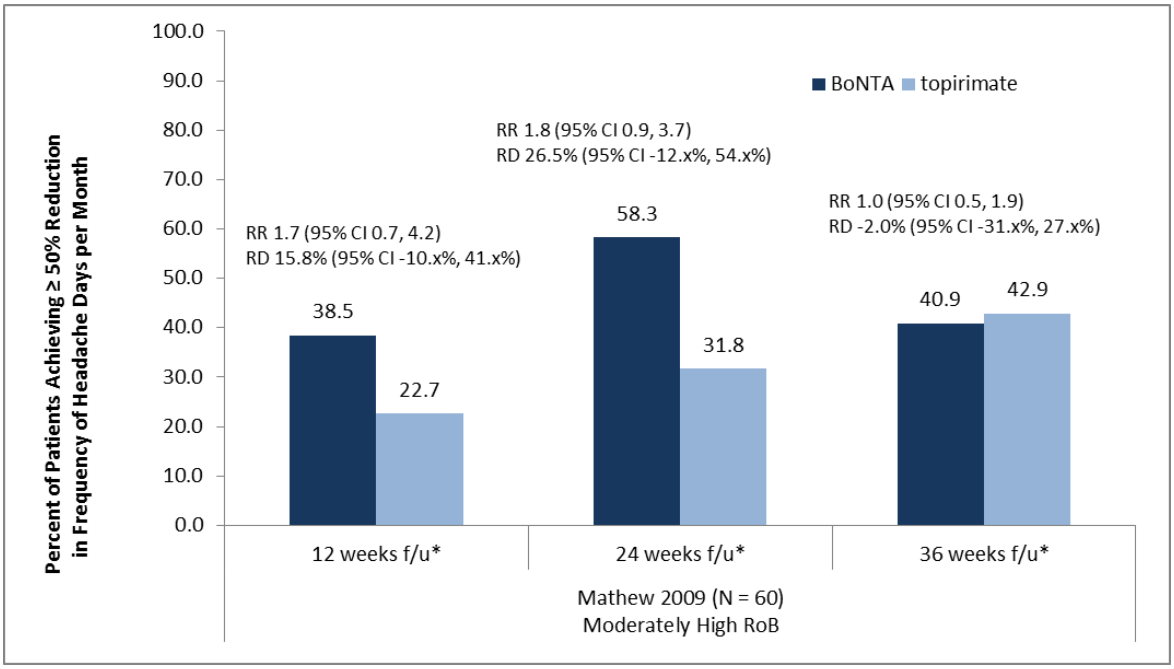
One small trial (n= 60) at moderately high risk of bias compared BoNTA with topiramate.[121] Authors excluded patients whose history indicated acute headache medication overuse as well as those who were unable to discontinue non-study migraine prophylaxis medications or other agents which might interfere with neuromuscular function. A majority of patients were taking triptans, nonsteroidal anti-inflammatory drugs, or nasal dihydroergotamine during the study. Loss to follow-up was substantial and there was differential loss to follow-up; Authors report that only 60% of the BoNTA group and 50% of the topiramate group completed the trial.

Treatment Responders

Treatment responders were defined as those who ≥ 50% reduction in the frequency of headache days per month.

Longer-term (12-36 weeks): The proportion of patients who achieved ≥ 50% reduction in the frequency of headache days per month were compared at 12, 24, and 36 weeks after initiation of treatment.[121] A greater proportion of participants who received BoNTA achieved ≥ 50% reduction in the frequency of headache days per month at 12 and 24 weeks but there were no statistically significant differences between the BoNTA and topiramate groups at any time point (12 weeks: RR 1.7 (95% CI 0.7, 4.2); 24 weeks: RR 1.8 (95% CI 0.9, 3.7); 36 weeks: RR 1.0 (95% CI 0.5, 1.9)) (Figure 14) Small sample size may have precluded ability to demonstrate a statistical difference between treatments. At 36 weeks, only 60% of the BoNTA and 50% of the topiramate recipients were available for analysis. Authors report using last observation carried forward to account for missing data from patients who discontinued, however, it is unclear if this may bias study results.

Figure 14. Percent of Patients Experiencing ≥ 50% Reduction in Frequency of Headache Days per Month over Longer-Term Follow-up (≥12 weeks), BoNTA versus Topiramate for CM



BoNTA: OnabotulinumtoxinA; CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio.
*60 patients were randomized. Data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks.

Function and Disability

Functional outcomes were measured with the MIDAS, HIT-6 and Migraine Impact Questionnaire, reporting changes from baseline scores.[121]

Short-term (4 weeks): There was no significant difference between the BoNTA and topiramate groups in change in the MIQ at 4 weeks post-treatment, MD -0.2 (95% CI -1.7, 1.3).

Longer-term (12 to36 weeks): There were no significant differences between the BoNTA and topiramate groups in the MIDAS at 12 weeks (MD 22.8, 95% CI -2.5, 48.1) or 24 weeks (MD 35.0, 95% CI -3.2, 73.2) after initiation of treatment. There also were no significant differences between the BoNTA and topiramate groups in the HIT-6 at 12 weeks (MD 3.2, 95% CI -1.1, 7.5), 24 weeks (MD 4.8, 95% CI 0.1, 9.6), or 36 weeks (MD 5.3, 95% CI 0.8, 9.8). Change in the MIQ was measured at 24 weeks with no difference between groups (MD -1.8, 95% CI -3.2, -0.4). Again substantial and differential loss to follow-up are noted.

Secondary Outcomes

Medication use: There were no significant differences over the longer-term between treatment groups in the change from baseline for the frequency of days taking headache medication per month.[121] This outcome was assessed at 12 weeks (MD -1.8, 95% CI -5.0, 1.4), 24 weeks (MD -2.0, 95% CI -5.8, 1.8), and 36 weeks (MD -0.5, 95% CI -4.9, 4.0).

Headache intensity: Results were similar between the BoNTA and topiramate groups for a reduction from baseline in the severity of headache episodes per month at longer-term follow-up: 12 weeks (MD 0.2, 95% CI -0.3, 0.7), 24 weeks (MD 0.4, 95% CI -0.1, 0.9), or 36 weeks (MD 0.2, -0.3, 0.7).[121]

Physician-reported treatment improvement: There were no significant differences between the BoNTA and topiramate treatment groups for physician-reported treatment improvement over short- (4 weeks) and longer-term (12, 24, and 36 weeks) follow-up (data not reported).[121]

BoNTA vs. Amitriptyline

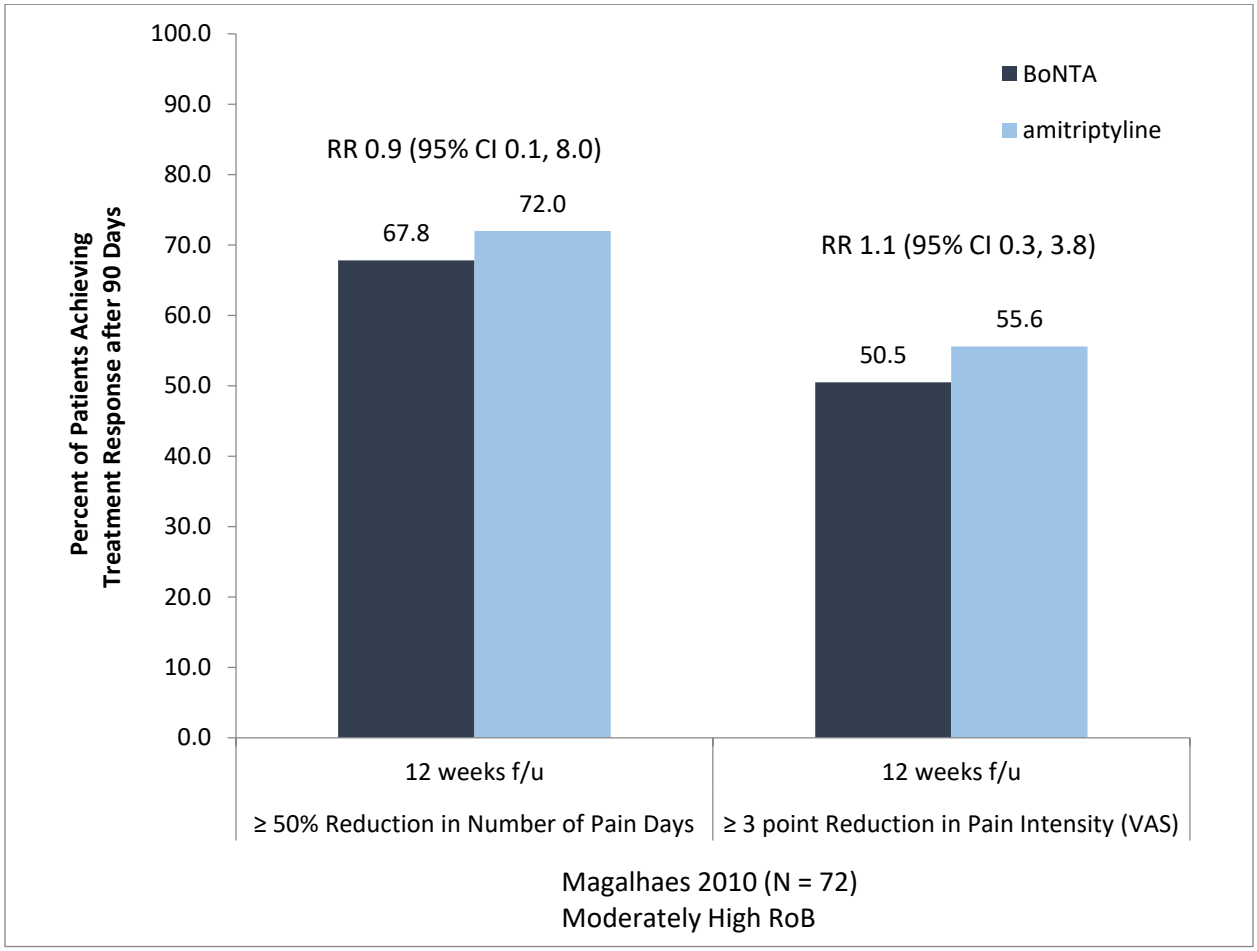
One small trial (N=72) at moderately high risk of bias was identified.[116] Medication overuse in participants was not well described; it appears that more BoNTA recipients reported use of medications for symptoms at baseline compared with amitriptyline recipients (39.7% versus 29.3%). While authors excluded patients who had used drugs with potentially preventative effects within 3 months prior to enrollment, they do not report on the proportion of participants that had used them prior to the study. Loss to follow-up was not clearly described.

Treatment Responders

Authors used two methods of determining treatment responders as described below.

Longer-term (12 weeks): Treatment response was defined as the proportion of patients who achieved ≥ 50% reduction in the frequency of pain days or a ≥ 3 point VAS reduction in pain intensity after 90 days.[116] The proportion of patients who achieved ≥ 50% reduction in the frequency of pain days after 90 days was similar between the BoNTA and amitriptyline groups, RR 0.9 (95% CI 0.1, 8.0). Further, there were no significant differences between groups in the proportion of patients who achieved a ≥ 3 point reduction in pain intensity after 90 days, RR 1.1 (95% CI 0.3, 3.8), Figure 15. Authors report that they did not control for medication overuse; it is not clear what proportion of participants overused medications.

Figure 15. Percent of Patients Experiencing Treatment Response atLong-term Follow-up (12 weeks), BoNTA versus Amitriptyline for CM



BoNTA: OnabotulinumtoxinA; CM: chronic migraine; f/u: follow-up; RoB: risk of bias; RR: risk ratio; VAS: visual analog scale.

Function and Disability

No evidence available from included studies.

Secondary Outcomes

Medication use: The percentage reduction in number of pain drug doses at longer-term follow-up (12 weeks after initiation of treatment) was statistically similar between the two treatment groups (77.0% BoNTA, 71.0% amitriptyline; RR 0.92, 95% CI 0.5, 1.9).[116]

Physician- and self-reported improvement: Physician-reported treatment improvement at longer-term follow-up (12 weeks) was similar between the BoNTA and amitriptyline treatment groups (BoNTA 88.0%, amitriptyline 87.0%; RR 1.0 (95% CI 0.9, 1.2)). There were no significant differences between groups in

self-reported treatment improvement at 12 weeks (BoNTA 84.0%, amitriptyline 88.0%; RR 1.0 (95% CI 0.9, 1.2)).[116]

4.2.1.3. Acupuncture versus Sham for Chronic Migraine

No studies were identified that met the inclusion criteria for this comparison.

4.2.1.4. Acupuncture versus Active Control for Chronic Migraine

Studies included

Two RCTs were included that compared acupuncture to an active control group for the treatment of chronic migraine; control groups included usual care in one trial[170] and topiramate in the other.[180] Brief overviews of each trial are provided below, and detailed information on patient and study characteristics is available in Appendix Table F2; for risk of bias ratings, see Appendix Table E4.

Acupuncture vs. Usual Care for Chronic Migraine

One study was identified which evaluated the efficacy of acupuncture compared with usual care for the treatment of chronic migraine.[170] Briefly, a total of 301 subjects were analyzed (out of 401 randomized) including 161 in the acupuncture and 140 in the usual care group; loss-to-follow-up was similar between groups. Patients who dropped out were slightly younger (43 vs. 46 years, p=0.01) and had higher headache score at baseline (29.3 vs. 25.6, p=0.04) than those who completed the trial, but were similar in terms of sex, diagnosis, and chronicity. Baseline characteristics were not robustly described but the groups were comparable regarding the proportion of females included (83% vs. 86%) and mean age (46.4 vs. 46.2 years). All patients received usual care from their general practitioner, which was not further defined (the authors refer to the control group as the "avoid acupuncture" strategy). Patients randomized to acupuncture additionally received up to 12 individualized treatments over 3 months from an experienced acupuncturist (no other details provided). No patient had received acupuncture treatment within the 12 months prior to enrollment (exclusion criteria). All patients were followed for 36 weeks (9 months) after the end of treatment.

Patients with migraine or tension-type headache according to IHS criteria were eligible for inclusion. Since the vast majority of patients were diagnosed with migraine (94% vs. 6% tension-type headache) we considered this a chronic migraine population. Regarding headache characteristics, the mean duration of symptoms (21.3 vs. 21.9 years) and mean number of headache days per month (15.6 vs. 16.2) were similar between groups; use of prophylactic medication (per week) at baseline was less in those randomized to acupuncture vs. control (mean 9.0 vs. 13.3). Patients with a diagnosis of medication overuse headache according the International Classification of Headache Disorders were specifically excluded.

This trial was considered to be at MODERATELY HIGH risk of bias due to an unclear intention-to-treat analysis (19 patients randomized to acupuncture and 3 to usual care did not receive treatment and are

unaccounted for by the authors), lack of blinded assessment (outcomes were patient-reported and patients were not blinded to treatment), and complete follow-up of less than 80% (75%; 301/401).

Acupuncture vs. Topiramate for Chronic Migraine

One study was identified which evaluated the efficacy of acupuncture compared with topiramate for the treatment of chronic migraine.[180] A total of 66 patients were randomized, 33 to each treatment group. The groups were well matched with regards to baseline characteristics; the mean patient age was 48 years and the majority were females (89%). Patients randomized to acupuncture underwent two sessions per week over 12 weeks (total of 24 sessions, 30 minutes in duration). All patients received the same standardized administration of fixed and classic acupuncture points; at each point the needle was manually twirled until the subject felt the typical tingling or warming sensation and then left in place for 30 minutes. Patients in the control group underwent a 4-week titration period (topiramate 25 mg/day at bedtime for 1 week, followed by weekly increases of 25 mg up to either 100 mg/day or to the maximal dose tolerated) and an 8-week maintenance period (stable topiramate dose of ≥50 mg/day). Starting in week two, topiramate was given twice daily in equal doses. The mean final topiramate maintenance dose was 84.0 mg/day. All patients were treated for 12 weeks and analyzed immediately after the end of the treatment period.

Regarding headache characteristics, the acupuncture and the topiramate groups reported a similar mean duration of symptoms (13.2 vs. 13.5 years, respectively), mean number of headache days per month (21.3 vs. 21.0; including moderate/severe headache days: 20.2 vs. 19.8), and mean number of days per month with acute headache medication use (15.1 vs. 14.5 days/month). At baseline, the percentage of patients that overused acute headache medication was 74% (49/66); 73% randomized to acupuncture and 76% randomized to topiramate. The authors did not report the proportion of patients who had tried and failed prior preventative treatments; however, the use of migraine prophylaxis agents in the 3 months prior to enrollment (such as beta-blockers, anti-depressants, calcium channel blockers, anti-epileptic agents, cycle-modulating hormonal drugs, or vessel dilatation agents) was an exclusion criteria.

This trial was considered to be at MODERATELY LOW risk of bias due to unclear concealment of allocation and a lack of blinded assessment (outcomes were patient-reported and patients were not blinded to treatment).

Efficacy Results

Acupuncture vs. Usual Care

One trial (n=301) at moderately high risk of bias compared acupuncture with usual care.[170] Patients with migraine or tension-type headache were eligible for inclusion; since 94% of patients were diagnosed with migraine as their primary headache we considered this a migraine population. Authors excluded patients whose history indicated acute headache medication overuse. Use of prophylactic medication at baseline was less in those randomized to acupuncture compared with usual care (mean 9.0 vs. 13.3 per week). The complete follow-up rate was 75%.

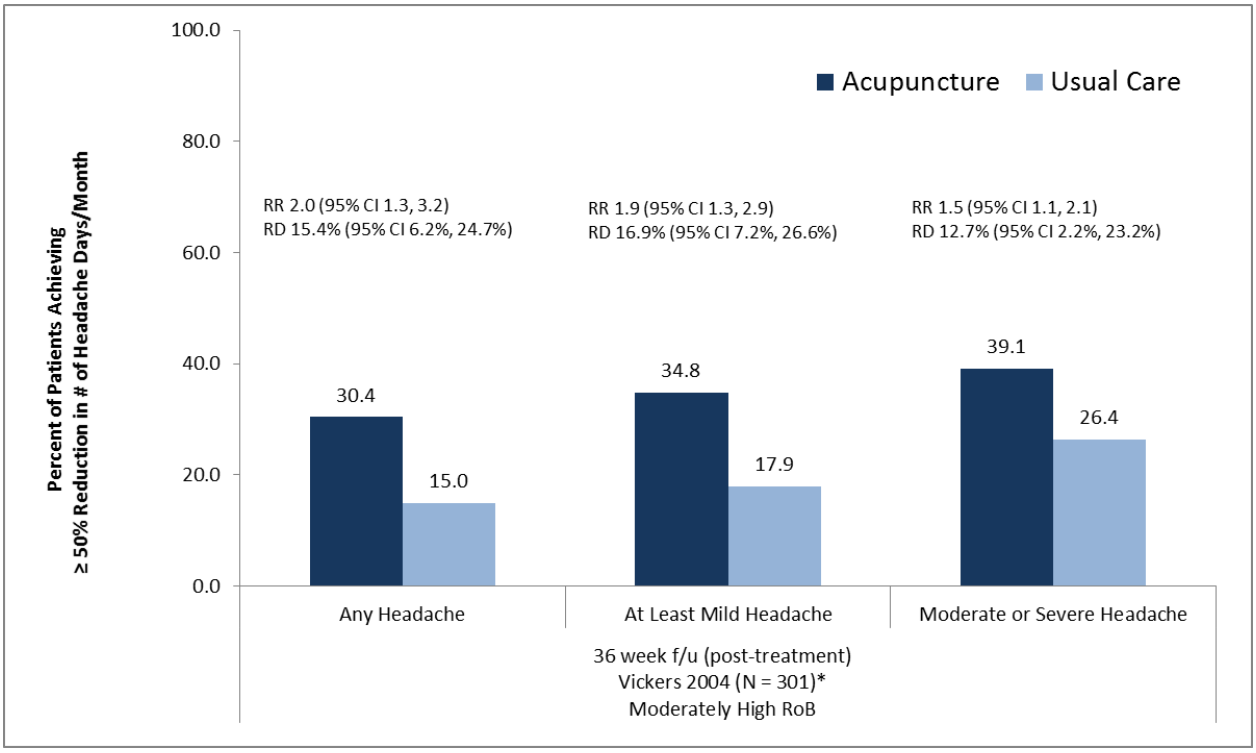
Treatment Responders

Longer-term (36 weeks): A statistically higher proportion of patients who received acupuncture experienced ≥50% reduction in the number of headache days from baseline (IHS definition) compared with usual care 36 weeks after the end of treatment: RR 2.0 (95% CI 1.3, 3.2), RD 15.4% (95% CI 6.2%, 24.7%); 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.[170] It is unclear whether the term headache used here refers specifically to migraine or to any headache. In order to analyze whether the results might be sensitive to the definition of headache, the authors applied this same criteria to more conservative definitions of days with headache (i.e., days with at least a mild headache and with a moderate/severe headache) and found that acupuncture continued to provided statistically superior results compared with usual care (Figure 16). It is unclear whether headache refers specifically to migraine or to any headache; 6% of the population was diagnosed with tension-type headache.

The proportion of patients with ≥35% improvement from baseline in headache score, defined as the summed total of headache severity recorded 4x day on a 6-point Likert scale, (study protocol definition of responder) was also assessed at 36 weeks post-treatment, with statistically more acupuncture patients achieving this outcome: 54.0% (87/161) versus 32.1% (45/140); RR 1.7 (95% CI 1.3, 2.2) and RD 21.9% (95% CI 11.0%, 32.8%).

Of note, the authors report that some patients continued to receive acupuncture after the initial 3 month treatment period (25 patients [16%] after 3 months, 10 patients [6%] after 6 months, and 6 patients [4%] after 9 months); only three patients (2%) in the control group reported receiving acupuncture outside the study.[170] It is unclear how this continuation of treatment may have affected the outcome.

Figure 16. Proportion of Patients Achieving ≥50% Reduction in the Number of Headache Days per Month at Long-term Follow-up, Acupuncture versus Usual Care for CM



CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio.
*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) continued to received acupuncture; only three patients (2%) in the control group reported receiving acupuncture outside the study.

Reduction in Frequency of Headache Days

Longer-term (36 weeks): Compared with usual care, acupuncture resulted in a statistically significant improvement (i.e., reduction) in the number of headache days per month compared with baseline 36 weeks after the end of treatment. The mean difference between groups, adjusted for baseline scores, was 1.8 days (95% CI 0.6, 2.9); this difference is equivalent to 22 fewer days of headache per year (95% CI 8%, 38%).[170] Similarly, the acupuncture group showed a statistically greater reduction in the mean number of mild headache days (adjusted MD 1.6; 95% CI 0.5, 2.6) and moderate or severe headache days (adjusted MD 1.2; 95% CI 0.4, 2.1) at this time-point (Appendix Table G4). Again, given that some patients continued to receive acupuncture after the initial 3 month treatment period (see paragraph on Treatment Responders above) it is unclear how this continuation of treatment may have affected the outcome.

Secondary Outcomes

Health Related Quality of Life: In general, individual SF-36 domain scores favored the acupuncture group (compared with usual care) over the longer-term; 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, 17.0), energy/fatigue (adjusted MD 4.2; 95% CI 0.6, 7.7), and change in health (adjusted MD 7.9; 95% CI 3.5, 12.3); MDs were adjusted for baseline scores,[170] (Appendix Table G4).

Frequency of Analgesic Use: Over the long-term (36 weeks post-treatment), statistically fewer patients who had received acupuncture reported using prophylactic medication in the month prior compared with usual care: 14% (22/161) vs. 26% (37/140); the mean difference between groups adjusted for baseline scores was 13% (95% CI 4%, 22%).[170] In an unplanned analysis, the authors summed and scaled all medication taken by patients after randomization and compared the groups with adjustment for baseline intake. Mean weekly intake of scaled prophylactic, but not scaled pain, medication was statistically reduced in the acupuncture compared with the usual care group (adjusted MD 3.9; 95% CI 0.5, 7.4) (Appendix Table G4).

Loss of working days: There was no statistical difference between the acupuncture and the usual care group in the mean number of sick days reported at long-term follow-up (36 weeks after the end of treatment): 2.0 ± 7.1 versus 2.3 ± 6.8 days, respectively; the incidence ratio was 0.84 (95% CI 0.64, 1.09) indicating that the acupuncture group had 16% fewer days off sick,[170] (Appendix Table G4).

Resource use: No statistical difference was seen between groups for mean number of visits to a general practitioner (1.7 ± 2.5 vs. 2.3 ± 3.6), complementary therapist (2.0 ± 7.1 vs. 2.3 ± 6.8), or specialist (0.22 ± 0.9 vs. 0.14 ± 0.6) over the study period; 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.[170]

Headache scores: A significant improvement was 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 usual care 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, 7.0) (Appendix Table G4). Authors report that the result was robust to sensitivity analysis incorporating imputation for missing data.[170] Again, the authors report that some patients continued to receive acupuncture after the initial 3 month treatment period (25 patients [16%] after 12 weekes, 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.

Acupuncture vs. Topiramate

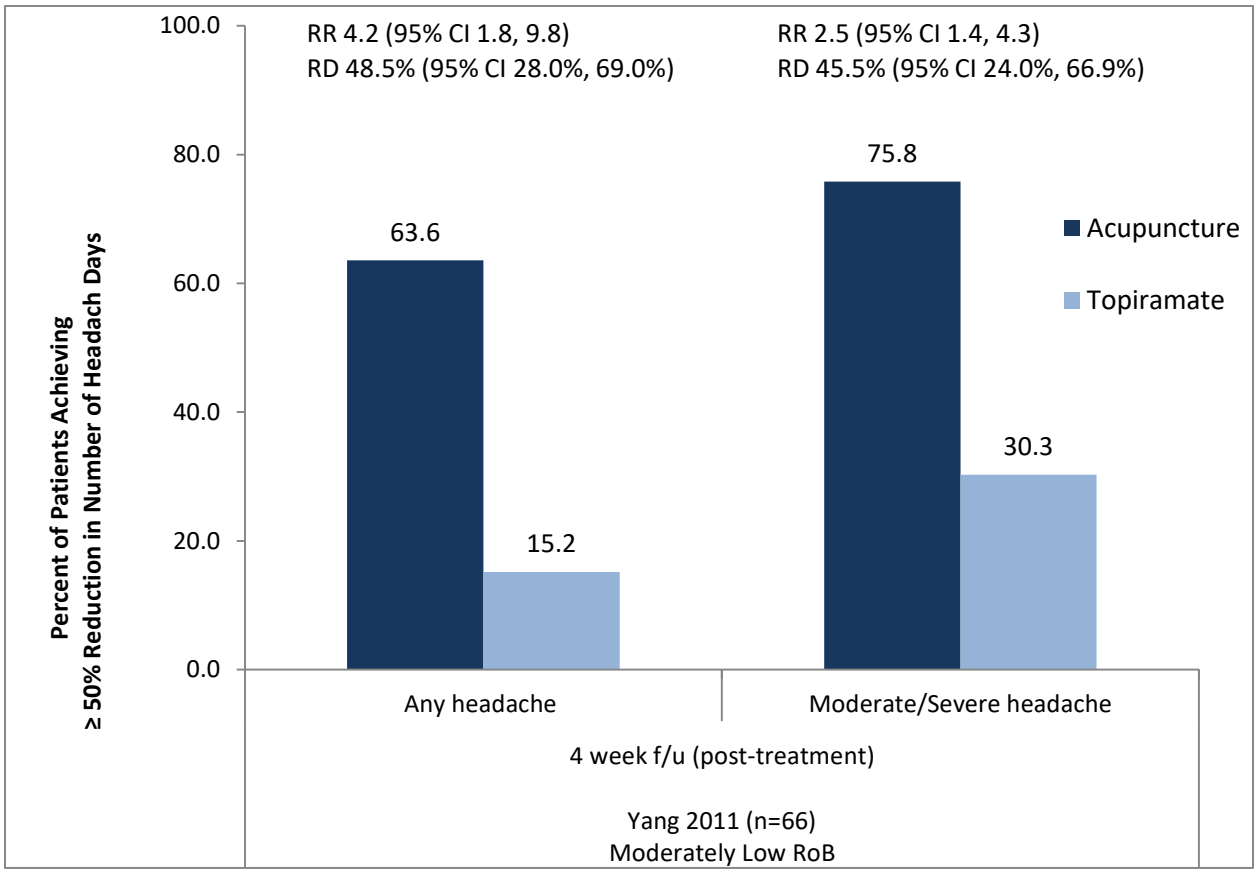
One small trial (n=66) at moderately low risk of bias compared acupuncture with topiramate.[180] A substantial proportion of the population (74%) was overusing acute headache medication at baseline, 73% randomized to acupuncture and 76% randomized to topiramate; the mean number of days per month with acute headache medication use was 15.1 and 14.5, respectively. Patients who had used migraine prophylaxis agents in the 3 months prior to enrollment were excluded. All analyses were

performed according to the intention-to-treat principle and a last-observation-carried-forward approach was used to impute missing data.

Treatment Responders

Post-treatment: Four times as many patients who received acupuncture compared with topiramate experienced a ≥50% reduction in the number of headache days from baseline recorded after the end of treatment: RR 4.2 (95% CI 1.8, 9.8), RD 48.5% (95% CI 28.0%, 69.0%).[180] Likewise, a statistically greater proportion of acupuncture patients reported a ≥50% reduction in the number of moderate or severe headache days (i.e., day with headache pain that lasted ≥4 hours with a peak severity of moderate or severe intensity, or any severity or duration if the participant took and responded to a triptan or ergot) compared with patients who received topiramate: RR 2.5 (95% CI 1.4, 4.3), RD 45.5% (95% CI 24.0%, 66.9%), Figure 17. As stated above 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.

Figure 17. Proportion of Patients Achieving ≥50% Reduction in the Number of Headache Days over the Short-Term, Acupuncture versus Topiramate for CM



CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio.

Reduction in Frequency of Headache Days

Post-treatment: Patients in the acupuncture group reported a statistically greater reduction in the number of headache (any) days and in moderate/severe headache days per month compared with the topiramate group: the MD between groups was 2.8 days (95% CI 1.2, 4.4) and 2.7 days (95% CI, 1.1, 4.3) after the end of treatment, respectively.[180] Again, a large proportion of patients were overusing acute headache medication at baseline and it is unclear how this may have affected the outcome.

Disability

Post-treatment: A statistically greater improvement (i.e., lower score) on the Migraine Disability Assessment (MIDAS) was seen in patients who received acupuncture compared with topiramate after the termination of treatment[180]: the MD between groups was 12.6 points (95% CI 7.7, 17.5); we were unable to find a MCID for this outcome so it is unclear if the difference is clinically meaningful. 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. It is unclear how medication overuse in this population (73% and 76%, respectively, met the criteria at baseline) may have affected the outcomes..

Secondary Outcomes

Health Related Quality of Life: Compared with the topiramate group, the acupuncture group showed statistically greater improvement from baseline (i.e., decrease in score) in both depression and anxiety as measured by the Beck Depression Inventory II (MD between groups, 2.1; 95% CI 0.2, 4.0) and the Hospital Anxiety and Depression Scale (MD between groups, 4.2; 95% CI 3.2, 5.2) immediately after the end of treatment.[180] Patients who received acupuncture also reported significantly greater improvement (i.e., increase in score) on all eight individual SF-36 domains compared with those who received topiramate (Appendix Table G1).

Frequency of Analgesic Use: A statistically significant reduction in the mean number of days per month with acute headache medication intake was reported by patients who underwent acupuncture compared with those randomized to topiramate: the MD between groups was 4.2 days (95% CI 2.2, 6.2) as assessed after the end of treatment[180] (Appendix Table G1).

4.2.1.5. Manual Therapy/Manipulation versus Sham for Chronic Migraine

No studies were identified that met the inclusion criteria for this comparison.

4.2.1.6. Manual Therapy/Manipulation versus Active Control for Chronic Migraine

Studies included

One study was identified which randomized 147 patients to receive spinal manipulation therapy (SMT) (n=77) or amitriptyline (n=70) for the treatment of chronic migraine[129]; this study also included a third group randomized to receive a combination of both treatments (n=71) which does not meet our inclusion criteria. Detailed information on patient and study characteristics is available in Appendix Table F3. Treatment groups were comparable with regards to demographics at baseline. The mean age of the population was 36.7 years and 81% were female. Almost all patients (96%) were working when they entered the study, with almost half (44%) indicating that migraine interfered substantially with their work. Patients randomized to SMT received a total of 14 treatments (no more than two treatments per week) over a 2 month period. Experienced chiropractors, using a spinal manipulation therapy type described as "high-velocity, low-amplitude, short-lever arm", treated cervical and/or thoracic spine levels as indicated; sessions were preceded by a short period (5-10 mins.) of massage and/or trigger point therapy. Patients randomized to amitriptyline therapy were supervised by a physician specializing in chronic pain management and prescribed the following regimen (which could be modified based on patient response): one 25 mg tablet before bedtime (at baseline), increasing to 50 mg after 1 week, 75 mg after 2 weeks, and a maximum of 100 mg after 3 weeks; patients in this group were seen three times during the same 2 month treatment period. Patients were followed for 4 weeks after the termination of treatment.

Of note, participants with concomitant tension headaches (proportion not reported) were not excluded from this trial as long as it was concluded that migraine headache represented the primary diagnosis. Subjects were also not instructed to differentiate between tension headache pain and migraine headache pain when recording pain scores. Thus, the impact of treatment on chronic migraine verses tension headache is unclear. Regarding headache characteristics, the treatment groups were comparable at baseline: 61% reported duration of migraine symptoms as greater than 10 years; a mean of 53.9% of days per month were spent with headache and the mean headache severity was 7.7 (out of 0-10 scale) (for these latter two characteristics it is unclear if headache refers to migraine specifically or any headache). Prior prophylactic treatments utilized by this population were not reported; patients under medical care (e.g., taking prescription medication) were excluded but it is unclear if this is referring to medication specifically for the treatment/prevention of headache. Also, the authors did not mention whether or not any of the patients may have been overusing medication. At baseline, the mean over-the-counter headache medication use was 2.1 ± 1.9 pills/day.

This trial was considered to be at MODERATELY LOW risk of bias, not meeting the criteria for blinded assessment (outcomes were patient-reported and patients were not/could not be blinded to treatment) or for complete follow-up of less than 80% (73%; 108/147). Risk of bias assessment for all studies is found in Appendix Table E6.

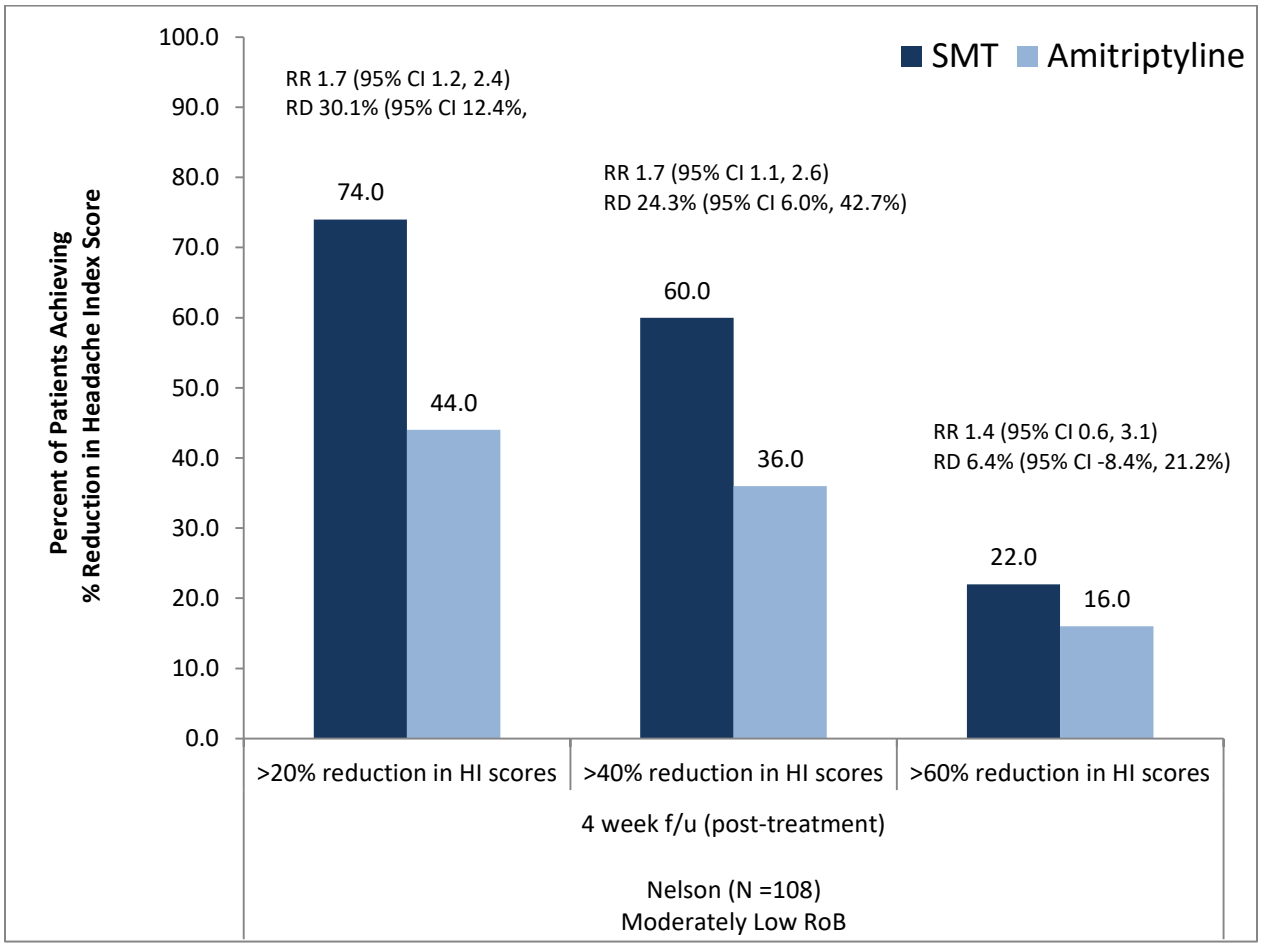
Efficacy Results

All analyses are based on completers. The authors performed various sensitivity analyses around missing data for all three outcomes reported (headache index, SF-36, and medication use) and the results were similar.

Treatment Responders

Short-term (4 weeks): A statistically greater proportion of patients who underwent SMT achieved >20% and >40% reduction from baseline in headache index (HI) scores compared with those treated with amitriptyline as recorded 4 weeks post-treatment: RR 1.7 (95% CI 1.2, 2.4), RD 30.1% (95% CI 12.4%, 47.9%) and RR 1.7 (95% CI 1.1, 2.6), RD 24.3% (95% CI 6.0%, 42.7%), respectively.[129] More patients in the SMT group also reported a >60% reduction in HI scores but the difference was not statistically significant, Figure 18 (Appendix Table G6). HI scores were defined as the weekly sum of each patient's headache pain score (0-10) on the days they report having headache; it is unclear whether the term headache refers to migraine headache specifically or to any headache. The authors performed additional analyses controlling for compliance, sex, weight, smoking, improvement expectations, duration of episodes, and duration of complaints, none of which changed the results of the primary analysis. Given that patients with concomitant tension-type headaches were not excluded (as long as migraine was primary) and patients were not asked to differentiate between migraine and tension headache when recording outcomes (as described above), it is unclear how the coexistence of these headache types may have affected the outcome.

Figure 18. Proportion of Patients Achieving >20%, >40%, and >60% Reduction in Headache Index Scores over the Short-Term, SMT versus Amitriptyline for CM



CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio; SMT: spinal manipulation therapy.

Reduction in Frequency of Headache Days

Short-term (4 weeks): No significant difference between the SMT and amitriptyline group was seen 4 weeks following the end of treatment in the percentage of days per month with headache: mean 36.9% ± 29.3% versus 40.5% ± 23.3%, respectively,[129] (Appendix Table G6). Compared with baseline, the mean decrease in percentage of headache days per month was 16.2% and 11.2%, respectively. Again, it is unclear if the term headache as used here refers to migraine specifically or to any headache and it is unclear how the coexistence of tension-type headaches in this population may have affected the outcome.

Secondary Outcomes

Health Related Quality of Life: There was no significant difference between the SMT and amitriptyline group in global SF-36 scores (0-100, best) assessed over the short-term (i.e., 4 weeks post-treatment): mean scores adjusted for baseline values were 73.6 ± 10.7 versus 71.2 ± 10.5, respectively (adjusted difference -2.5; 95% CI -8.0, 3.1) (Appendix Table G6).[129]

Frequency of analgesic use: No significant difference was seen between the SMT and amitriptyline group in the use over-the-counter pain medication (number of pills per day over 1 month) at short-term follow-up: adjusted mean scores 1.1 ± 1.1 versus 0.9 ± 1.0 at 4 weeks, respectively (adjusted difference -0.2.; 95% CI -0.7, 0.2),[129] (Appendix Table G6).

Headache intensity: Four weeks after the end of treatment (short-term), no significant difference between the SMT and amitriptyline group was seen in headache severity as measure on a 0-10 (worst) scale: mean 4.4 ± 1.7 versus 4.5 ± 1.3, respectively,[129] (Appendix Table G6). Compared with baseline, the mean decrease in headache severity was 0.6 and 0.1, respectively.

Headache scores: There was no significant difference between the SMT and amitriptyline group in Headache Index (HI) scores (mean of the 4 weeks post-follow-up) over the short-term: mean scores adjusted for baseline values were 9.8 ± 7.0 versus 12.6 ± 7.0, respectively (adjusted difference 2.8; 95% CI -0.07, 6.3),[129] (Appendix Table G6). HI scores were defined as the weekly sum of each patient's headache pain score (0-10, worst) on the days they reported having headache; the scale ranged from 0 to 70 with a score of 70 indicating the patient reported a pain score of 10 all 7 days of the week.

4.2.1.7. Massage versus Sham and versus Active Control for Chronic Migraine

No studies were identified that met the inclusion criteria for these comparisons.

4.2.1.8. Transcranial Magnetic Stimulation vs. Sham for Chronic Migraine

Studies included

Two RCTs that evaluated the efficacy of transcranial magnetic stimulation (TMS) with sham for the treatment of chronic migraine were identified.[124,165] A brief summary of patient and study characteristics is provided below; detailed information is available in Appendix F4. One trial randomized 100 patients (50 to each group)[124]; the other included only 27 patients (out of 32 randomized), 14 in the TMS group and 13 in the sham group.[165] The trial conducted by Misra et al. provided a detailed set of demographics at baseline whereas in the trial by Teepker et al., baseline demographics were not as robustly described. The overall age of the populations (mean 35.3 vs. 35.5 years) and proportion of females (82% vs. 88%) were similar between the trials. However, in the trial by Teepker et al, patients in the TMS group were a mean 10 years younger than those in the sham group and were almost entirely female (93% vs. 69% for sham); the treatment groups were well balanced in the other trial. Patients in one trial received repetitive, low-frequency TMS over the vertex (1 Hz, 500 pulses in 2 trains separated by 1 minute intervals) in five sessions on consecutive days,[165] while the other employed repetitive, high-frequency TMS delivered anterioposteriorly parallel to midline on the left frontal cortex corresponding to the hot spot of the right abductor digiti minimi muscle (10 Hz, 600 pulses in 10 trains, with an intertrain interval of 45 seconds) delivered during three session on alternate days.[124] In both trials, the sham stimulation was delivered in the same manner as the real TMS using a sham coil, which produces the same sound and similar sensory feedback on the subject's head without delivering active stimulation. One trial followed patients for a total of 4 weeks after the termination of treatment[124] and the other for 8 weeks post-treatment.[165]

Of note, in the trial by Misra et al., 60 patients (60%) had chronic daily headache, 28 of whom used analgesics for more than 15 days/month for 3 months, which may be consistent with medication overuse based in ICHD-3 criteria. At baseline, the mean number of rescue analgesics taken per month in this trial was 19.1; in the other trial, the mean at baseline was only 14.7 pills per 8 weeks and there was no mention of chronic daily headache or medication overuse in this population.[165] One trial (Misra et al.) reported that migraine prophylaxis drugs (i.e., amitriptyline, divalproate, propranolol, flunarizine, and antidepressants (escitalopram, duloxetine)) were taken by 98% of patients for a median duration of 12 months; however, these medications were withdrawn 1 month prior to enrollment. The second trial (Teepker et al.) listed any prophylactic treatment of migraine as an exclusion criteria, but no other information was provided. Regarding other headache characteristics, more patients enrolled in the trial by Teepker et al. were diagnosed with migraine with aura than those in the Misra trial (48% vs. 7%) and the frequency of migraine attacks was much less in the Teepker trial (mean 9.3 attacks during 8 weeks vs. 18.9 attacks per month in the trial by Misra). The duration of headache was a mean 10.5 years in one trial[124] it is unclear if this refers to migraine specifically or to any headache. The duration of migraine symptoms was not reported in the other trial.[165]

The trial by Misra et al.[124] was considered to be at MODERATELY LOW risk of bias due to unclear reporting of allocation concealment and lack of controlling for frequency of attacks per month (mean 20.8 vs. 17.0) and migraine index scores (mean 62.5 vs. 51.1) at baseline (though the authors did not find a significant difference between groups in these characteristic, p=0.06 for both, the p-value approach significance). Teepker et al.[165] was considered to be a MODERATELY HIGH risk of bias due to

multiple methodological concerns including unclear random sequence generation, allocation concealment and intention to treat; unclear differential loss-to-follow-up; and lack of controlling for confounding. Risk of bias assessment for all studies is found in Appendix Table E10.

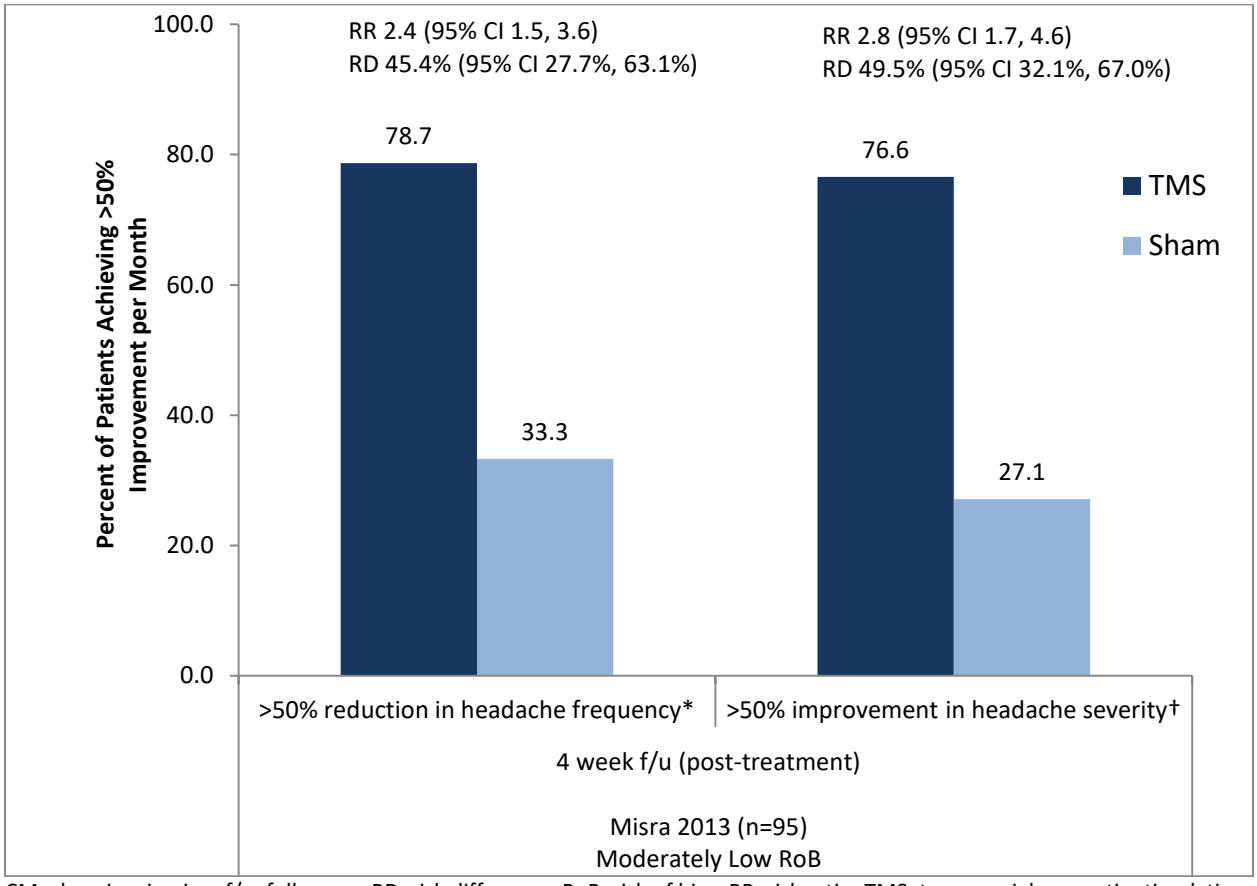
Efficacy Results

Due to heterogeneity in patient populations and treatment regimens, variation in the definition of primary outcomes and differences in study quality, results were not pooled across the two trials.

Treatment Responders

Short-term (4 weeks): In one RCT[124] the proportion of patients that experienced >50% reduction in headache frequency (i.e., number of migraine attacks per month) from baseline was statistically higher following high-frequency TMS compared with sham at 4 weeks post-treatment: RR 2.4 (95% CI 1.3, 3.2), RD 45.4% (95% CI 27.7%, 63.1%), Figure 19; similarly, a statistically greater proportion of TMS patients reported a >50% improvement in headache severity (i.e., pain on 0-100 VAS, considering frequency and average severity) from baseline versus sham patients at the same time-point: RR 2.8 (95% CI 1.7, 4.6), RD 49.5% (95% CI 32.1%, 67.0%). Of note, this trial included 60 patients (60%) with chronic daily headache, 28 of whom consumed analgesic for more than 15 days/month, which may be consistent with medication overuse based in ICHD-3 criteria. It is unclear how the coexistence of these headache types may have affected the outcome.

Figure 19. Proportion of Patients Achieving >50% Improvement in Headache Frequency and Severity at Short-Term Follow-up, TMS versus Sham for CM



CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio; TMS: transcranial magnetic stimulation.
*Percent of patients with reduction in mean number of attacks per month.
†Measured on a 0–100 (worst) Visual Analogue Scale considering frequency and average severity.

Reduction in Frequency of Headache Attacks

Short-term (4-8 weeks): A statistically greater reduction in the mean number of migraine attacks per month in one RCT employing high-frequency TMS was seen following TMS versus sham at 4 weeks (5.2 ± 4.9 attacks (a reduction of 15.6 compared with baseline) versus 8.9 ± 6.6 attacks (a reduction of 8.1 compared with baseline), p<0.001).[124] No statistical difference between groups was seen in the other trial at the 8 week follow-up post-treatment (mean 6.8 ± 4.3 versus 7.7 ± 4.2 attacks) with low-frequency TMS,[165] (Appendix Table G8). Of note, the trial that employed high-frequency TMS included 60 patients (60%) with chronic daily headache, 28 of whom consumed analgesic for more than 15 days/month, which may be consistent with medication overuse based in ICHD-3 criteria. It is unclear how the coexistence of these headache types may have affected the outcome.

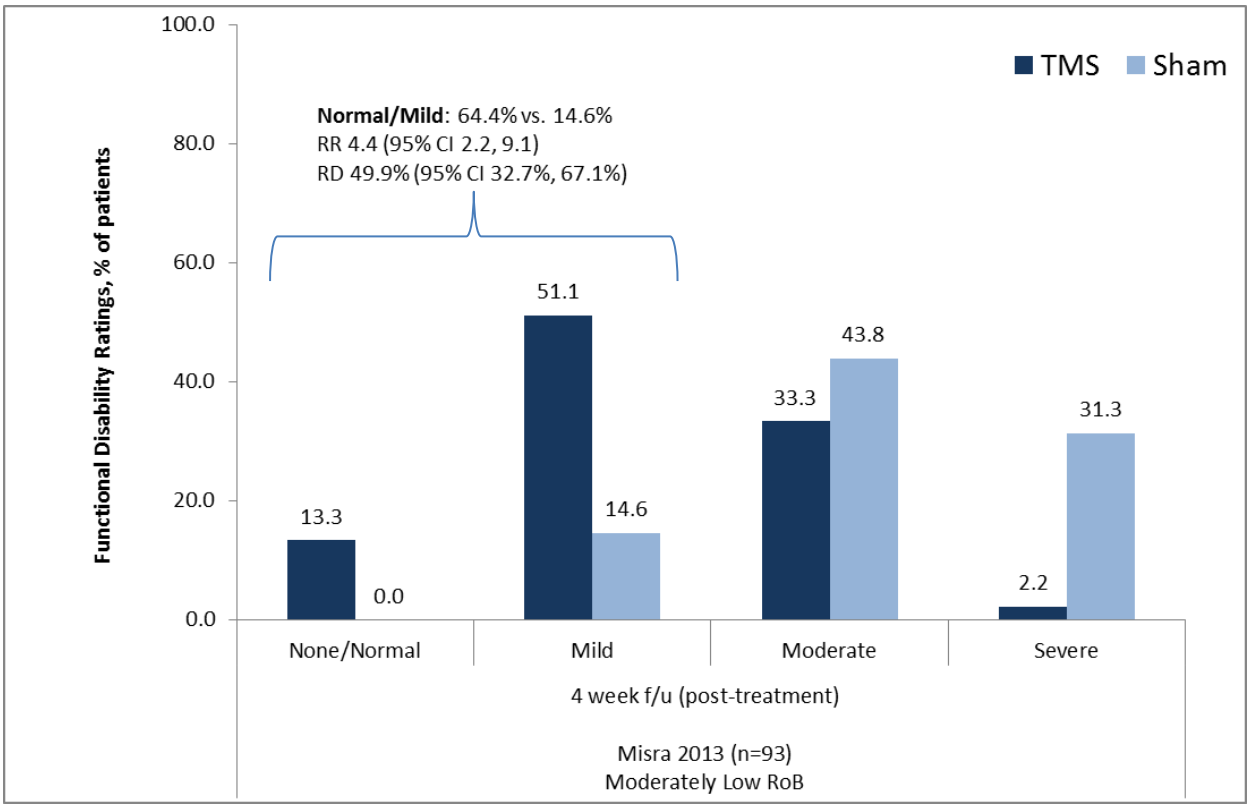
Reduction in Number of Headache Days

Short-term (8 weeks): No statistical difference between the low-frequency TMS and the sham group in mean number of headache days during the 8 week period following treatment was seen in one trial (9.5 ± 6.8 versus 13.2 ± 9.3); mean change compared with baseline was similar also between groups (4.8 and 4.5 fewer headache days, respectively),[165] Appendix Table G8. Again, it is unclear how the coexistence of migraine and medication overuse headache in this population may have affected the outcome.

Functional disability

Short-term (4 weeks): A statistically greater improvement in functional disability following treatment with high-frequency TMS was observed compared with sham (p=0.0001) in one trial.[124] Functional disability was graded on a 0 to 4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe impairment of activities of daily living (ADL), 4 = inability to perform ADL requiring bed rest) and recorded by the patient in a daily headache diary. At baseline, all patients had moderate to severe functional disability associated with their migraine. At 4 weeks post-treatment, over four times as many patients in the TMS group improved to a functional disability rating of normal or mild compared with sham: RR 4.4 (95% CI 2.2, 9.1), Figure 20. In the high-frequency TMS group, the majority of patients rated themselves as normal/none (13.3%; 6/45) or mild (51.1%; 23/45) disability; conversely, the majority of sham patients still had a functional disability ratings of moderate (43.8%; 21/48) or severe (31.3%; 15/48), with no patient in the sham group rated as normal/having no impairments of ADL (Appendix Table G8). Of note, this trial included 60 patients (60%) with chronic daily headache, 28 of whom consumed analgesic for more than 15 days/month, which may be consistent with medication overuse based in ICHD-3 criteria. It is unclear how the coexistence of these headache types may have affected the outcome.

Figure 20. Functional Disability Ratings at Short-Term Follow-up, TMS versus Sham for CM



CM: chronic migraine; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio; TMS: transcranial magnetic stimulation.

Secondary Outcomes

Frequency of analgesic use: No statistical difference in analgesic use was seen during short-term follow-up (at 4 or 8 weeks post-treatment) across the two trials (Appendix Table G8). In one trial, the monthly analgesic consumption was 5.1 ± 5.9 in the high-frequency TMS group vs. 6.7 ± 5.8 in the sham group (p=0.18) at 4 weeks post-treatment.[124]. In the second trial, the mean number of analgesics consumed during the 8 week period following treatment was 9.5 ± 6.8 (low-frequency TMS) versus 13.2 ± 9.3 (sham), p=0.58.[165]

Patient satisfaction: Significantly more patients in the high-frequency TMS group expressed satisfaction in the short-term (4 weeks post-treatment) compared with the sham group: 78.7% vs. 29.2%, RR 2.7 (95% CI 1.7, 4.3) in one trial,[124] Appendix Table G8.

Headache intensity: One RCT reported a statistically greater improvement in headache severity following treatment with high-frequency TMS versus sham (p=0.0001).[124] The severity of headache was graded on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and recorded by the patient in a daily headache diary. At baseline, all patients had severe migraine. At 4 weeks post-treatment (short term), only 8.5% (4/47) of patients who received high-frequency TMS still considered their headache intensity severe compared with 39.6% (19/48) in the sham group; RR 0.22 (95% CI 0.08, 0.58),

RD 31.1% (15.1%, 47.0%). In both groups, most patients rated their headaches as moderate (46.8% vs. 45.8%, respectively); 6.4% of TMS patients reported none/normal severity compared with no patient in the sham group. Appendix G8. Of note, this trial included 60 patients (60%) with chronic daily headache, 28 of whom consumed analgesic for more than 15 days/month, which may be consistent with medication overuse based in ICHD-3 criteria. It is unclear how the coexistence of these headache types may have affected the outcome.

In the second trial, patients measured their headache pain intensity on VAS 0-10 (worst). No statistical difference was seen between the low-frequency TMS and the sham group during the 8 week period following treatment (short term): mean 6.11 ± 1.26 vs. 5.17 ± 2.51, respectively.[165]

4.2.1.9. Transcranial Magnetic Stimulation versus Active Control for Chronic Migraine

No studies were identified that met the inclusion criteria for this comparison.

4.2.1.10. Trigger Point Injection versus Sham and versus Active Control for Chronic Migraine

No studies were identified that met the inclusion criteria for these comparisons.

4.2.2. Chronic Tension-Type Headache

Summary of results

The general findings for chronic tension-type headache (CTTH) treatment for the primary outcomes are briefly summarized below by treatment and comparator. Detailed findings (including results for secondary outcomes) are then presented. We report following primary outcomes:

- The proportion of treatment responders is a primary outcome of interest; it was variable defined across trials.
- Reduction in mean frequency of headache. This may include frequency of attacks/episodes (e.g. migraine episodes), overall headache days or headache days for a specific headache type (e.g. migraine days)
- Function as measured by validated measures

For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Most trials were at moderately high risk of bias; assessment details are provided in Appendix E.

BoNTA versus Placebo

Although five trials met the inclusion criteria, reporting on primary outcomes was limited. All but one trial enrolled 60 or fewer patients.

- Short-term outcomes are as follows:
  - A lthough more patients the BoNTA experienced ≥ 25% reduction in pain intensity at 8 weeks, results did not reach statistical significance in one small RCT (insufficient evidence).
  - At 4 weeks in one small trial, BoNTA was associated with significantly lower Headache Disability Index scores indicating improved function compared with placebo (insufficient evidence).
- Longer-term outcomes are as follows:
  - At 12 weeks), although more patients the BoNTA experienced ≥ 45% reduction in pain intensity, results did not reach statistical significance in one small RCT (insufficient evidence).
  - Across two RCTs, BoNTA was associated with a reduction in the mean number of headache days per month at 12 weeks (insufficient evidence).
  - In one small RCT, BoNTA was associated with significantly lower Headache Disability Index scores at 12 weeks indicating improved function compared with placebo (insufficient evidence).
- No data on intermediate-term outcomes were available.

BoNTA versus Active Control

- No studies identified that met the inclusion criteria.

Acupuncture versus Sham

- Two small RCTs provided data on primary outcomes for this comparison:
  - In the short-term, no statistical differences were seen between the acupuncture and the sham group in the proportion of patients achieving >33% and >50% improvement from baseline on the Headache Index (HI) in one small trial with 4 weeks of follow-up, or in the pooled mean reduction in headache episodes per month across two small trials at 4-6 weeks follow-up (insufficient evidence for all outcomes).
  - In the longer term, as reported by one small trial, no statistical differences were seen between groups in the proportion of patients achieving >33% and >50% improvement from baseline on the Headache Index at 52 weeks, or in the mean reduction in headache episodes per month at 26 and 52 weeks (insufficient evidence for all).
  - No data for the intermediate-term was available.

Acupuncture versus Active Control

- Acupuncture vs. Physical Training/Exercise and vs. Relaxation Training: one small RCT provided data on primary outcomes for this comparison
  - No data for the short- or intermediate-term were available.
  - In the longer-term (12 and 26 weeks), no statistical differences were seen between the acupuncture and the physical training/exercise group or the relaxation training group in the number of headache-free periods and headache-free days per week (insufficient evidence for all outcomes and comparisons)
- Acupuncture vs. Physiotherapy: one small RCT provided data on primary outcomes for this comparison
  - Over the short- and intermediate term (4-9 weeks), the authors provide insufficient data to assess comparative efficacy for the reduction in number of headache episodes and overall Sickness Impact Profile (SIP) score. The authors state that the acupuncture group improved significantly 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; no data was provided to support these statements. All evidence is in sufficient for this trial.
  - No data over the longer-term were available.

Manual Therapy/Manipulation versus Sham

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Usual Care

One small RCT provided data on primary outcomes for this comparison

- No data for the short- or intermediate-term were available.
- At long-term follow-up (18 weeks) in one small trial, statistically greater improvements in all outcomes reported were seen in patients who received manual therapy compared with usual care: proportion with >50% reduction in headache days per 2 weeks, mean reduction in number of headache days per 2 weeks, the Headache Impact Test (HIT-6), and the Headache Disability Inventory (HDI); the difference between groups on the HIT-6, but not on the HDI, was clinically meaningful (low strength of evidence).

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria for either comparison.

Trigger Point Injections versus Sham

One small RCT provided data on primary outcomes for this comparison

- No data for the short- or intermediate-term were available.
- At 12 weeks (longer-term) in one small trial, a statistically greater reduction in the number of headache days per month was seen following trigger point injections compared with sham; however the strength of evidence is insufficient.

Trigger Point Injections versus Active Control

- No studies were identified that met the inclusion criteria.

4.2.2.1. OnabotulinumtoxinA (BoNTA) versus Placebo for Chronic Tension-Type Headache

Studies included

Five RCTs[82,104,135,147,154] were included that compared BoNTA with placebo for the treatment of chronic tension-type headache (CTTH). A brief summary of patient and study characteristics is provided below and outlined in Table 17; detailed information is available in Appendix Table F5. The majority of trials were small and enrolled between 28 and 60 participants treated at a single center; one trial (Silberstein et al. 2006)[154] included 300 participants (250 randomized to BoNTA and 50 to placebo) and was a multicenter trial including a total of 29 sites (22 in North America and 7 in Europe). Three trials were supported by industry (Allergan)[104,135,154] and the remaining two did not report their source of funding.[82,147] Most of the trials employed a double-blind design; the trial by Hamdy et al. 2009 was the only single-blind trial. The total units of BoNTA administered varied across the trials ranging from 50 U[104] to 150 U[154] and, in all trials, the placebo injection consisted of similar volumes of saline (as used in the respective BoNTA groups). Silberstein et al. 2006 randomized patients to 6 different treatment groups: five groups received BoNTA, three receiving either 50 U, 100 U or 150 U distributed in five muscle groups and two received 86 U or 100 U injected into only three muscle groups (and placebo into 2 muscle groups); and one group received saline injections in all five muscle groups (placebo group).[154] For analysis in this report, doses from Silberstein 2006 were combined to evaluate the effect of "any" BoNTA versus placebo. Injection strategies used were fixed site in three trials,[104,147,154] follow-the-pain in one trial[135] and combined fixed site/follow-the-pain in one trial[82]; participants across all trials received one round of treatment. The number of injection sites varied (range, 4-10; unreported in one trial[135]) and injections were distributed in as few as two and as many as seven head/neck muscle areas across trials. The treatment periods varied in length and included 8 weeks (1 RCT),[147] 12 weeks (2 RCTs),[82,135] 24 weeks (1 RCT)[104] and 36 weeks (1 RCT).[154] All RCTs included a 4-week baseline period.

The trial populations were comprised primarily of females (range, 60% to 77.5%) with mean ages ranging from 36.6 to 46.5 years. Regarding headache characteristics, the mean duration of headache symptoms ranged from 4.8 years[82] to 22.3 years[147] across three trials[82,147,154] (two trials did not report mean chronicity[104,135]), and the mean frequency of headache ranged from 19.6 to 27.8 days per month across four trials[82,104,135,154] (headache frequency was not reported by one trial[147]). (Of note, in the trial by Silberstein et al 2006, 13 patients (4.3%) had <15 headache days per month at baseline and should not have been enrolled per protocol). Across the three RCTs reporting the use of prior prophylactic treatments, almost all participants (range, 87.9%-100%) had tried and failed various preventative headache medications prior to enrollment.[82,104,154] Patients with medication overuse were specifically excluded from three trials[82,135,154]; one trial stated that intake of analgesic drugs was not an exclusion criteria (in this trial the mean monthly intake of analgesics at baseline was 24.4 units and 32.5% of

patients took 30 or more units/month)[147] and other trial did not provided any information.[104] The mean number of days with acute headache medication use/month in two of the trials that excluded patients with medication overuse was 8.4 days[135] and 10.9 days[82]; in the third trial,[154] 87.9% of patients reported relying on analgesics to control headache pain at baseline (doses/day and days/month were not reported). Regarding coexisting headaches, three trials listed as an exclusion criteria more than one migraine headache per month[135,147,154] and two trials simply stated that patients with migraine as the primary headache type would be excluded.[82,104] Concomitant migraine was not uncommon in these populations and was reported by three trials: 23.3%,[147] 31.7%,[154] and 48.7%[104]; Silberstein et al. 2006 further documented that patients experienced a mean of 0.7 migraines per month with a mean duration of 1.2 days per month. All trials including concomitant migraine indicated that CTTH was the primary headache type.

Two trials were considered to be at MODERATELY LOW risk of bias (Schmitt 2001, Silberstein 2006)[147,154]; both lacked a clear statement of concealed allocation and one each failed to report how random sequence generation was achieved and intention-to-treat. Three trials were at a MODERATELY HIGH risk of bias (Hamdy 2009, Kokoska 2004, Padberg 2004).[82,104,135] These trials also all had limitations regarding randomization/allocation approaches and intention-to-treat analyses, as well as lack of assessor blinding in one trial[82] and unclear loss-to-follow-up in two.[82,104] Risk of bias assessment is available in Appendix Table E2.

Table 17. Summary of Patient, Baseline and Procedural Characteristics, BoNTA versus Placebo Comparator in CTTH

Patient demographics	Study			
	Hamdy 2009		Kokoska 2004	
Population	N = 28		N = 40	
	BoNTA	**Placebo**	**BoNTA**	**Placebo**
Randomization	n=14	n=14	n=20	n=20
Treated	n=14	n=14	n=20	n=20
Age, years; mean ± SD	36.29 (7.75)	36.86 (7.75)	43.8	49.1
% Female	71.4%	64.3%	80%	75%
Mean duration of chronicity (SD)	4.86 (2.93)	4.71 (2.27)	NR	NR
Mean # HA days/month (SD)	19.92 (3.75)	19.21 (3.17	NR	NR
Mean # Migraine days/month (SD)	NA	NA	NA	NA
Mean # HA attacks/month	NR	NR	23.3	23.2
Mean # Migraine attacks/month	NA	NA	NA	NA
Percent with medication overuse	0% (exclusion criteria)	0% (exclusion criteria)	NR	NR
Patients who had prior preventative treatments	100%	100%	95%	90%
Procedural characteristics				
Doses of Botox, placebo (saline)	range, 30-80 U* Mean U (SD): 50.1 (13.5)	Range, 30-80 U* Mean U (SD): 50.1 (13.5)	50 U	50 U
Number of Treatments	1	1	1	1
Number of Muscle Areas	6	6	3	3
Number of Injection sites	7	7	10	10
Length of F/U past treatment	12 weeks		24 weeks†	
% F/U at Last F/U	NR	NR	60%	
Cross-over (timing)	NR		NR	
Co-interventions	NR		NR	
Country	Egypt		United States	
Funding	NR		Allergan, Inc.	

	Padberg 2004		Schmitt 2001		Silberstein 2006	
Population	N = 40		N = 60		N = 300	
	BoNTA	**Placebo**	**BoNTA**	**Placebo**	**BoNTA**	**Placebo**
Randomized	n=19	n=21	n=30	n=29	n=250	n=50
Treated	n=19	n=21	n=30	n=29	n=250	n=50
Age, years; mean ± SD	43	46	45.8 (15.6)		42.6	

Patient demographics	Study					
% Female	73.7%	66.7%	60		62.3%	
Mean duration of chronicity (SD)	NR	NR	27.7 (20.7)	19.4 (15.7)	14.7	
Mean # HA days/month (SD)	26.0‡	25.8‡	NR	NR	24.0	
Mean # Migraine days/month (SD)	NA	NA	NA	NA	NA	NA
Mean # HA attacks/month	NR	NR	NR	NR	NR	NR
Mean # Migraine attacks/month	NA	NA	NA	NA	NA	NA
Percent with medication overuse	0% (exclusion criteria)	0% (exclusion criteria)	NR§	NR§	0% (exclusion criteria)	0% (exclusion criteria)
Patients who had prior preventative treatments	NR	NR	NR	NR	87.9%	
Procedural characteristics						
Doses of Botox, placebo (saline)	100 U (max) 10-20 U per muscle	100 U (max) 10-20 U per muscle	20 U per injection (80 U total)	20 U per injection (80 U total)	150 U (n=49) 100 U (n=51) 100 Usub (n=52)** 86 Usub (n=51)** 50 U (n=47)	NR
Number of Injections	1	1	1	1	1	1
Number of Muscles Areas	7	7	2	2	3 or 5††	5
Number of Injection sites	NR	NR	4	4	10	10
Length of F/U past treatment	12 weeks		4 weeks 8 weeks		4 weeks 8 weeks 12 weeks 16 weeks	
% F/U at Last F/U	100%	100%	93%	80%	93%	
Cross-over (timing)	NR		NR		NR	
Co-interventions	NR		NR		NR	
Country	The Netherlands		Switzerland		29 sites across United States, Canada, Germany, UK, Belgium, and Denmark	
Funding	In part by Allergan, Inc.		NR		Allergan, Inc.	

BoNTA, onabotulinumtoxinA; COI, conflict of interest; F/U, follow-up; HA, headache; NA, not applicable; NR, not reported; SD, standard deviation; U, units;

* Dosage varied between patients, but each patient received equal dose for each injection site

† Twenty-four patients had a full 6 month follow up and all patients turned in HA diaries

‡ Imputed based on percentage of days/month (reported as 92.5%)

§This trial stated that intake of analgesic drugs was not an exclusion criteria; mean monthly intake of analgesics at baseline was 24.4 units and 32.5% of patients took 30 or more units/month.
** "Sub" was used as an identifier in the study for the groups in which only 3 muscle groups received BoNTA and 2 muscle groups received placebo. Other groups received treatment in 5 muscle groups
†† Three groups received injections at 5 muscle areas (50U, 100U, 150U) while two groups received injections at 3 muscle areas (86Usub, 100Usub) and placebo at 2 muscle sites.

Efficacy Results

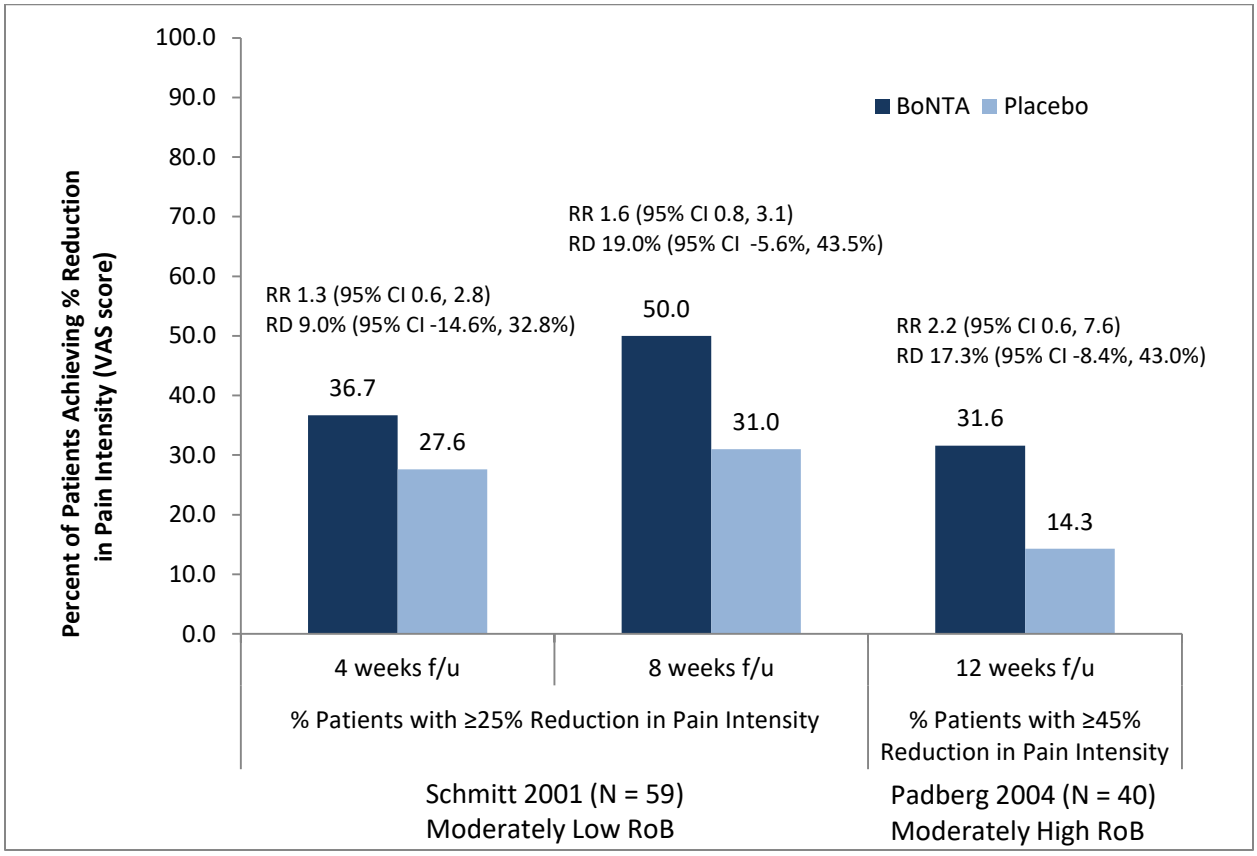
Responders

Responders were defined as the percent of patients achieving specific thresholds for reduction of pain intensity.

Short-term (4 to 8 weeks): The percent of participants achieving a reduction in pain severity via VAS score was reported in two studies. There was a greater percentage of participants in the BoNTA group reporting ≥ 25% reduction in pain intensity at 4 and 8 weeks after treatment initiation in one small trial at moderately low risk of bias (Schmitt et al 2001); however, statistical significance was not reached, possibly due in part to small sample size (Figure 21).[147] The mean monthly intake of analgesics at baseline was 24.4 units and 32.5% of patients took 30 or more units/month.

Longer-term (12 Weeks). There was also a greater percentage of BoNTA group participants achieving a ≥ 45% reduction in pain intensity at 12 weeks, with nonsignificant differences across treatment groups in another small trial at moderately high risk of bias (Padberg),but statistical significance was not reached,[135] Figure 21. Small sample size may have contributed to failure to detect a significant difference. Patients with medication overuse were excluded from this trial.

Figure 21. Percent of Patients Achieving a % Reduction in VAS Score, BoNTA versus Placebo for CTTH



BoNTA: OnabotulinumtoxinA; CTTH: chronic tension-type headache; f/u: follow-up; RD: risk difference; RoB: risk of bias; RR: risk ratio; VAS: visual analog scale.

Reduction in Frequency of Headache Episodes and Days

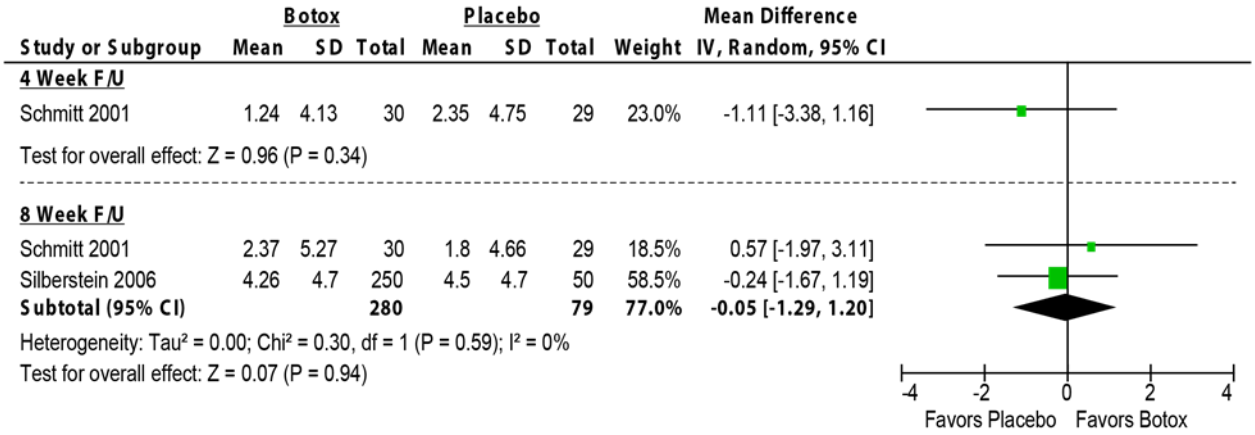
Short-term (4 to 8 weeks):

Headache-free days: An increase in number of pain-free days was reported in one study (moderately high risk of bias)[147] at 4 weeks after initiation of treatment and in two studies at 8 weeks (moderately low and moderately high risks of bias).[147,154] At 4 weeks, there were no significant differences between groups, mean difference, in one small trial (Schmitt 2001) which was likely underpowered to detect a difference between treatments. -1.11 (95% CI -3.38, 1.16).

There were also no significant differences between the BoNTA and placebo groups at 8 weeks in a pooled analysis, -0.05 (95% CI -1.29, 1.20), I^2 = 0% across two trials,[147,154] both of which were at moderately low risk of bias, Figure 22. Data from all BoNTA doses from the largest trial (Silberstein 2006) were pooled to compare with placebo. When individual doses were considered, authors report that there were no statistically significant differences between placebo and four of the BoNTA dose groups (50 U and 100U injected into 5 muscle groups and 86 U and 100 U injected into 2 muscle groups) with regard to headache-free days but a statistically significant difference favoring placebo was observed with 150U of BoNTA. Baseline differences in headache-free days at baseline were noted

between some BoNTA doses (100U in 5 muscle groups and 86U in 2 muscle groups) and placebo. It is not clear if this difference was controlled in statistical analysis.

Figure 22. Pooled Analysis of Increase in Frequency of Pain-Free Days (Short-erm Follow-up), BoNTA versus Placebo for CTTH*

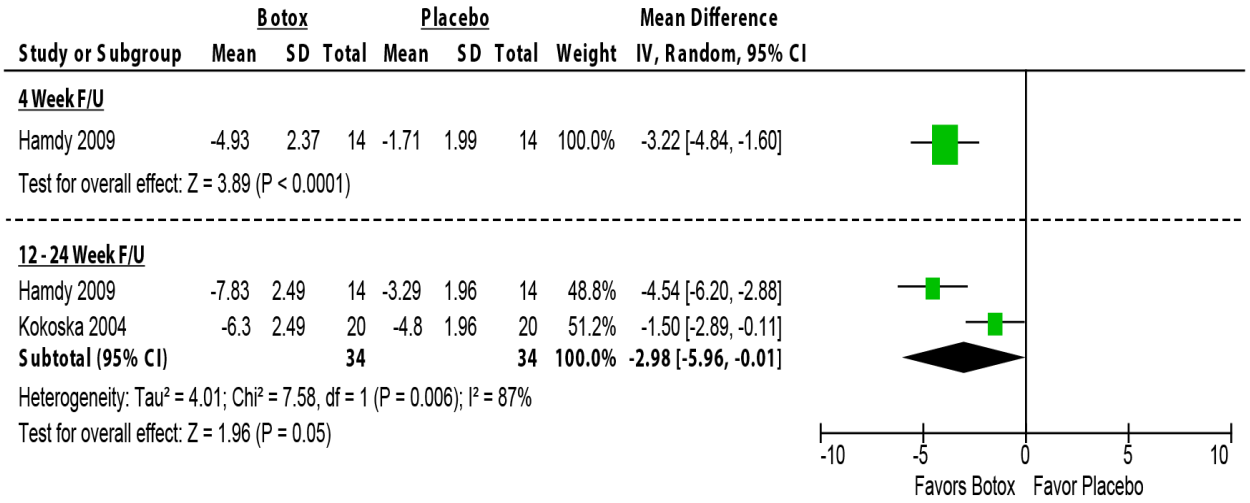


*Both Schmitt and Silberstein were at moderately low risk of bias; data on all doses from Silberstein were pooled for comparison with placebo and were estimated from authors' figure.

Headache frequency: The reduction in frequency of headache days per month was reported in one trial (moderately high risk of bias)[82] at 4 weeks after initiation of treatment and was significantly greater in the BoNTA group compared to placebo mean difference -3.22 (95% CI -4.84, -1.60), Figure 23. and two studies (moderately high risk of bias)[82,104] at 12 to 24 weeks after treatment.

Longer-term (12-24 weeks): The reduction in frequency of headache days per month was reported by two studies (moderately high risk of bias)[82,104] over longer-term follow-up. In a pooled analysis at 12 to 24 weeks, the reduction in frequency of headache was significantly greater in the BoNTA group compared to placebo, mean difference -2.98 (95% CI -5.96, -0.01), I^2 = 87%, Figure 23. The almost 3 day difference may be clinically important. Substantial heterogeneity is noted in the pooled estimate; factors for this are not clear. The Hamdy trial excluded patients with medication overuse and those presenting with migraine as a primary headache type. Kokoska did not provide information on overuse and concomitant migraine was present in 48.7% of patients.

Figure 23. Pooled Analysis of Reduction in Frequency of Headache Days per Month, (Short- and Longer-term Follow-up), BoNTA versus Placebo for CTTH*



* Both Hamdy and Kokoska were at moderately high risk of bias.

The reduction in percentage of headache days was reported in one small trial with a moderately high risk of bias.[135]There were no significant differences between the BoNTA and placebo groups at 12 weeks after treatment initiation (BoNTA 12 ± 20%, placebo 5 ± 14%; MD 7.0 (95% CI -4.0, 18.0).

Function and Disability

Longer-term (12 weeks): One small trial with a moderately high risk of bias[82] reported the percent reduction in the Headache Disability Inventory (HDI) score and percent reduction in the number of days with acute headache medication after 12 weeks of follow-up, Table 13. The percent reduction in HDI score was greater in the BoNTA group (40.6%) compared with placebo group (6.6%). Mean HDI scores at 4 and 12 weeks were significantly lower in the BoNTA group, indicating improvement in function compared with placebo (4 weeks MD -11.85 (95% CI - 22.23, -1.47), 12 weeks MD -18.28 (95% CI - 31.11, -5.45)), Table 18. This trial excluded patients with medication overuse.

Table 18. Function and Disability Measures of Chronic Tension-Type Headache: BoNTA vs. Placebo

Risk of Bias	Study	F/U	BoNTA Mean ± SD	Placebo Mean ± SD	MD (95% CI) *	p-value
HDI Score (0—100 worst)						
Moderately High	Hamdy 2009 (N=28)	4 weeks	44.29 ± 14.84	56.14 ± 11.70	-11.85 (-22.23, -1.47)	p=0.027
		12 weeks	38.29 ± 19.84	56.57 ± 12.31	-18.28 (-31.11, -5.45)	p=0.007
% reduction in HDI score, Δ from baseline						
Moderately High	Hamdy 2009	12 weeks	40.6 ± 5.5%	6.6 ± 14.5%	34.0 (25.5, 42.5)	< 0.0001

* Calculated by SRI

HDI = Henry Ford Hospital Headache Disability Inventory, scale 0-100 (worst); 16 point improvement may be considered clinically significant

Secondary Outcomes

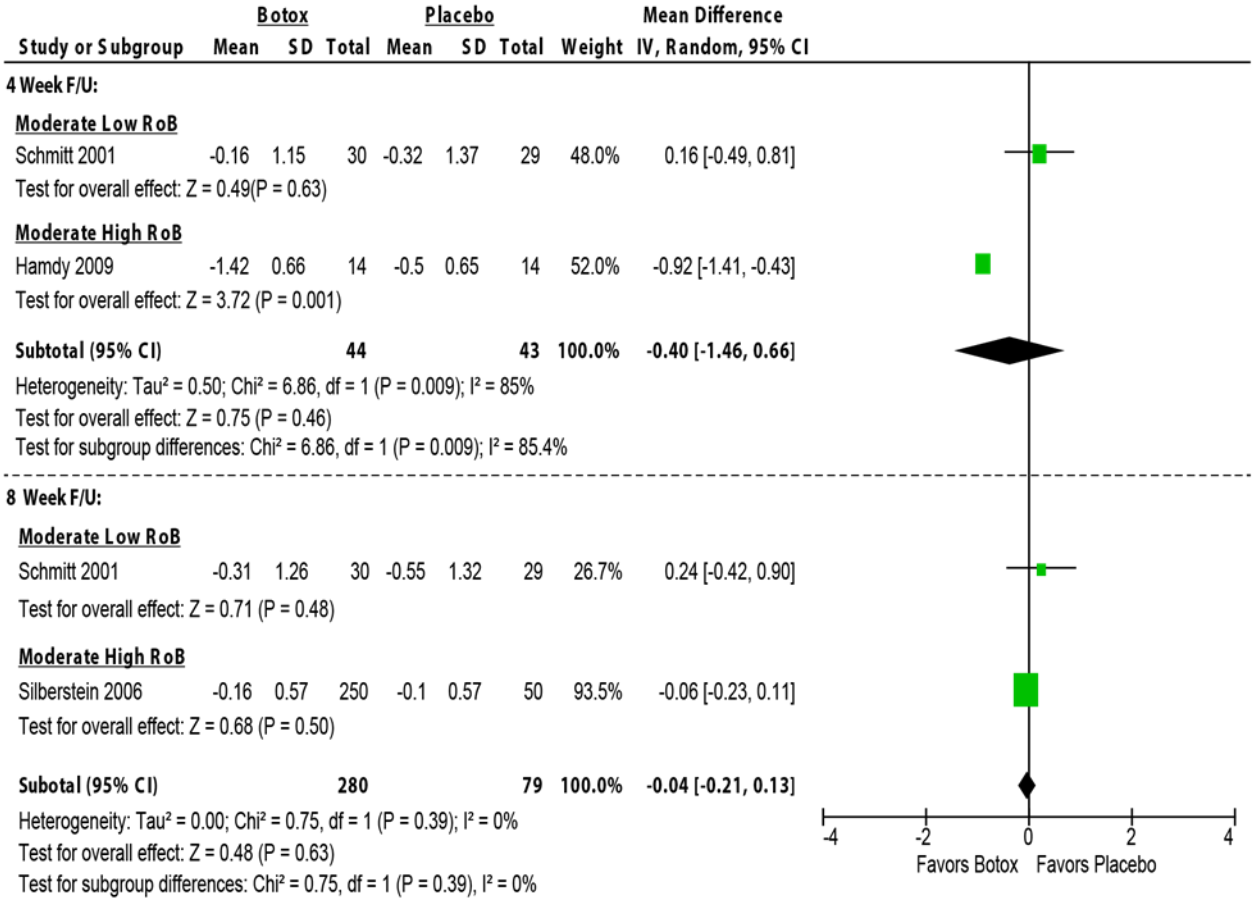
Health Related Quality of Life: One study with a moderately low risk of bias reported no significant differences between the BoNTA and placebo groups in the Headache Pain Specific Quality of Life score, Tension-type Headache Impact score, and SF-36 (data not provided).[154] Another study with a moderately low risk of bias reported no significant differences between treatment groups in the West Haven-Yale Multidimensional Pain Inventory.[147]

Medication use: There were no significant differences between the BoNTA and placebo treatment groups in the reduction in percentage of days on which analgesics were taken at 12 weeks (long-term) in one trial (BoNTA: 0.1±0.3%, placebo: 0.1±0.4%; MD 0.02%, 95% CI: -0.2, 0.3).[135] There were no significant differences between groups in the monthly intake of analgesic medication at 4 and 8 weeks after treatment initiation (short and intermediate term) in a second trial (4 weeks BoNTA: -0.6 ± 17.2, placebo: 0.4 ± 14.3, MD: -0.6, 95% CI -8.9, 7.7; 8 weeks BoNTA: -0.6 ± 17.2, placebo 1.4 ± 16.3, MD: -1.9, 95% CI -10.6, 6.8). [147]

Reduction in Pain Severity: Three trials reported reduction in pain severity at various time frames.

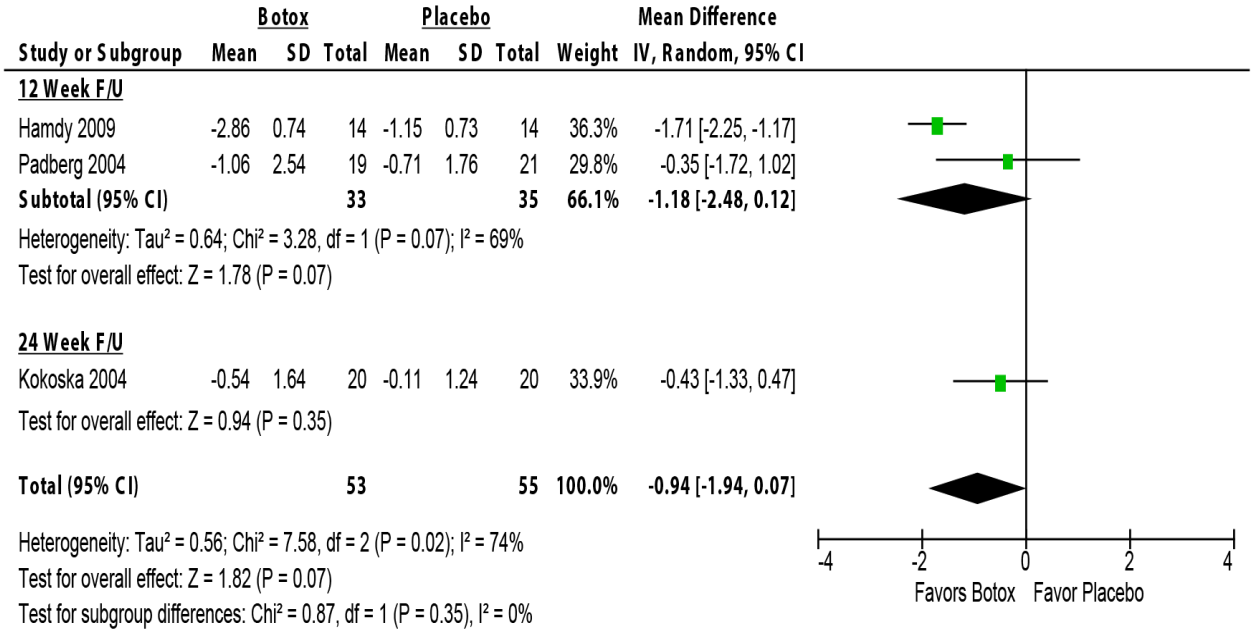
Short term (4-8 weeks): The reduction in pain severity from baseline was reported from 4 to 8 weeks after initiation of treatment in three studies with a moderately low to moderately high risk of bias.[82,147,154] At 4 weeks, there were no significant differences between the BoNTA and placebo groups in a pooled analysis, mean difference, -0.40 (95% CI -1.46, 0.66). Results were also similar across groups at 8 weeks in a pooled analysis, mean difference, -0.04 (95% CI -0.21, 0.13), Figure 24.

Figure 24. Pooled Analysis of Reduction in Pain Severity over the Short-term (4 to 8 Weeks), BoNTA versus Placebo for CTTH



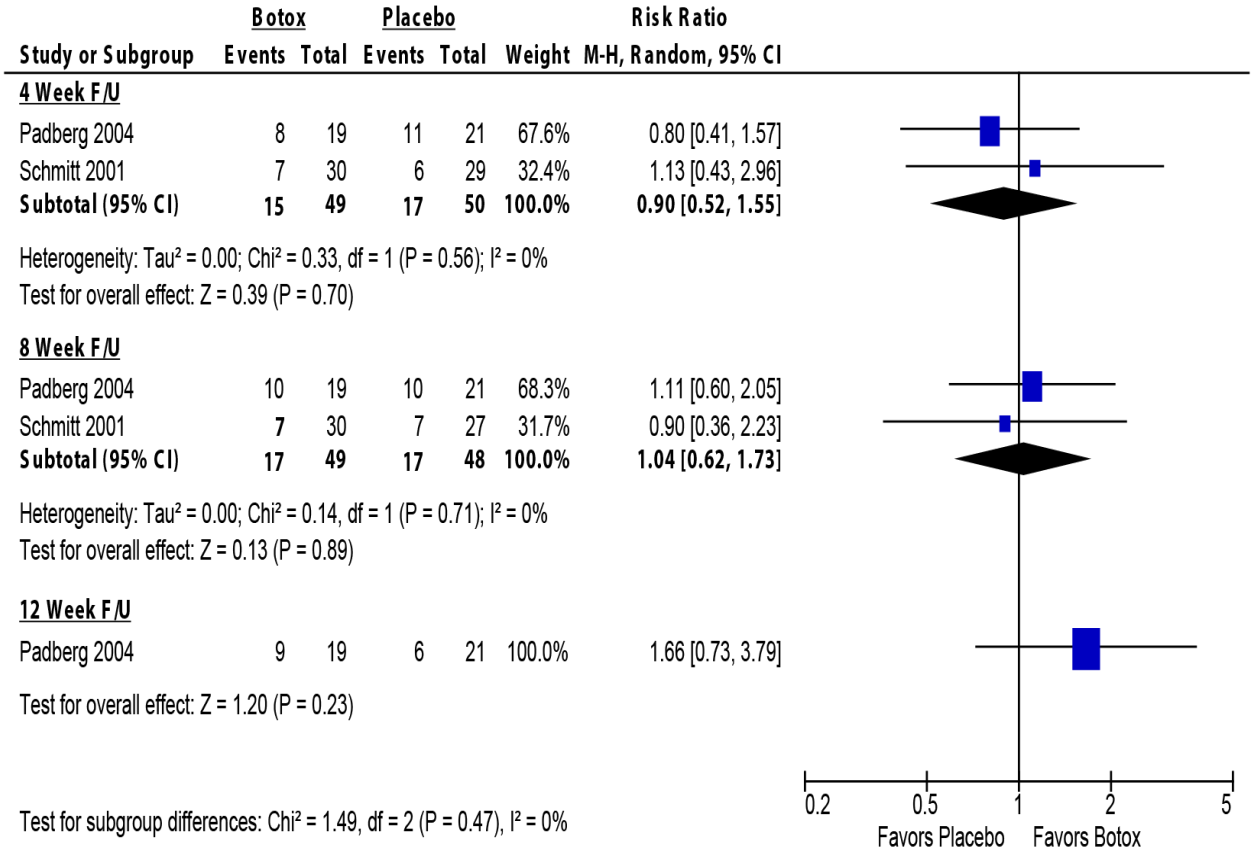
Longer term (12-24 weeks): The reduction in pain severity from baseline at 12 weeks after initiation of treatment was reported in two studies[82,135] and at 24 weeks in one study,[104] all with a moderately high risk of bias. At 12 weeks, the reduction in pain severity was greater for the BoNTA group compared to placebo, though the differences were not statistically significant across groups in a pooled analysis, mean difference, -1.18 (95% CI -2.48, 0.12). Results also favored BoNTA at the 24 week follow-up, with no significant differences across groups, -0.94 (95% CI -1.94, 0.07), Figure 25.

Figure 25. Pooled Analysis of Reduction in Pain Severity over the Longer-term (12 to 24 Weeks), BoNTA versus Placebo for CTTH



Self-reported improvement: Self-reported improvement from baseline was reported by one study with a moderately low risk of bias[147] and one study with a moderately high risk of bias.[135] At short-term follow-up (4 weeks after initiation of treatment), there were no significant differences in the percentage of patients reporting improvement between groups in a pooled analysis, RR 0.90 (95% CI 0.52, 1.55). Results were also similar between the BoNTA and placebo groups at 8 weeks after baseline in a pooled analysis, RR 1.04 (95% CI 0.62, 1.73). At long-term follow-up (12 weeks), results favored the BoNTA group, though there were no significant differences between groups, RR 1.66 (95% CI 0.73, 3.79), Figure 26.

Figure 26. Pooled Analysis of Self-Reported Improvement from Baseline over Short- (≤8 weeks) and Long-term (≥12 weeks), BoNTA vs. Placebo for CTTH



4.2.2.2. OnabotulinumtoxinA versus Active Cotnrol for Chronic Tension-Type Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.2.3. Acupuncture versus Sham for Chronic Tension-Type Headache

Studies included

Two small RCTs (samples sizes 30 and 39) were identified that evaluated the efficacy of acupuncture compared with a sham procedure.[99,164] A brief summary of patient and study characteristics is provided below; detailed information is available in Appendix Table F6. The study populations differed between the trials with regards to the mean age (32.9 vs. 48.9 years) and proportion of females (86.7% vs. 48.7%). Both trials employed traditional Chinese acupuncture but the treatment regimens differed slightly; in one trial, patients underwent one 20-minute session per week for 8 weeks (total of 8

sessions)[164] while in the second trial, patients received two 30-minute sessions per week over 5 weeks (total of 10 sessions).[99] The needles were left in place without the use of any manual or electrical stimulation as specified by one trial[164]; the second trial did not mention using a form of stimulation. For placebo, one RCT inserted the same number of needles, but more superficially, in the same region used in the verum acupuncture but in areas without acupuncture points.[164]The second trial used a blunt placebo needle which creates a pricking sensation when it touches the skin, simulating puncturing of the skin; it was placed using a cube-shaped elastic foam which was fixed upon the area of the acupoint, masking the fact that the placebo needle is not inserted into deeper tissue layers.[99] One trial followed patients for a total of 6 weeks after the end of treatment[99] while the other followed patients up to 52 weeks post-treatment.[164]

Headache characteristics also differed between the trials. The mean headache frequency per month in one trial was 17.5 attacks and the disease duration was 7.8 (range 1-31) years[164]; the other trial reported a mean of 27.0 attacks per month and did not provided information on disease duration (other than it was "chronic" in nature).[99] The use or prior use of prophylactic headache treatment was not detailed by either trial but one trial did require patients to abstain from all other therapies previously undertaken (with the exception of rescue analgesics) for the duration of the trial[164]; the second trial simply stated that concomitant medication was permitted.[99] 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 their home diaries. Of note, one trial specifically excluded patient with rebound analgesic headache syndrome as well as other concomitant headaches; in particular, patients with any history of migraine were excluded.[99] 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 MODERATELY HIGH risk of bias due to a number of methodological flaws. Common concerns across both studies were unclear random sequence generation, concealment of allocation, and intention-to-treat. Further, in one RCT, there was no accounting for loss to follow-up and no control for baseline characteristics that were unevenly distributed between treatment groups (the acupuncture group had fewer females compared with the sham group: 38% vs. 61%).[99] Detailed information on risk of bias ratings is available in Appendix Table E5.

Efficacy results

All analyses were reported out of the number of patients randomized at baseline. One trial reported that no patient was lost to follow-up and the other did not describe of loss-to-follow-up or provide sufficient information for us to calculate loss-to-follow-up.

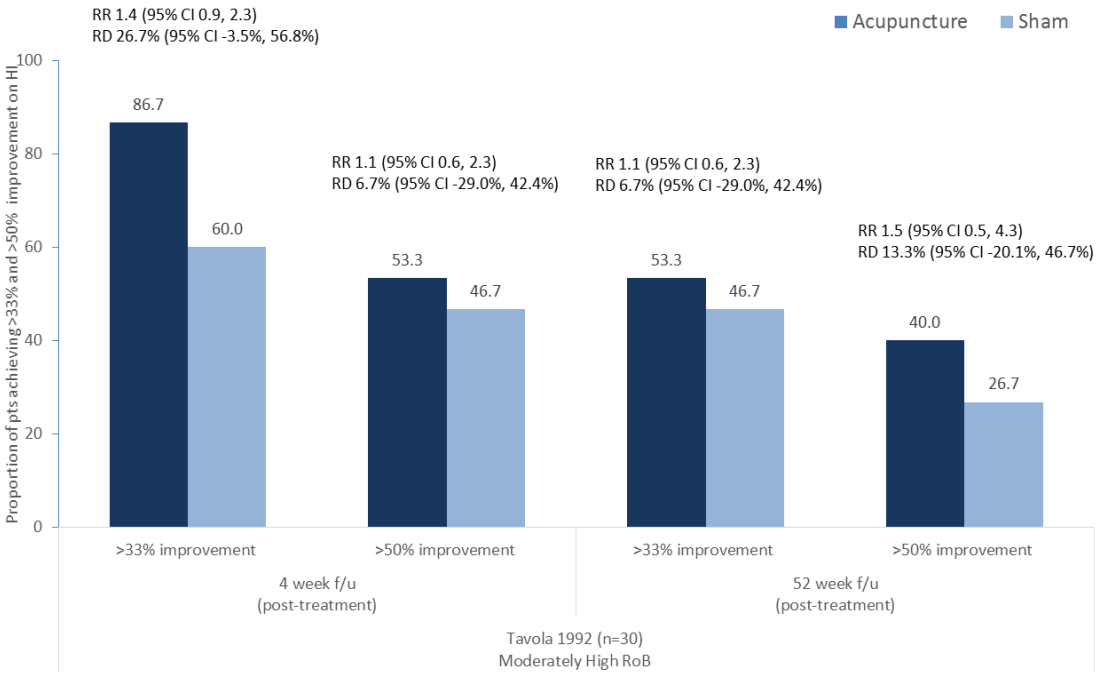
Treatment Responders

Short-term (4 weeks): In one RCT,[164] 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 27). The

small sample size is a likely a factor in this finding as 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,[164] (Figure 27). Again, the small sample size is a likely a factor in this finding.

Figure 27. 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.

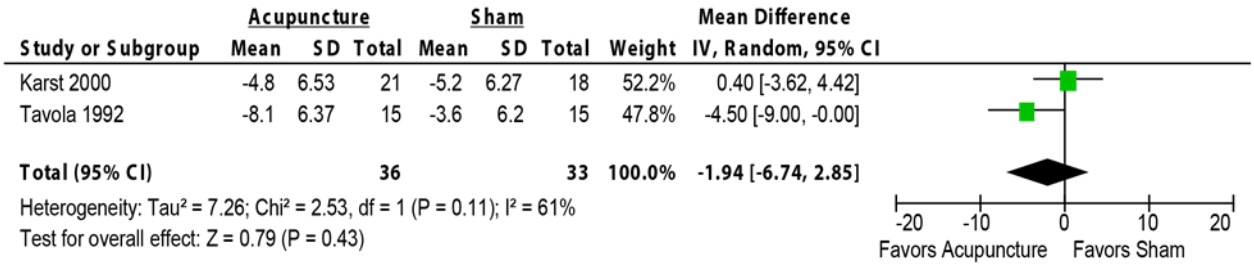
Reduction in Frequency of Headache Attacks

Short-term (6 weeks): No statistical difference was seen between the acupuncture and the sham group in mean change from baseline in the number of headache episodes per month as reported by two trials[99,164]; the pooled MD was -1.9 (95% CI -6.7, 2.9) measured at 4-6 weeks post-treatment, Figure 28 (Appendix Table G5). This analysis resulted in a large amount of heterogeneity. Both trials were considered to be at moderately high risk of bias and there were several difference in study populations that may account for some of the heterogeneity (females comprised 86.7% of one population vs. 48.7% of the other; patients in one trial were a mean 16 years younger than those in the other, 32.9 vs. 48.9

years; and mean headache frequency at baseline was 17.5 attacks in one trial vs. 27.0 attack in the other). However the sample sizes were too small to explore heterogeneity in any detail.

Longer-term (26-52 weeks): In one small trial, authors state that 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.[164]

Figure 28. 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.



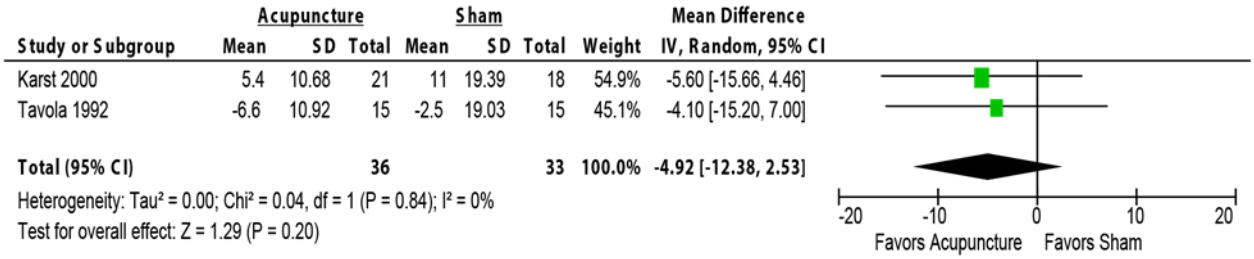
Secondary Outcomes

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.[99]

Patient perception of improvement: In one RCT,[99] patients were asked to give their impression of improvement on a clinical global impressions (CGI) scale (range -4 to 4, best) with no significant difference seen between the two groups at short-term follow-up (6 weeks post-treatment): acupuncture 1.3 ± 1.4 vs. sham 1.1 ± 1.7 (Appendix Table G5).

Analgesic consumption: No statistical difference was seen between groups in the mean change from baseline in analgesic consumption per month; the pooled MD was -4.9 (95% CI -12.4, 2.5) as measured over the short-term (4-6 weeks post-treatment),[99,164] Figure 29. One small RCT[164] 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 vs. 11.5 ± 12.7; 26 weeks, 5.0 vs. 8.5; and 52 weeks, 6.5 vs. 9.5 (all scores expect baseline were estimated from graphs in the article) (Appendix Table G5).

Figure 29. Mean Change from Baseline in Analgesic Consumption at Short-term Follow-up (4-6 weeks), Acupuncture versus Sham for CTTH.



Headache intensity: In one RCT,[99] no statistical difference was seen in headache intensity, rated on a 0-10 (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 vs. 3.9 ± 2.7, respectively Appendix Table G5.

Headache Index scores: In one small RCT,[164] 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 statistical 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 G5.

Pressure Point Threshold (PPT): In one RCT,[99] PPT 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 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 G5). The clinical significance of this finding is unclear.

4.2.2.4. Acupuncture vs. Active Control for Chronic Tension-Type Headache

Studies included

Two RCTs were identified that evaluated the efficacy of acupuncture compared with an active control group; comparisons included physical training/exercise or relaxation therapy in one trial[158,159] and physiotherapy in the other.[52] Patient and study characteristics are briefly summarized below; detailed information is available in Appendix Table F6. Both trials were considered to be at moderately high risk of bias (see Appendix Table E5 for details regarding risk of bias ratings).

Acupuncture vs. Physical training/exercise for Chronic Tension-Type Headache

One trial (two publications) included a total of 90 patients and randomized 30 each to receive acupuncture, physical training or relaxation therapy for the treatment of chronic tension-type headache (CTTH); the latter group will be analyzed in a separate section.[158,159] Patients allocated to undergo acupuncture or physical training were well matched at baseline regarding 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). In both groups, treatment was conducted by registered, experienced physiotherapists and lasted 10-12 weeks. Patients who received acupuncture underwent 10-12 sessions, each 30 minutes in duration; the needles were twilled by hand three times during each session. A total of 29 patents underwent 12 sessions and one patient underwent 10 sessions. Patients randomized to physical training performed 10 training sessions at the clinic (performed according to the 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 (except for weights which were individually adjusted). All exercises focused on the neck and shoulder muscles. Patients were followed for a total of 26 weeks post-treatment.

Regarding headache characteristics, 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 (this difference was non-significant according to the authors). At baseline, 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 (0-7 days/weeks), 0.73 and 0.97, respectively (authors state these were not statistically different between groups). No information was provided related to current or prior prophylactic treatments.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 prior to enrollment (the proportion of patients who had coexisting migraine and tension-type headache was not reported).

This RCT was considered to be a MODERATELY HIGH risk of bias due to a number of methodological flaws to include lack of random sequence generation, unclear concealment of allocation, lack of blinded assessment (outcomes were self-reported and patients could not be blinded due to the nature of the treatments), unclear reporting of co-interventions, >80% loss to follow-up (61%) at 26 weeks (but not at 12 weeks, 88% follow-up rate), and lack of control for the difference in headache duration between groups.

Acupuncture vs. Physiotherapy for Chronic Tension-Type Headache

One trial that randomized 62 female subjects to receive either acupuncture or physiotherapy for the treatment of CTTH was identified.[52] The authors do 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". Overall, the mean age of the population was 34 ± 12 years; the majority of patients had completed higher-level education (80%) and were gainfully employed (70%). In the acupuncture group, classic Chinese acupuncture was performed; the needles were

twiddled by hand and electrical stimulation via the needles was sometimes used. Patients receiving acupuncture underwent a trial period of 2-4 weeks, during which 4-5 treatments (each lasting 20 minutes) were given, with a further 4-5 treatments performed if the patient reported clear pain relief following the trial. In the physiotherapy group, the program was tailored to each patient with the goal of teaching 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 10-12 sessions (1-2 sessions/week) over 2-3 months, each with 30-45 minutes of individualized instruction. Patients were asked to reduce or stop their intake of analgesics. Patients were followed for 4 to 9 weeks after termination of treatment.

Regarding headache characteristics, the population had a mean headache duration of 9 ± 8 years and a mean headache intensity of 47 on VAS (0-100, worst) at baseline. The criteria used to diagnose tension headache in this trial was based on the criteria established for muscle contraction headache by the National Institute of Health in 1962 and is 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 initated). Baseline analgesic consumption was unclear but all but two of the patients (97%) had previously tried some form of prophylactic therapy for their headache which included analgesics, either exclusively or in combination with other therapies (such as relaxation, TENS, ultrasound, or acupuncture); in all cases, these therapies had no or little effect on the patients' symptoms. 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. Medication overuse was not reported/unclear.

This RCT was considered to be at MODERATELY HIGH risk of bias due to numerous methodological flaws including: unclear random sequence generation, allocation concealment, and intention to treat; lack of blinded assessment (outcomes were self-reported and patients could not be blinded due to the nature of the treatment); differential loss-to-follow-up (26% in the acupuncture vs. 6% in the physiotherapy group); and uncertainty regarding controlling for possible confounding due to lack of information.

Acupuncture vs. Relaxation training for Chronic Tension-Type Headache

One trial (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; the latter group will be analyzed in a separate section.[158,159] There were several difference in baseline demographics between the acupuncture and the relaxation training group: 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 higher level education and work (80% vs. 27%) than those allocated to relaxation. In both groups, treatment was conducted by registered, experienced physiotherapists and lasted 10-12 weeks. Patients who received acupuncture underwent 10-12 sessions, each 30 minutes in duration; the needles were twilled

by hand three times during each session. A total of 29 patents underwent 12 sessions and one patient underwent 10 sessions. Patients randomized to the control group underwent the Larsson-Daleflod relaxation training program based on progressive and autogenic relaxation techniques; patients also practiced relaxation, breathing, and stress coping techniques. A total of 8 to 10 individual, supervised relaxation training sessions were performed once a week; 29 patients performed 10 sessions and one patient performed eight sessions. The patients also received an audiotape for home practice. Patients were followed for a total of 26 weeks post-treatment.

Regarding headache characteristics, the duration of headache was the same between the groups: median 10.0 years (range, 2.0-37.0). At baseline, the mean number of headache-free periods per week (0-28 periods/week) was 4.13 and 3.32, respectively, and the mean number of headache-free days (0-7 days/weeks), 0.73 and 0.38, respectively (authors state these were not statistically different between groups). No information was provided related to current or prior prophylactic treatments. 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 prior to enrollment (the proportion of patients who had coexisting migraine and tension-type headache was not reported).

This RCT was considered to be a MODERATELY HIGH risk of bias due to a number of methodological flaws to include unclear concealment of allocation, lack of blinded assessment (outcomes were self-reported and patients could not be blinded due to the nature of the treatments), unclear reporting of co-interventions, >80% loss to follow-up (61%) at 6 months (but not at 3 months, 88% follow-up rate), and lack of controlling for difference between groups at baseline (acupuncture had fewer females, was younger, and had more patients with higher level education and work, as delineated above).

Efficacy Results

Acupuncture vs. Physical training/exercise

One trial (two publications), considered to be at moderately high risk of bias, randomized 30 each to receive acupuncture or physical training for the treatment of CTTH.[158,159] 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 prior to enrollment (the proportion of patients who had coexisting migraine and tension-type headache, if any, was not reported). No information was provided related to current or prior prophylactic treatments. The follow-up rate at final assessment was only 61%. Data were analyzed based on imputed values using the last-value-carried-forward method, assuming no change for non-completers.

Treatment Responders

No evidence available from included studies.

Reduction in Frequency of Headache Attacks

Longer-term (26 weeks): No statistical differences were seen between the acupuncture and the physical training group in the number of headache-free periods per week (0-28 periods/week) over the course of follow-up, respectively (Appendix Table G5): 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.[158] The authors report that the physical therapy group, but not the acupuncture group, showed significant improvement at 26 weeks compared with baseline.

Reduction in Number of Headache Days

Longer-term (26 weeks): No statistical differences were seen between the acupuncture and the physical training group 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),[158] (Appendix Table G5) Authors report that the physical therapy group, but not the acupuncture group, showed significant improvement at 26 weeks compared with baseline.

Functional disability

No evidence reported in included studies.

Secondary Outcomes

Quality of Life: 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 3 primary dimensions (contentment, vitality, and sleep), are measured on a VAS scale with low scores reflecting positive feelings and high scores reflecting negative feelings. When 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 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, 0.92); RD 30.0% (95% CI 8.5%, 51.5%))[159]; 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, 1.0), RD 23.3% (95% CI 0.5%, 46.1%). The small sample size likely played a factor in these results. Additionally, there was no statistical difference between the groups 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 G5 for details).

Headache intensity: No statistical differences were seen between the acupuncture group and the physical training group in headache intensity rated on a 0-100 (worst) VAS (recorded four times a day in the patients' diaries) at 12 weeks post-treatment (mean 18.93 (range, 0.00–53.38) versus 16.88 (range, 0.00–61.67), respectively) or at 26 weeks post-treatment (mean 17.72 (range, 0.00–50.27) versus 14.66 (range, 0.00–56.75), respectively),[158] (Appendix Table G5). 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.

Acupuncture vs. Physiotherapy

One small trial (moderately high risk of bias) that randomized 62 female subjects to receive either acupuncture or physiotherapy for the treatment of chronic tension-type headache was identified.[52] Almost all patients had previously tried some form of therapy for their headache which included analgesics, either exclusively or in combination with other therapies. Medication overuse was not reported/unclear. Twenty-three (37%) patients had a combination of tension headache 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. There was differential loss-to-follow-up between the groups (26% in the acupuncture vs. 6% in the physiotherapy group) 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: of the eight non-completers, six lived alone (as compared with 54% in the study group) and four were students (as compared with 6% in the study group). Data for patients completing the study are reported as that was what was provided by the authors

Treatment Responders

No evidence.

Reduction in Frequency of Headache Attacks

Short- to Intermediate-Term (4 to 9 weeks): The authors state that headache frequency (measured on a 1 to 5 scale: 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 were provided and no information regarding the between group difference was provided.[52]

Functional disability

Short- to Intermediate-Term (4 to 9 weeks): At 4 to 9 weeks post-treatment, the acupuncture group and the physiotherapy group 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 significant difference between the treatment groups.[52] 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 G5 for more detail.

Secondary Outcomes

Quality of Life: The mental well-being of the patients was evaluated using 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,[52] Appendix Table G5.

Headache intensity: The acupuncture group showed 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, [52] (Appendix Table G5). The mean group scores for headache intensity on VAS were 40 versus 28, respectively, at 4 to9 weeks post-treatment and 52 versus 29, respectively, at 28-52 weeks (estimated from graphs provided in the article); no data was provided for the 5-point pain scale.

Acupuncture vs. Relaxation training

One trial (two publications), considered to be at moderately high risk of bias, randomized 30 each to receive acupuncture or physical training for the treatment of CTTH.[158,159] 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 prior to enrollment (the proportion of patients who had coexisting migraine and tension-type headache, if any, was not reported). No information was provided related to current or prior prophylactic treatments. There were differences between groups at baseline that were not controlled for (i.e. acupuncture had fewer females, was younger, and had more patients with higher level education and work). The follow-up rate at final assessment was only 61%.

Data were imputed for missing values and analyzed by the authors using the last-value-carried-forward method, assuming no change for non-completers.

Treatment Responders

No evidence available from included studies.

Reduction in Frequency of Headache Attacks

Longer-term (26 weeks): No statistical differences were seen between the acupuncture and the relaxation training group in the number of headache-free periods per week (0-28 periods/week) over the course of follow-up, respectively (Appendix Table G5): 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.[158] The authors report that the relaxation training group, but not the acupuncture group, showed significant improvement at both timepoints compared with baseline.

Reduction in Number of Headache Days

Longer-term (26 weeks): No statistical differences were seen between the acupuncture and the relaxation training group 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),[158] (Appendix Table G5). Authors report that the relaxation training group, but not the acupuncture group, showed significant improvement at both timepoints compared with baseline.

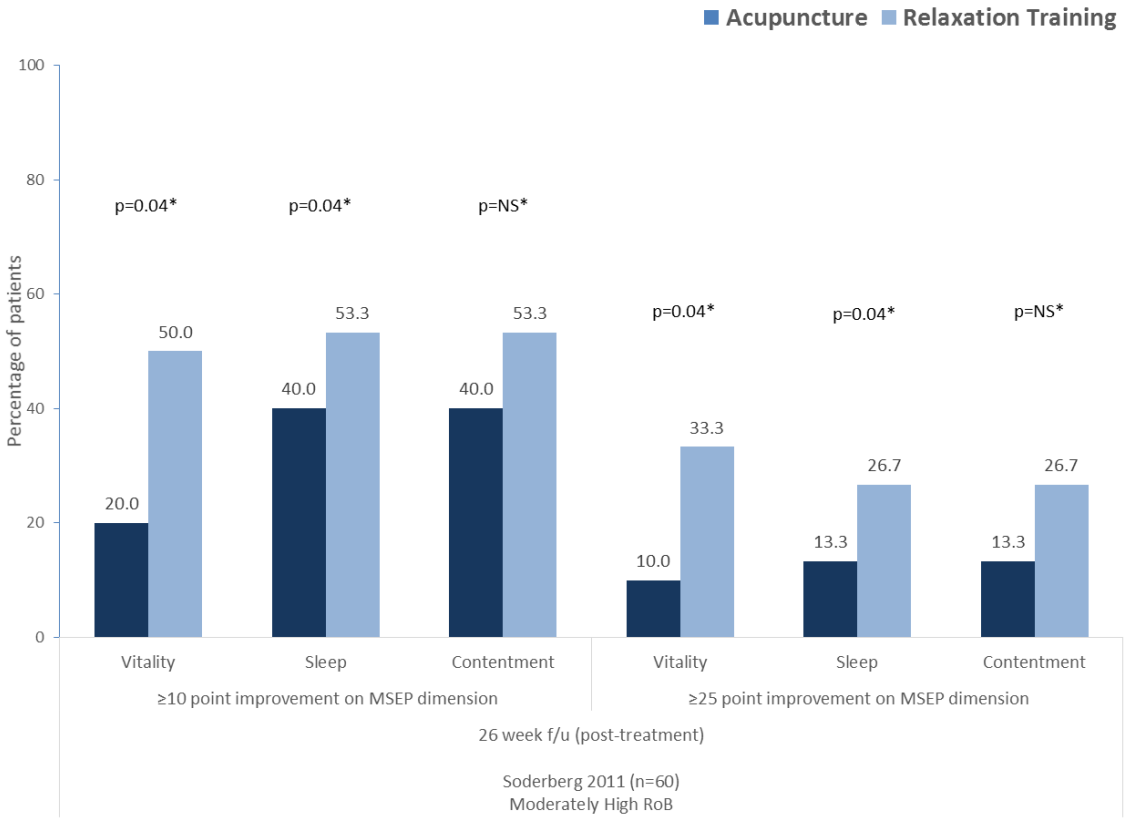
Functional disability

No evidence available from included studies.

Secondary Outcomes

Quality of Life: Patient's 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. When 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 not statistically different 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.[159] The small sample size may have played a factor in these results. When comparing improvement of ≥10 or ≥25 points on VAS for the three MSEP dimensions, however, 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 (Figure 30); 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 (see Appendix Table G5 for details).

Figure 30. 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: No statistical differences were seen between the acupuncture group and the relaxation training group 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),[158] (Appendix G5). 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.

4.2.2.5. Manual Therapy/Manipulation versus Sham for Chronic Tension-Type Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.2.6. Manual Therapy/Manipulation versus Active Control for Chronic Tension-Type Headache

Studies included

One RCT was identified that evaluated the efficacy of manual therapy (MT) compared with an active control for the treatment of chronic tension-type headache.[54] Detailed information regarding patients and study characteristics is available in Appendix Table F7. A total of 82 patients were randomized to receive MT (n=41) or usual care (n=41). The groups were well matched at baseline regarding age (40.2 vs. 40.6 years) and sex distribution (78% female in both groups). The manual therapy intervention consisted of a combination of three approaches: mobilizations of the cervical and thoracic spine, craniocervical muscle exercises and posture correction. Each session was 30 minute long and patients received a maximum of nine treatments over 2 months. Usual care consisted of information, reassurance and advice, discussion of lifestyle changes, and analgesics or non-steroidal anti-inflammatory drugs if needed all provided a general practitioner (GP); on average the patients had two or three visits with their GP over a two month period. Patients were excluded if they had received manual therapy treatment in the 8 weeks before enrollment into the study. Patients were followed for 18 weeks after the end of treatment.

Regarding headache characteristics, groups were similar with regarding to mean duration of headache (12.5 vs. 13.1 years) and the number of headache days per month (23.7 vs. 24.0 days). Of note, 29% of patients randomized to MT and 22% randomized to usual care had comorbid migraine. Current or past use of other prophylactic treatments was not reported. Patients were excluded if their intake of either triptans, ergotamines or opioids was ≥10 days/month or simple analgesics on ≥15 days/month on a regular basis for ≥3 months. At baseline, the mean number of pills/doses per week of NSAIDs was 1.2 ± 2.4 in the MT versus 1.5 ± 3.1 in the usual care group (23.3% and 34.1% of patients were using NSAIDs at baseline, respectively) and of analgesics, 2.8 ± 3.9 versus 3.5 ± 5.1, respectively (58.5% of patients in both groups were using analgesics at baseline).

This RCT was considered to be at MODERATELY LOW risk of bias due to unclear reporting of concealed allocation and lack of blinded assessment (outcomes were patient reported and due to the nature of the interventions the patients could not be blinded). Risk of bias assessment for all studies is found in Appendix Table E8.

Efficacy Results

The data presented below was analyzed according to the intention-to-treat (ITT) principle using the numbers included at baseline. (In addition, the authors performed a per-protocol analysis evaluating only those participants with no serious protocol deviations (2 patients received alternative treatment during the first 8 weeks); there were no differences between this analysis and the ITT).

Treatment Responders

Longer-term (18 weeks): The proportion of patients that experienced >50% reduction from baseline in the number of headache days (per 2 weeks) was statistically higher following MT compared with usual care at 18 weeks post-treatment: 81.6% (31/38) versus 40.5% (15/37); RR 2.0 (95% CI 1.3, 3.0); NNT 3 (95% CI 1.6, 4.8), RD 41.0% (95% CI 21.0%, 61.1%), [54] Appendix Table G6. Given that 29% of MT patients and 22% of usual care patients had comorbid migraine, it is unclear how the coexistence of these headache types may have affected the outcome.

Reduction in Number of Headache Days

Longer-term (18 weeks): Patients who received MT reported a statistically greater reduction in the number of headache days per 2 weeks compared with usual care at 18 weeks follow-up (Appendix Table G6): the mean difference (MD) between groups in change scores from baseline was 4.9 ± 0.99 (95% CI 2.98, 6.95).[54] Again, it is unclear how the coexistence of migraine and tension-type headache in this population may have affected the outcome.

Functional disability

Longer-term (18 weeks): At 18 weeks post-treatment, a statistically significant and clinically meaningful improvement (defined by the authors as >2.3 point decrease) in Headache Impact Test (HIT-6) (range 36-78, worst) scores was observed for MT compared with usual care: MD between groups in change scores from baseline was 5.0 ± 1.97 (95% CI 1.16, 9.02).[54] The mean difference between groups on the Headache Disability Inventory (HDI) (score range 0-100, severe disability) also statistically favored the MT group (MD 10.1 ± 4.74; 95% CI 0.64, 19.5), however, the difference did not meet the author-defined clinically important threshold of ≥16-point reduction. (Appendix Table G6). Given that 29% of MT patients and 22% of usual care patients had comorbid migraine, it is unclear how the coexistence of these headache types may have affected the outcome.

Secondary Outcomes

Patient-perceived recovery: A significantly greater proportion of patients who underwent MT considered themselves improved or much improved at the long-term follow-up (18 weeks post-treatment) compared with those who received usual care: 87.5% (35/40) versus 25.0% (10/40); RR 3.5 (95% CI 2.0, 6.1); RD 62.5% (95% CI 45.6%, 79.4%),[54] Appendix Table G6.

Sick leave: The proportion of patients who used at least one day of sick leave was statistically lower in the MT group compared with the usual care group as assessed over the long-term (18 weeks post-treatment): 7.9% (3/38) versus 32.4% (12/37); RR 0.24 (95% CI 0.07, 0.79); RD -24.5% (95% CI -41.9%, -7.2%),[54] Appendix Table G6.

Additional health care utilization: The proportion of patients who used any additional health care (i.e., physical therapy, medical specialists, other) was statistically lower in the MT group compared with the usual care group as assessed at the long-term follow-up (18 weeks post-treatment) (Appendix Table G6): 13.2% (5/38) versus 59.4% (22/37); RR 0.22 (95% CI 0.09, 0.52); RD -46.3% (95% CI -65.4%, -27.2%).[54] Of note, additional physical therapy was sought by 2.6% (1/38) of patients in the MT group compared with 40.5% (15/37) in the usual care group.

Frequency of analgesic use: Authors report no statistically significant differences between treatments in analgesic or NSAID use; data were not provided.[54]

Headache intensity: Patients who received MT reported a statistically greater improvement (i.e., reduction) in headache pain intensity scores on NRS (0-10, worst) compared with usual care at 18 weeks post-treatment: the mean difference in change scores from baseline was 1.4 ± 0.63 (95% CI 0.16, 2.69). It is unclear if this represents a clinically important difference,[54] (Appendix Table G6).

4.2.2.7. Massage versus Sham and versus Active Control for Chronic Tension-Type Headache

No studies were identified that met the inclusion criteria for these comparisons.

4.2.2.8. Transcranial Magnetic Stimulation versus Sham and versus Active Control for Chronic Tension-Type Headache

No studies were identified for this comparison.

4.2.2.9. Trigger Point Injection versus Sham for Chronic Tension-Type Headache

Studies included

One RCT was identified that compared trigger point injections (TPI) with placebo injections for the treatment of chronic tension-type headache.[98] Detailed information regarding patients and study characteristics is available in Appendix Table F8. A total of 47 patients (24 in the TPI and 23 in the placebo group) were included. Mean age and sex distribution was similar between the TPI and placebo group (mean 40.4 ± 12.0 vs. 40.7 ± 13.2 years and 83.3% vs. 79.2% female, respectively). Patients in the TPI group underwent bilateral, local lidocaine injections into myofascial trigger points of muscles that had dominant areas with pain; the dosage of lidocaine varied depending on the location of the injection and ranged from 1 ml to 6 ml. The placebo group received a local injection of saline (0.9% NaCl).

Lidocaine and saline injections were given to the same muscles; applications in repetitive injections were made to the same trigger points. Patients in both group underwent 1 session every 3 days; each patient received 3 sessions. Patients were followed for 12 weeks after the end of treatment.

Regarding headache characteristics, the mean number of headache days per month was similar between groups (20.2 ± 3.9 days in TPI vs. 19.1 ± 3.5 days in sham group); the mean duration of symptoms was not reported but history of chronic tension-type headache for a least 6 months was an inclusion criteria. Patients with medication-overuse headache according to The International Classification of Headache Disorders were excluded, as were patients who had used any kind of prophylactic treatment for headache in the month prior to enrollment. At baseline, the number of NSAIDs used per month was 9.8 ± 2.1 versus 10.1 ± 2.6 tablets, respectively. The authors also excluded patients with primary headaches other than tension-type headache but do not mention whether any patients had concomitant headache.

This RCT was considered to be at MODERATELY HIGH risk of bias violating every criteria for a good quality RCT except for blind assessment of outcomes (double-blind, placebo controlled trial). Risk of bias assessment for all studies is found in Appendix Table E10.

Efficacy Results

Loss-to-follow-up was not reported for this study; therefore it is assumed that all analyses are based on number of patients at baseline.

Treatment Responders

No evidence.

Reduction in Number of Headache Days

Longer-term (12 weeks): TPI resulted in a statistically greater decrease in the number of headache days per month compared with placebo injection at 12 weeks post-treatment; the mean difference in change scores between groups was 11.2 days (95% CI 9.2, 13.2),[98] Appendix Table G9.

Functional disability

No evidence.

Secondary Outcomes

Improvement in Depression/Anxiety: TPI resulted in a statistically greater improvement (i.e. decrease) in Hamilton Depression and Anxiety Scale scores compared with placebo injection (Appendix Table G9); the mean difference in change scores between groups at longer-term follow-up (12 weeks after the end of treatment) was 4.2 points (95% CI 2.4, 6.0) for the Depression Scale and 5.9 points (95% CI 4.0, 7.8) for the Anxiety Scale.[98] It is unclear if these differences are clinically meaningful.

Frequency of analgesic use: Compared with placebo, TPI resulted in a statistically greater decrease in the number of analgesics used per month as measured over the long-term (12 weeks post-treatment); the mean difference in change scores between groups was 4.8 tablets (95% CI 3.9, 5.7),[98] Appendix Table G9.

Headache intensity: TPI resulted in a statistically greater improvement (i.e. decrease) in pain severity on VAS (0-100, worst) compared with placebo injection; the mean difference in change scores between groups at longer-term follow-up (12 weeks) was 32.6 points (95% CI 26.8, 38.4),[98] Appendix Table G9.

4.2.2.10. Trigger Point Injection vs. Active Control for Chronic Tension-Type Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.3. Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Summary of results

The general findings for chronic daily headache (CDH) treatment for the primary outcomes are briefly summarized below by treatment and comparator. Detailed findings (including results for secondary outcomes) are then presented. We report following primary outcomes:

- The proportion of treatment responders is a primary outcome of interest; it was variable defined across trials.
- Reduction in mean frequency of headache. This may include frequency of attacks/episodes (e.g. migraine episodes), overall headache days or headache days for a specific headache type (e.g. migraine days)
- Function as measured by validated measures

For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Most trials were at moderately high risk of bias; assessment details are provided in Appendix E.

BoNTA vs. Placebo
Three RCTs provided limited data on primary efficacy outcomes.

- No data on short- or intermediate term outcomes were available.
- At long-term follow-up (24 weeks) in one RCT, there is low evidence that more BoNTA recipients had a ≥50% reduction frequency of headache days compared with placebo (low evidence)

There was no statistically significant difference across two RCTS in the change in mean number of headache-free days over the long-term (24 weeks) (low evidence); while one of these trials reported a statistical difference, it didn't meet their criteria for clinical significance.

BoNTA vs. Active Control (Topiramate):
One small RCT provided limited data on primary outcomes.

- At short- (4 weeks) and long-term (12 weeks) follow-up in one small RCT, there was no difference between BoNTA and topiramate in the reduction of mean headache days per month (low evidence).
- At long-term follow-up (12 weeks) there no differences between groups with regard to function or disability based on HIT-6 or MIDAS scores in the same RCT (low evidence).
- No data on intermediate-term outcomes were available.

Acupuncture vs. Sham and vs. Active Control
- No trials were identified that met the inclusion criteria.

Manual Therapy/Manipulation vs. Sham and vs. Active Control
- No trials were identified that met the inclusion criteria.

Massage vs. Sham
One small RCT provided data on primary outcomes for this comparison.

- At both short- (3 weeks) and intermediate-term (9 weeks) follow-up in one small RCT, no statistical differences were seen between the massage and sham groups in the reduction in headache attacks per month and Headache Disability Index (low strength of evidence).
- No data on longer term outcomes were available.

Massage vs. Active Control
- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation vs. Sham and vs. Active Control
- No trials were identified that met the inclusion criteria.

Trigger Point Injection vs. Sham and vs. Active Control
- No trials were identified that met the inclusion criteria.

4.2.3.1. OnbotunlinumtoxinA (BoNTA) versus Placebo for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

The nomenclature and classification related to headache type has evolved over the decades, as previously described in the background. The terminology related to chronic migraine in particular and coexistent migraine and tension type headache appears to vary substantially in clinical practice, in the literature,[19] and in available patient information. For the purposes of this 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 (CDH) consistent with the how this is described in the included trials.

Studies included

Three, double-blind, placebo-controlled RCTs[120,134,155] that enrolled as few as 60 and as many as 702 patients were included that evaluated the efficacy of BoNTA for the treatment of chronic daily headache. A brief overview of the patient and study characteristics is provided below and in Table 19; detailed information is available in Appendix Table F9. All three trials were comprised primarily of females (range, 81.7%–84.5%) with mean ages ranging from 43.2 to 47 years. All trials compared BoNTA injections with saline (placebo) injections and included a 4-week baseline screening period. In addition, two trials (Silberstein et al. 2005, Mathew et al. 2005)[120,155] included a 4-week placebo run-in period (following the baseline period) after which participants were randomized to a treatment group. Both of these trials provided secondary analyses comparing those who responded to the placebo injections (i.e., "placebo responders" defined in both trials as patients with less than 16 headache days or at least a 30% decreased from baseline in the frequency of headache days) and those who did not (i.e., "placebo nonresponders"). Except where noted, data for placebo responders and nonresponders were pooled.

Participants in Mathew 2009 and Silberstein 2005 were given three treatments at 12-week intervals over a 36-week period, whereas those in Ondo 2004 received only one injection and were followed for a total of 12 weeks. Two trials utilized a "follow-the-pain" injection strategy: Mathew 2005 et al. administered a total of 105 to 260U of BoNTA into 23 to 58 injection sites across seven head/neck muscle groups[120]; Ondo et al injected 200U across an unreported number of sites.[134] The third trial (Silberstein 2005) followed a fixed injection site protocol and patients received 225U, 150U, or 75U of BoNTA via 20 injection sites across seven muscle areas. In all studies, placebo injections were done in an identical fashion as the BoNTA injections. Of note, the trial by Ondo et al. 2004 included an open-label phase, which began after the final blinded evaluation at 12 weeks. During this phase (unblinded), all patients were offered BoNTA injections and followed for an additional 12 weeks. Data for the open-label phase, which was un-blinded and not randomized, are reported separately following the efficacy data below.

Patients in the Matthew 2005 and Silberstein 2005 trials were included if they had any combination of migraine (with or without aura), migrainous headache, probably migraine and/or episodic or chronic tension-type headache based on the International Headache Society's 1998 International Classification of Headache Disorders [IDHD-I).[4] Ondo 2004 reports inclusion of patients with either CM or CTTH as subtypes of CDH and acknowledges that there are overlapping clinical features between these.
There is substantial heterogeneity across included studies with regard to headache characteristics reported. Regarding headache characteristics, the mean duration of headache symptoms was 13.7 and 14.5 years as reported by two trials[120,155]; chronicity was not reported in the third.[134] In the trials by Silberstein et al. 2005 and Mathew et al. 2005, the mean number of headaches per month was 13.7 and

13.1, respectively, and the mean number of migraines per month was 10.4 and 11.0, respectively. In the trial by Ondo et al., 76.7% of patients suffered from chronic tension-type headaches while the remaining 23.3% had a diagnosis of chronic migraine; at baseline, the mean number of headaches (not defined further) per month in this population was 23, which was substantially higher than the frequencies reported in the other two trials. The trials by Silberstein et al. and Mathew et al. reported that 49.4% and 35.8% of patients, respectively, were using prophylactic headache medication at baseline and that almost half (42.0% and 47.3%, respectively) were overusing acute headache pain medication (defined as ≥15 days and ≥2 days/week per month). Similarly, in the trial by Ondo et al., prior to enrollment, subjects had tried and discontinued a mean of 4.0 ± 3.0 (range, 0-18) prophylactic medications and 4.5 ± 2.4 (range, 0-13) rescue medications; at baseline, the mean number of rescue medication doses per month was 45.4 (the mean number of prophylactic medications is unclear) and over half of the patients (57.6%) were overusing narcotics (>12 per month), to include 60% in the BoNTA group and 53.3% in the placebo group.

Two trials (Mathew et al. 2005 and Silberstein et al. 2005) were considered to be at MODERATELY LOW risk of bias[120,155]; limitations included lack of a statement regarding allocation concealment and complete follow-up of less than 80% (76.9% and 72.8%). The third trial, conducted by Ondo et al. 2004, was considered to be at MODERATELY HIGH risk of bias[134] due to unclear reporting of random sequence generation and allocation concealment approaches; it is also unclear whether differences in headache days during the run-in phase (i.e., baseline) was adequately controlled (the BoNTA group had fewer (4.8 ± 0.8) compared with placebo (25.5 ± 0.9)); this may be a typographical error given that the mean number of headache days across groups was 23 days. See Appendix Table E3 for details regarding risk of bias ratings. Matthew 2005 and Silberstein 2005 were sponsored by Allergan, Inc. and authors of both studies report associations with Allergan. Funding for Ondo 2004 is not described.

Table 19. Summary of Patient, Baseline and Procedural Characteristics, BoNTA versus Placebo for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Patient demographics	Study					
	Mathew 2005		Ondo 2004		Silberstein 2005	
Population	N = 355		N = 60		N = 702	
Comparators	**BoNTA**	**Placebo**	**BoNTA**	**Placebo**	**BoNTA**	**Placebo**
Randomized	n=173	n=182	n=30	n=30	n=524	n=178
Treated	n=173	n=182	n=30	n=30	n=524	n=178
Age, years; mean ± SD	43.5		46.3 (9.4)	47.7 (12.7)	43.25	43.7
% Female	84.5%		76.7%	86.7%	82.9%	
Mean duration of chronicity (SD)	14.8 (12.4)	14.2 (12.5)	NR		13.7 (12.2)	
Mean # HA days/month (SD)	13.5 (7.7)	12.7 (8.3)	4.8 (0.8)*	25.8 (0.9)	13.8 (8.6)	
Mean # Migraine days/month (SD)	11.0 (7.3)	10.8 (7.9)	NR	NR	10.4 (7.2)	10.5 (8.5)
Mean # HA attacks/month	NR	NR	NR	NR	NR	NR
Mean # Migraine attacks/month	NR	NR	NR	NR	NR	NR
Percent with medication overuse	52.6%	42.3%	60.0%	53.3%	41.8%	43.3%
Patients who had prior preventative treatments	32.4%	39.0%	66.6%	66.6%	50.0%	48.3%
Procedural characteristics						
Doses of Botox, placebo (saline)	105-260 U	105-260 U	200 U	200 U	225 U (n=182 150 U (n=168) 75 U (n=174)	0.9mg sodium chloride reconstituted with saline
Number of Treatments	3	3	NR	NR	3	3
Number of Muscle Areas	NR	NR	NR	NR	7	7
Number of Injection sites	23-58	23-58	1	1	20	20
Length of F/U past treatment	9 mos.		3 mos.		6 mos.	
% F/U at Last F/U	77.2%		96.7%	96.7%	71.9%	75.6%
Cross-over (timing)	NR		At 3 month f/u, patients were offered open-label BoNTA injections[1]		NR	
Co-interventions	NR		NR		NR	
Country	United States (multicenter)		United States		United States, Canada (multicenter)	
Funding	Allergan, Inc.		NR		Allergan, Inc.	

BoNTA, onabotulinumtoxinA; COI, conflict of interest; F/U, follow-up; HA, headache; NA, not applicable; NR, not reported; SD, standard deviation; U, units

*This is likely a typo in the article given that authors report a mean of 23 headache days for the full population.

Efficacy Results

Treatment Responders

Treatment responders were defined as those achieving a ≥ 50% reduction in frequency of headache days per month.

Longer-term (24 weeks): Two RCTs with a moderately low risk of bias reported on the percent of participants achieving ≥ 50% reduction in frequency of headache days per month (Appendix Table G3).[120,155] A small, but statistically significantly greater percentage of participants in the BoNTA group achieved ≥ 50% reduction in frequency of headache days per month (40.3%) compared to placebo (25.3%) at 24 weeks (RR 1.6, 95% CI 1.2, 2.2; RD 15.2%, 95% 5.5, 24.9) based on pooled data from placebo responders and nonresponders.[120] Medication overuse was reported in 52.6% of BoNTA recipients and 42.3% of placebo recipients and approximately one third of patients reported use of prophylactic treatments.

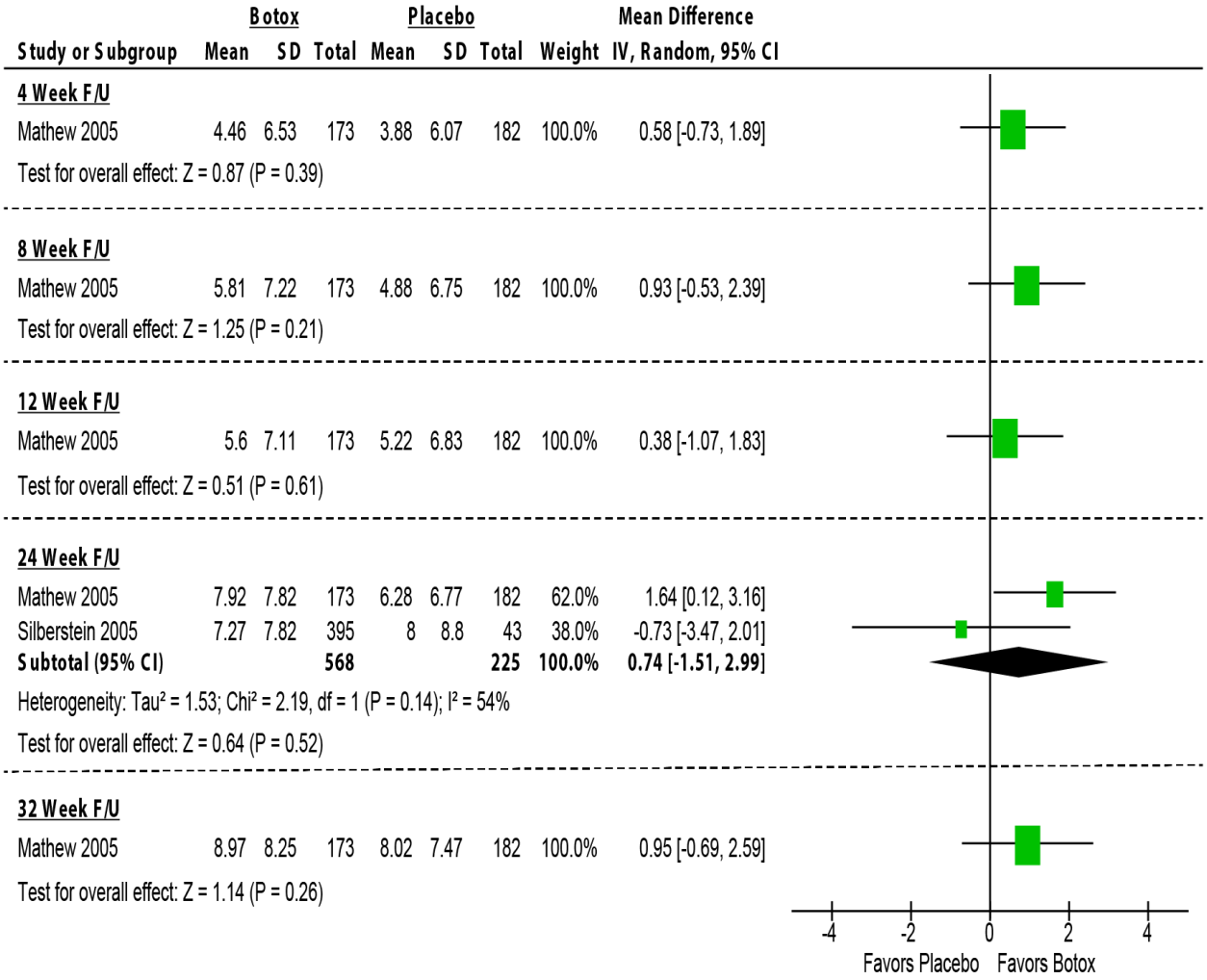
In contrast, in the Silberstein 2005 trial, no significant differences were reported between the BoNTA treatment groups compared to placebo at 24 weeks after initiating treatment for placebo nonresponders, which comprised 76% of the study population in the other trial. Authors report that more placebo responders receiving the highest BoNTA dose (225U) experienced ≥ 50% reduction in frequency of headache days per month versus placebo; pooled data across BoNTA doses for placebo responders and nonresponders were not calculable, thus pooling was not possible).[155] At baseline, medication overuse was reported in approximately 40% of patients and approximately 50% reported using prophylactic medications.

Reduction in Frequency of Headache Episodes and Days

Short- and Longer-term (4-32 weeks): The reduction in headache-free days per month was reported in two studies with a moderately low risk of bias.[120,155] In the Matthew 2005 trial, at 4, 8 and 12 weeks after initiation of treatment, results favored the BoNTA group, though there were no significant differences in headache-free days between the BoNTA and placebo groups in one study (4 weeks: mean difference 0.58 (95% CI -0.73, 1.89), 8 weeks: mean difference 0.93 (95% CI -0.53, 2.39), 12 weeks: mean difference 0.38 (95% CI -1.07, 1.83), Figure 31. As previously noted, approximately one half of patients reported medication overuse at baseline.

Data at 24 weeks were available from both Matthew 2005 and Silberstein 2005. At the 24 week follow-up, results varied across studies, with no significant differences between groups in a pooled analysis, mean difference 0.74 (95% CI -1.51, 2.99), I2 = 54%. This pooled analysis included placebo nonresponders only (N=438) for one study since sufficient data was not available to include placebo responders (N=164); [155] it is unclear if this may partially explain the observed heterogeneity. At 32 weeks, there were no significant differences between groups, mean difference 0.95 (95% CI -0.69, 2.59) in one trial (Matthew 2005). Mathew, et.al considered a mean change from baseline of three headache-free days to be clinically significant, Figure 31.

Figure 31. Pooled Analysis of Change in Headache-Free Days per Month at Short- (≤8 weeks) and Longer-term (≥12 weeks) Follow-up, BoNTA versus Placebo for CDH



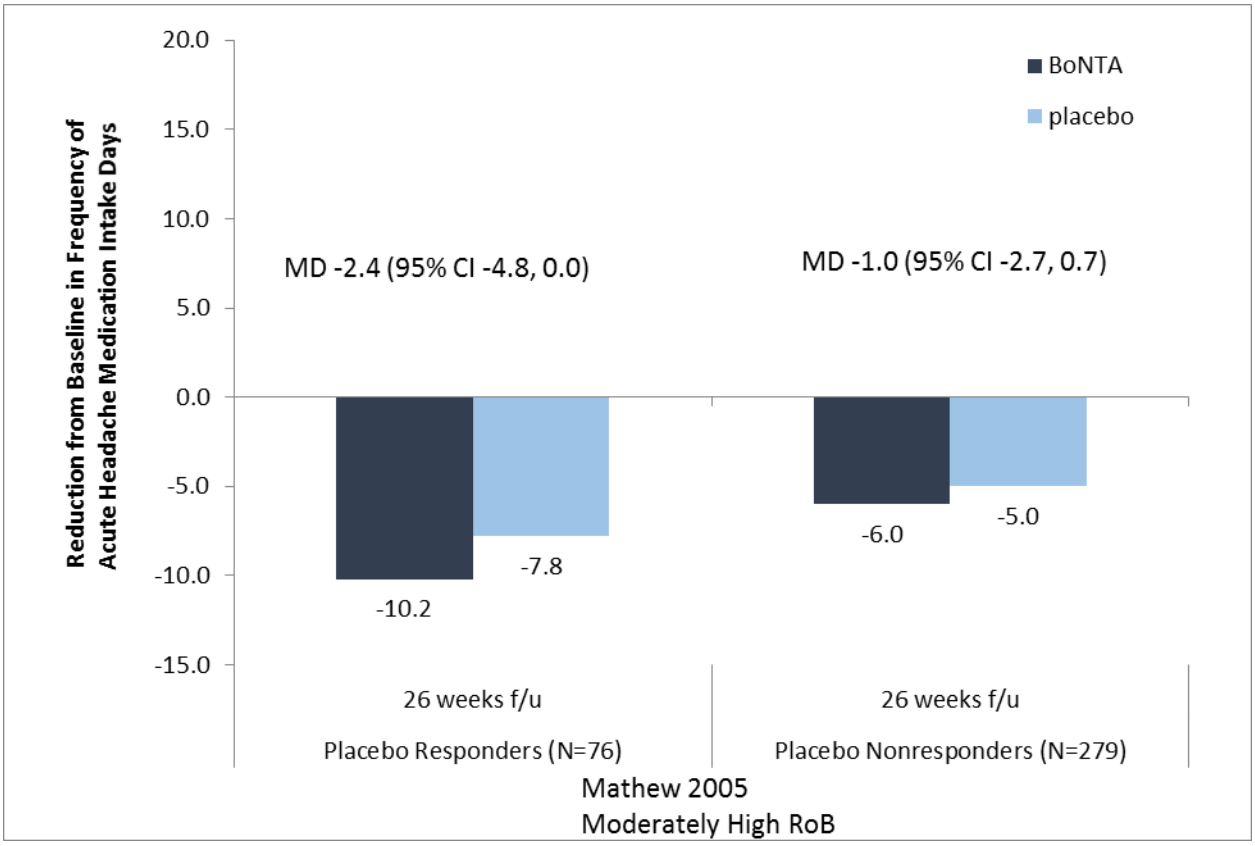
Function and Disability

No functional outcomes were reported in included studies.

Secondary Outcomes

Medication use: One trial with a moderately low risk of bias and another trial with a moderately high risk of bias reported on acute headache medication intake over the longer-term.[120,134] There were no significant differences between the BoNTA and placebo treatment groups in the reduction in frequency of abortive headache medication intake at 12 weeks (BoNTA: 106 ± 76, placebo: 135 ± 81; MD: -29.0, 95% CI -70.3, 12.3).[134] At 26 weeks, authors reported that there were no significant differences between treatment groups in the placebo nonresponders or placebo responders for reduction in frequency of acute headache medication intake days, Figure 32.

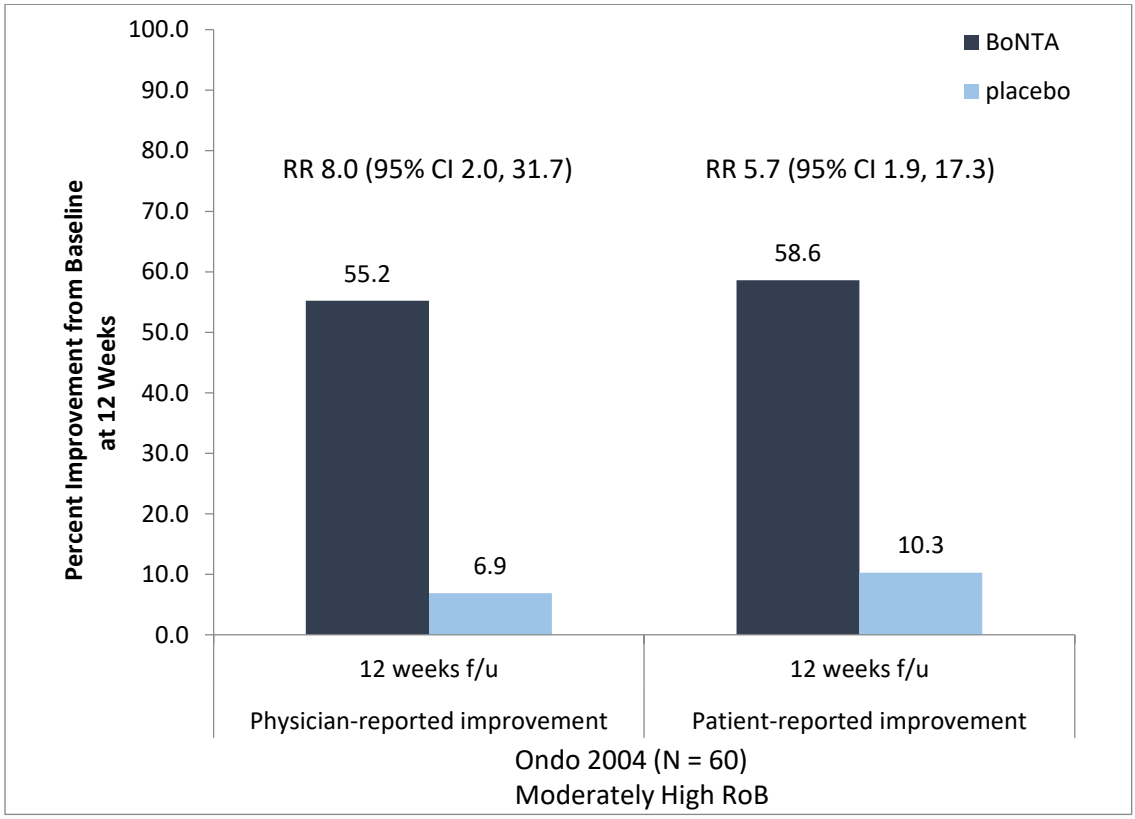
Figure 32. Reduction from Baseline in Frequency of Acute Headache Medication Intake Days at Long-term Follow-up, BoNTA versus Placebo for CDH



BoNTA: OnabotulinumtoxinA; CDH: chronic daily headache; f/u: follow-up; MD: mean difference; RoB: risk of bias.

Physician and Patient Reported Improvement: One small trial (Ondo 2004) with a moderately high risk of bias reported significantly greater proportion of individuals with improvement from baseline from both a physician- and patient perspective in the BoNTA compared to placebo group at long-term follow-up, 12 weeks after initiation of treatment (physician: RR 8.0, 95% CI: 2.0, 31.7; patient: RR 5.7, 95% CI: 1.9, 17.3),[134] Figure 33. Over half of the patients (57.6%) were overusing narcotics (>12 per month), to include 60% in the BoNTA group and 53.3% in the placebo group.

Figure 33. Physician- and Patient- Reported Improvement from Baseline at Long-term Follow-up, BoNTA versus Placebo for CDH



BoNTA: OnabotulinumtoxinA; CDH: chronic daily headache; f/u: follow-up; RoB: risk of bias; RR: risk ratio.

Health Related Quality of Life: One small trial (Ondo 2004) reported no significant differences between treatment groups in Beck Depression Inventory (BDI) and Psychosocial Adjustment to Illness Scale (PAIS) scores at longer-term follow-up (12 weeks) (data not reported).[134] Over half of the patients (57.6%) were overusing narcotics (>12 per month), to include 60% in the BoNTA group and 53.3% in the placebo group.

Open-Label (un-blinded case series): The Ondo trial included an open label phase. After completion of the double-blind, placebo controlled phase at 12 week evaluation, participants were offered one 200 U of BoNTA injection and were followed for an additional 12 weeks. Those originally randomized to the BoNTA group, thus received a total of 2 injections, those originally randomized to placebo received one. At 24 weeks, the group with two BoNTA treatments experienced a significantly greater reduction in frequency of headache days compared to the group that received one treatment (2 treatments: -40 ± 26, 1 treatment: -26 ± 19; MD -14, 95% CI -26.8, -1.1).[134]

4.2.3.2. OnabotulinumtoxinA vs. Active Control for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Studies included

One small, double-blind, multicenter (3 sites) RCT[50] was included that compared BoNTA to an active control for the treatment of chronic daily headache. A brief overview of patient and study characteristics is provided below and in Table 20; detailed information is available in Appendix Table F9. A total of 59 subjects were randomized, 29 to receive BoNTA plus an oral placebo and 30 to receive topiramate (25 mg at baseline, titrated to a maximum of 200mg/day) plus placebo saline injections. A maximum of 200 U of BoNTA or placebo were injected, 100 U into fixed sites (number of site and muscle groups not reported) and up to 100 additional units using a "follow the pain" approach at the investigators discretion. The mean dosage of BoNTA was 109 U and of tompiramate, 136 mg. All patients underwent a 4-week baseline period and were subsequently followed for a total of 12 weeks. At the 12 week follow-up, participants who did not report a ≥ 50% reduction of headache frequency were invited to participate in a 12-week open label extension period, receiving BoNTA treatment at week 14 (after tapering off oral study medications over a 2-week period).

Most patient demographics were not reported by treatment group. Overall the population was 95.1% female, with a mean age of 39.6 (range, 19.6-64.0) years; the majority of patients were Caucasian (94.9%). Twenty-seven percent of patients identified themselves as smokers (24% in the BoNTA group and 30% in the topiramate group) with those in the BoNTA group smoking twice as many cigarettes a day compared with the control group (21.4 vs. 9.8). Regarding headache characteristics, the mean duration of migraine/headache symptoms was 16 years. Other baseline headache characteristics were similar between the BoNTA and topiramate groups including the number of headache days (mean 21.8 vs. 20.5, respectively) and migraine days (mean 11.9 vs. 10.3, respectively) per month; headache severity (2.9 vs. 2.7, respectively, on a 3-point scale); and the number of days per month on headache medication (13.9 vs. 15.1, respectively). Many of the patients enrolled had utilized prior preventative treatments (both prescription and non-prescription medication) with a high rate of dissatisfaction; of note, at baseline, significantly more patients randomized to BoNTA reported they were dissatisfied with their current prescription treatment compared with those randomized to topiramate (44.8% vs. 16.7%; $p<0.05$). Subjects with overuse of acute medication or with recent evidence of alcohol or drug abuse were excluded. Medication overuse was not defined.

This trial was considered to be at MODERATELY HIGH risk of bias.[50] Methodological limitations included unclear reporting of random sequence generation and intention-to-treat; complete follow-up of less than 80% at final follow-up (75% at 12 weeks; 93% were followed up to 4 weeks) and lack of controlling for potential confounders, such as the number of cigarettes smoked per day (see above) and dissatisfaction with current preventative prescription medications (44.8% in the BoNTA group vs. 16.7% in the topiramate group). Risk of bias assessment is available in Appendix Table E3. Authors do not report who funded the study.

Table 20. Summary of Patient and Procedural Characteristics, BoNTA versus Topiramate for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Patient Characteristics	Cady 2011	
Population	N = 59	
Comparators	BoNTA	Topiramate
Randomized	n=29	n=30
Treated	n=29	n=30
Age, years; mean ± SD	39.6	
% Female	91.5%	
Mean Chronicity of Headache (years)	NR	NR
Mean # HA days/month	20.5	21.8
Mean # Migraine days/month	10.3	11.9
Mean # HA attacks/month	NR	NR
Mean # Migraine attacks/month	NR	NR
Percent with medication overuse	NR	NR
Patients who had prior preventative treatments	100%	96.6%
Procedural Characteristics		
Doses of Botox, placebo	100-200 U	25mg daily increased to 100 mg in weekly incremental increases of 25 mg
Number of Treatments	1	
Number of Muscle Areas	NR	
Number of Injection sites	NR	
Length of F/U past treatment	4 weeks 12 weeks	4 weeks 12 weeks
% F/U at Last F/U	85.7%	80.0%
Cross-over (timing)	At 3 month F/U, patients who had not reduced no. of headache days per month by ≥50% were offered open-label BoNTA injections*	
Co-interventions	NR	
Country	NR (multicenter)	
Funding	NR	

BoNTA, onabotulinumtoxinA; CM, chronic migraine; COI, conflict of interest; F/U, follow-up; HA, headache; mg, milligrams; NA, not applicable; NR, not reported; SD, standard deviation; U, units;

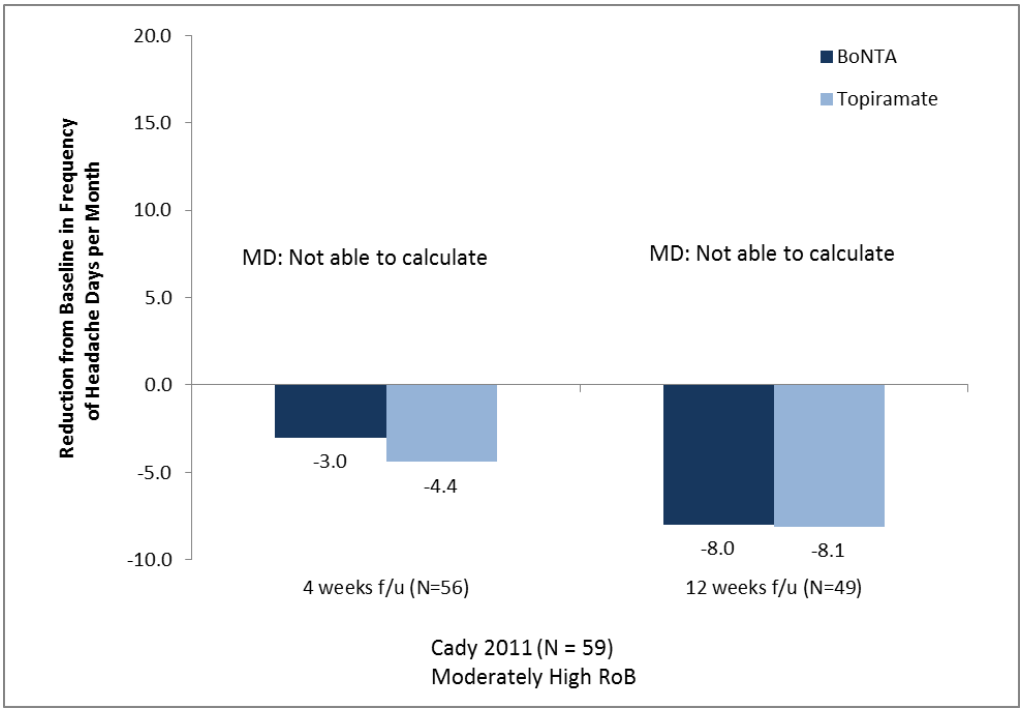
*Of the 27 subjects that did not have at least a 50% reduction in headache days per month, 9 from the topiramate group and 11 from the BoNTA group started the open-label phase

Efficacy Outcomes

Reduction in Frequency of Headache Episodes and Days

Short- and Longer-term (4 and 12 weeks): In the one available trial (Cady 2011) there were no significant differences between the BoNTA and topiramate treatment groups in the reduction of headache days per month at 4 and 12 weeks after initiation of treatment, Figure 34. Authors do not provide sufficient data for calculation of effect size.[50] Although patients with medication overuse were excluded, authors report a mean of 14.5 days of headache medication use among participants. Data were available for 75% of patients at 12 weeks.

Figure 34. Reduction in Frequency of Headache Days per Month at Short- (4 weeks) and Long-term (12 weeks) Follow-up, BoNTA versus Topiramate for CDH



BoNTA: OnabotulinumtoxinA; CDH: chronic daily headache; f/u: follow-up; MD: mean difference; RoB: risk of bias.

Function and Disability

HIT-6, short- and longer-term (4 and 12 weeks): There were no significant differences between treatment groups in improvement from baseline of HIT-6 scores at 4 or 12 weeks (4 weeks: BoNTA -4.8, topiramate -5.9; 12 weeks: BoNTA -6.3, topiramate -6.0; MDs: authors do not provide sufficient data for effect size calculation),and only 75% of the randomized population had data at 12 weeks,[50] Table 21.

MIDAS, longer-term (12 weeks): There were no significant differences between treatment groups in improvement from baseline of MIDAS scores at 12 weeks (BoNTA -38.5, topiramate -26.7; MDs: authors do not provide sufficient data for effect size calculation),[50] Table 21.

Table 21. Function and Disability Measures of Chronic Daily Headache Patients in BoNTA Treatment

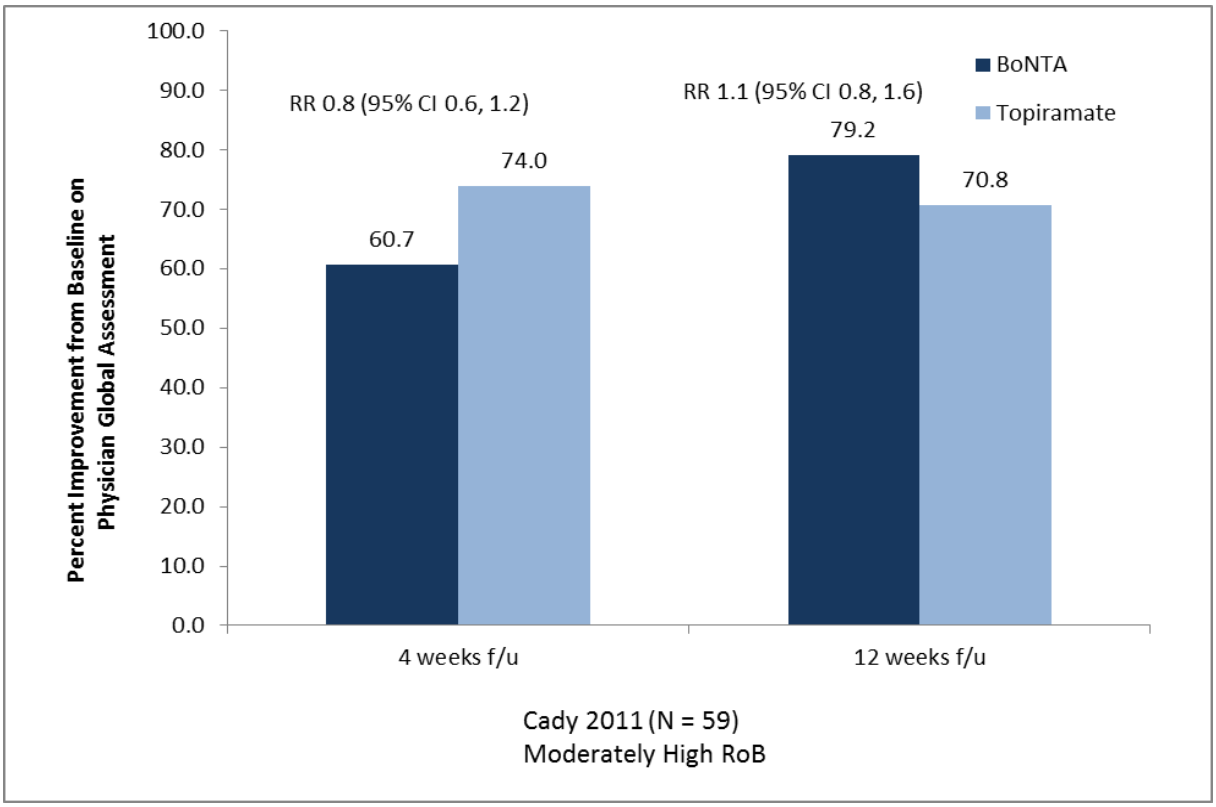
Risk of Bias	Study	F/U	BoNTA Mean Δ	Comparator Mean Δ	RD (95% CI) RR (95% CI)	p-value
Migraine Disability Assessment Scale, Δ from baseline (greater decrease indicates greater decrease of disability)						
Mod high	Cady 2011 *Botox vs. Amitriptyline*	12	-38.5 (n=21)	-26.7 (n=21)	IC	IC
Headache Impact Test-6 score, Δ from baseline (36—78 worst)						
Mod high	Cady 2011 *Botox vs. Amitriptyline*	4	-4.8 (n=25)	-5.9 (n=23)	IC	IC
		12	-6.3 (n=21)	-6.0 (n=19)	IC	IC

BoNTA, OnabotulinumtoxinA; CI, confidence interval; F/U, follow-up; IC, incalculable; Mod, moderately; RD, risk difference; RR, risk ratio; SD, standard deviation

Secondary Outcomes

Physician-Reported Improvement: Physician-reported improvement from baseline using the Physician Global Assessment favored the topiramate group at 4 weeks (short term) and the BoNTA group at 12 weeks (longer term) after baseline.[50] Regardless, there were no significant differences between treatment groups at either time point (4 weeks: RR 0.8, 95% CI: 0.6, 1.2; 12 weeks: RR 1.1, 95% CI: 0.8, 1.6), Figure 35.

Figure 35. Percent Improvement from Baseline in Physician Global Assessment at Short- (4 weeks) and Long-term (12 weeks) Follow-up, BoNTA versus. Topiramate for CDH



BoNTA: OnabotulinumtoxinA; CDH: chronic daily headache; f/u: follow-up; RoB: risk of bias; RR: risk ratio.

Open-Label (un-blinded case series): Cady 2011, et. al. included an open label phase. At the end of the 12 week double blinded, placebo-controlled phase, patients from either treatment group who had not experienced a ≥ 50% reduction in headache frequency were invited to participate in the open label portion; 20 patients agreed to participate. Those originally randomized to BoNTA received an additional injection for a total of two, patients originally randomized to placebo received one injection. At 26 weeks, there were no significant differences in the reduction of headache days per month between the group that received two BoNTA treatments (BoNTA group for RCT) and those who received one BoNTA treatment (topiramate group for RCT) (2 treatments, mean reduction: -6.0, n=8; 1 treatment, mean reduction: -8.5, n=4), however the small numbers of patients make it difficult to draw meaningful conclusions.[50] This portion of the study was considered to be at high risk of bias.

4.2.3.3. Acupuncture versus Sham and versus Active Control for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.3.4. Manual Therapy/Manipulation versus Sham and versus Active Control for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.3.5. Massage versus Sham for Chronic Daily Headache

Studies included

One RCT that evaluated the efficacy of massage therapy compared with sham treatment for chronic daily headache was identified.[59] Detailed information on patient and study characteristics is available in Appendix Table F10. Briefly, a total of 72 patients were randomized (36 in each group); the groups were comparable at baseline. The mean age of the population was 27.4 years and the majority of patients were female (76%). Patients randomized to the intervention group received traditional Thai massage from an experience massage therapist, which combined 25 minutes of massage therapy and 5 minutes of passive stretching. Patients in the control group underwent sham ultrasound (US) using a detuned device with circular kneading motions that imitate manual massage; the authors state that these motions may provide some massage effects. Both treatment groups received nine 30-minute sessions over a period of 3 weeks. Patients who had received massage therapy within the month prior to study entry were excluded. All participants were allowed to take medication already prescribed for them, which was monitored daily. Patients were followed for a total of 9 weeks post-treatment.

Regarding headache characteristics, the diagnosis was chronic tension type headache in 58% of the population and chronic migraine in 42%, with a mean number of headache times per month of 16.3 and a mean headache intensity of 5.1 (on a 0-10 (worst) on VAS). No information was provided on prior or current prophylactic treatment utilized by the patients. Baseline medication use was not reported but it appears that over 65% of patients were relying on some form of analgesic medication.

This trial was considered to be at LOW risk of bias, meeting all the criteria for a good quality RCT. Risk of bias assessment for all studies is found in Appendix Table E8.

Efficacy Results

Treatment Responders

No evidence.

Reduction in Frequency of Headache Attacks

Short-term (3 weeks): Three weeks after the end of treatment, the massage group showed a greater reduction in headache attacks per month compared with the sham US group, however, the mean difference in change scores between groups did not reach statistical significance (MD adjusted for baseline scores: 2.56; 95% CI -0.04, 5.17),[59] Appendix Table G7.

Intermediate-term (9 weeks): Similarly, no statistical difference was seen in the frequency of headache attacks per month between groups at 9 weeks post-treatment: mean between-group difference adjusted for baseline values was 0.16 (95% CI –1.10 to 0.78),[59] Appendix Table G7.

Function/Disability

Short-term (3 weeks): No statistical difference was seen between the groups in Headache Disability Index (HDI) scores (0-100, worst) at 3 weeks post-treatment; the mean difference between groups in changes scores from baseline (adjusted for baseline values) was 1.85 (95% CI –6.25, 9.97),[59] Appendix Table G7.

Intermediate-term (9 weeks): Similarly, no statistical difference was seen in the frequency of headache attacks per month between groups at 9 weeks post-treatment: mean difference between groups in changes scores from baseline (adjusted for baseline values) was 0.35 (95% CI –7.32 to 8.01),[59] Appendix Table G7.

Secondary Outcomes

Frequency of analgesic use: Both groups showed a similar reduction in the intake of analgesic medication over the study period, from 25 (69.4%) to 10 (27.8%) in the massage group and from 25 (66.7%) to 9 (25.0%) in the sham US group (Appendix Table G7); it is unclear from the description provided what these numbers mean.[59]

Headache intensity: There were no statistical differences between the massage and the sham ultrasound group in headache intensity, measured as pain during the past 24 hours on VAS (0-10, worst), at either the short- or longer-term time-points (Appendix Table G7): 3 weeks (MD 0.61 (95% CI –

0.56, 1.77)) and 9 weeks (MD 0.07 (95% CI –1.04, 1.18)); mean differences in change scores from baseline were adjusted for baseline values.[59]

Pressure pain threshold: Massage resulted in statistically significant improvement in Pressure Pain Thresholds (PPTs) compared with sham US at both the short- and longer-term follow-up times: mean difference between groups in change scores from baseline (adjusted for baseline scores) was 1.22 (95% CI 0.69, 1.76) at 3 weeks and 0.84 (95% CI 0.28, 1.40) at 9 weeks post-treatment,[59] Appendix Table G7. PPTs were defined as the minimal amount of pressure required from the initial sense of pressure to the first sense of pain. An algometer with a rubber-tipped plunger that was applied to each trigger point was used to measure PPT levels; the average of three measures was used in the analysis.

4.2.3.6. Massage versus Active Control for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.3.7. Transcranial Magnetic Stimulation versus Sham and versus Active Control for Chronic Daily Headache/ Co-existent Chronic Migraine and Tension Headache

No studies were identified that met the inclusion criteria for this comparison.

4.2.3.8. Trigger Point Injection versus Sham and versus Active Control for Chronic Daily Headache/ Co-existent Chronic Migraine and Tension Headache

No studies were identified that met the inclusion criteria for this comparison.

4.3. Key Question 2: Harms and Complications

4.3.1. Number of studies retained

All included comparative studies identified were evaluated for harms and complications. The overall strength of evidence for most efficacy outcomes was considered low or insufficient across interventions and comparators with the exception of treatment-related adverse events and serious adverse events following BoNTA compared with placebo which are primarily based on two large RCTs at low risk of bias.

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 strength of evidence determination for each outcome.

4.3.2. Chronic Migraine

Summary of results

BoNTA versus. Placebo

Two large Phase III trials provide the primary evidence regarding safety for this comparison.

- At long-term follow-up (24 weeks), across two RCTs, treatment-related and serious adverse events were 2 times more common following BoNTA compared with placebo (moderate evidence) and discontinuation of treatment due to treatment related adverse events was three times more common following BoNTA (low evidence). All results were statistically significant.
- Over the longer-term (24 weeks), treatment-related serious adverse events were rare; there was likely insufficient power to detect such events precluding firm conclusions (insufficient evidence).
- No deaths occurred in any of the trials

BoNTA versus Active Control

- BoNTA versus Topiramate (1 RCT):
  - At 36 weeks, although the result was not statistically significant, fewer BoNTA patients experienced drug-related adverse events compared with topiramate recipients and fewer BoNTA patients discontinued treatment, however sample size was small; Differential attrition between treatment groups and substantial loss to follow-up should be also considered when interpreting this finding. Data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks. (low evidence)
- BoNTA versus Amytriptyline (1 RCT):
  - Limited data were reported for adverse events over the long-term (12 weeks) in one small trial. More BoNTA recipients reported injection site pain and edema compared with amitriptyline; no one in the amitriptyline group experienced these effects (low evidence)

Acupuncture versus Sham

- No trials were identified that met the inclusion criteria.

Acupuncture versus Active Control

- Acupuncture versus Usual Care (1 RCT):
  - Over the longer-term (36 weeks), authors reported that no adverse events occurred in either group and no difference was seen between groups in the proportion of patients that withdrew from the trial due to adverse events; however, limited data was provided and sample size was small (insufficient evidence for both). No difference was seen in proportion of patients with headache following treatment (low evidence); again sample size was small.
- Acupuncture versus Topiramate (1 RCT):
  - At short-term follow-up (4 weeks), authors reported that no adverse events or deaths occurred in either group, however limited data was provided and the sample size was small (insufficient evidence for both). Statistically fewer side-effects occurred following acupuncture compared with topiramate, but no statistical difference was seen between groups in the proportion of patients that withdrew from the trial due to adverse events (low strength of evidence for both outcomes); however, the sample size was small.

Manual Therapy/Manipulation versus Sham

- No trials were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Active Control

- Spinal Manipulation Therapy (SMT) versus Amitriptyline (1 RCT):
  - At short-term follow-up (4 weeks), withdrawal from the study due to adverse effects occurred with a lower frequency in patients who received SMT versus amitriptyline (low evidence). The frequency of any adverse event was not reported in a way that we could evaluate comparative efficacy (insufficient evidence).

Massage versus Sham and versus Active Control

- No trials were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation (TMS) versus Sham

Two small RCTs provided limited evidence regarding safety for this comparison.

- At short-term follow-up (4 weeks), no statistical difference was seen between the TMS and the sham group in the frequency of study withdrawal due to adverse events in one trial; however the sample size was small (insufficient evidence). In this same trial, more patients receiving high-frequency TMS experienced discomfort (no to mild pain) during treatment compared with sham (low evidence).

- At short-term follow-up (8 weeks), as reported by a second small trial, no differences were seen between groups in the frequency of minor adverse events or of study withdrawal due to adverse events; however, all data was insufficient.

Transcranial Magnetic Stimulation (TMS) versus Active Control

- No trials were identified that met the inclusion criteria.

Trigger Point Injection (TPI) versus Sham and versus Active Control

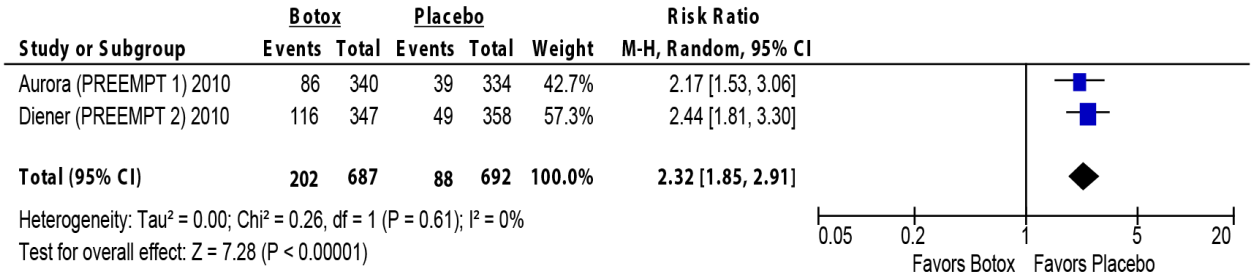
- No trials were identified that met the inclusion criteria.

4.3.2.1. BoNTA versus Placebo for Chronic Migraine

Three RCTs[25,64,74] were included that reported adverse events. These studies have been previously described under Key Question 1. Detailed information on participant and study characteristics is available in Appendix Table F1

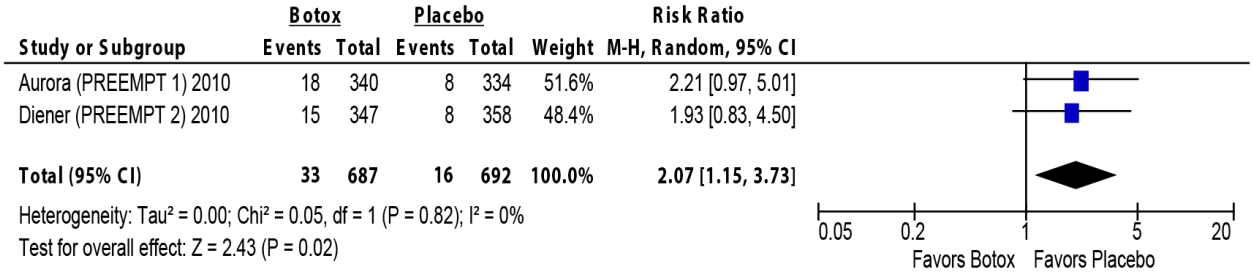
Data from the PRREMPT 1 and 2 trials provided the most complete trial data on adverse events.[25,64] Treatment-related adverse events (AEs) at 24 weeks after initiation of treatment (longer-term follow-up) were significantly greater in the BoNTA group compared to placebo, pooled analysis RR 2.32 (95% CI 1.85, 2.91), Figure 36.

Figure 36. Pooled Analysis of Treatment-Related Adverse Events over Long-term Follow-up (24 weeks), BoNTA versus Placebo for CM



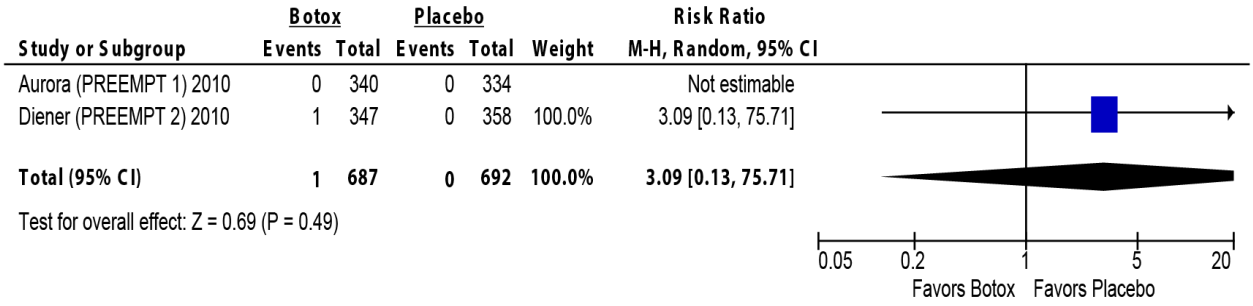
Serious AEs at 24 weeks after initiation of treatment were significantly greater in the BoNTA group compared to placebo, pooled analysis RR 2.07 (95% CI 1.15, 3.73), Figure 37.[25,64]

Figure 37. Pooled Analysis of Serious Adverse Events over Long-term Follow-up (24 weeks), BoNTA versus Placebo for CM



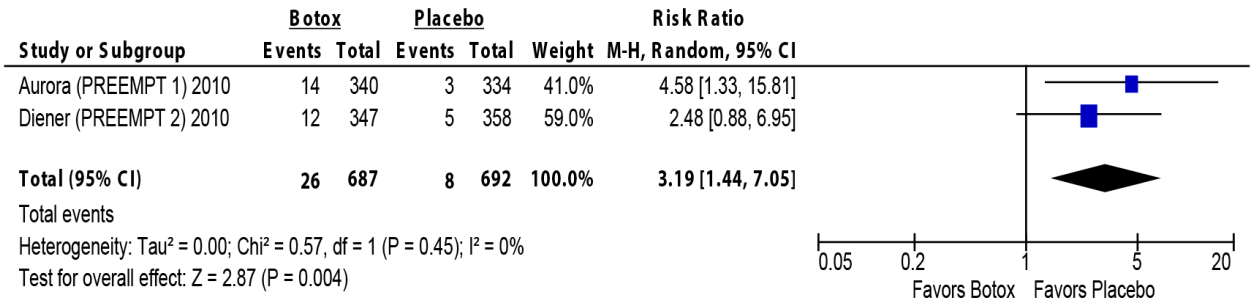
There was a nonsignificant difference in treatment-related serious AEs at long-term follow-up (24 weeks after initiation of treatment) between the BoNTA and placebo groups, pooled analysis RR 3.09 (95% CI 0.13, 75.71), Figure 38.[25,64] To the extent that these are rare events, it is likely that there was not sufficient power to detect rare events or a difference between groups.

Figure 38. Pooled Analysis of Treatment-Related Serious Adverse Events over Long-term Follow-up (24 weeks), BoNTA versus Placebo for CM



Discontinuation of treatment related to AEs at 24 weeks after initiation of treatment was significantly greater for the BoNTA group compared to placebo, pooled analysis RR 3.19 (95% CI 1.33, 7.05), Figure 39.[25,64]

Figure 39. Pooled Analysis of Discontinuation Related to Adverse Events over Long-term Follow-up (24 weeks), BoNTA versus Placebo for CM



No deaths occurred in either PREEMPT trial at any time.[25,64] Table 22 below provides pooled data for individual adverse events from these two trials through 24 weeks. [26,67]

Table 22. Summary of Individual Adverse Events through Long-term Follow-up (24 weeks): Pooled data from PREEMPT 1 and 2 trials, BoNTA versus Placebo in CM

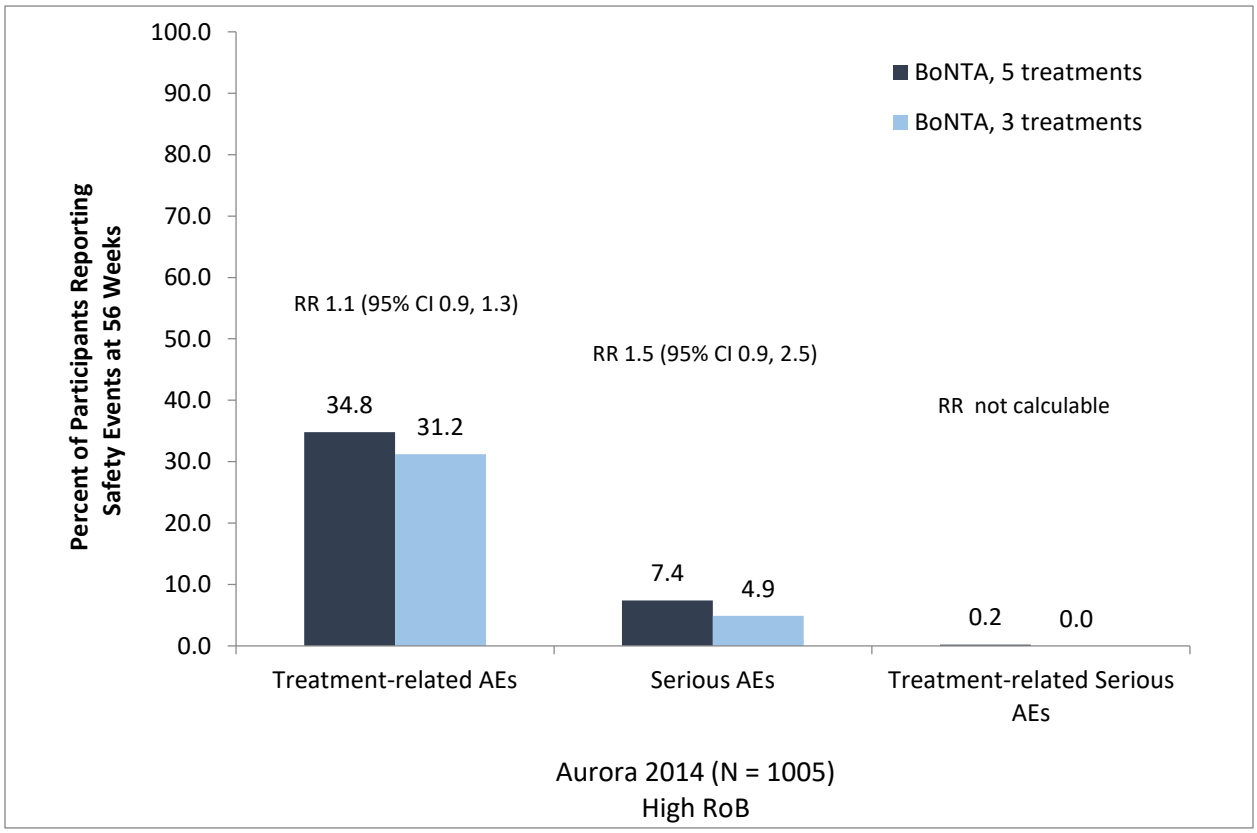
		Results, n/N (%)	
Author	**Outcome**	**BoNTA**	**Placebo**
Aurora 2011 (PREEMPT 1 & 2) (Low Risk of Bias)	All adverse events	429/687 (62.4%)	358/692 (51.7%)
	Death	0 (0.0)	0 (0.0)
	Neck pain	46/687 (6.7%)	15/692 (12.7%)
	Muscular weakness	38/687 (5.5%)	2/692 (0.3%)
	Eyelid ptosis	23/687 (3.3%)	2/692 (0.3%)
	Musculoskeletal pain	15/687 (2.2%)	5/692 (0.7%)
	Injection site pain	22/687 (3.2%)	14/692 (2.0%)
	Headache	20/687 (2.9%)	11/692 (1.6%)
	Myalgia	18/687 (2.6%)	2/692 (0.3%)
	Musculoskeletal stiffness	16/687 (2.3%)	5/692 (0.7%)
	Muscle tightness	9/687 (1.3%)	1/692 (0.1%)

BoNTA, onabotulinumtoxinA; F/U, follow-up; tx, treatment

One small RCT[74] reported no differences between groups for any adverse event. The most common event in the BoNTA group was sinus infection (2/20 participants). The small sample size may have limited the trial's ability to detect adverse events. See Appendix Table H1.

Open-Label: At the end of the open-label phase of the PREEMPT 1 and 2 studies at 56 weeks,[26,67] participants receiving five BoNTA treatments reported more safety events than those with 3 BoNTA treatments, but there were no significant differences between groups for treatment-related AEs (RR 1.1, 95% CI 0.9, 1.3), serious AEs (RR 1.5, 95% CI 0.9, 2.5), or treatment-related serious AEs (RR not calculable), Figure 40.[24]

Figure 40. Percent of Participants Reporting Safety Events at 56 Weeks, BoNTA for CM (Open Label Phase, PREEMPT 1 and 2 Trials)



AE: adverse event; BoNTA: OnabotulinumtoxinA; CI: confidence interval; CM: chronic migraine; RoB: risk of bias; RR: risk ratio.

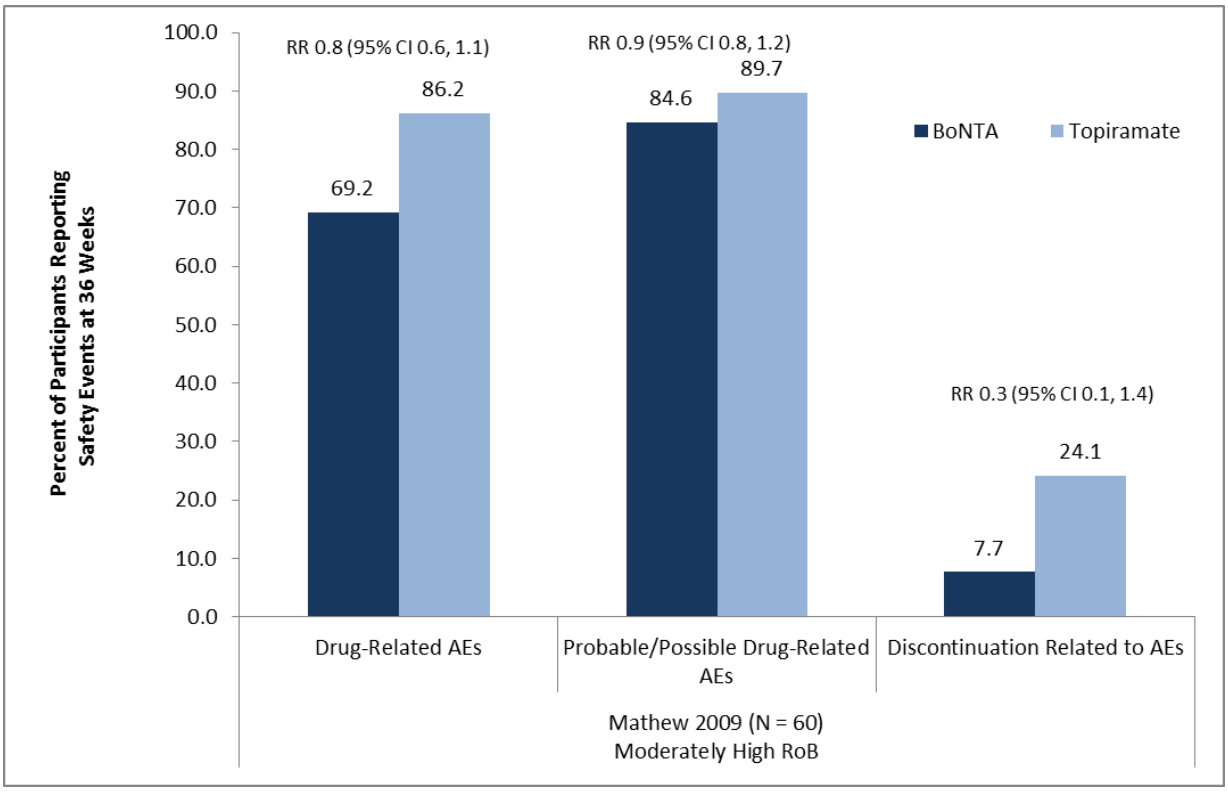
4.3.2.2. BoNTA versus Active Control for Chronic Migraine

Two RCTs with a moderately high risk of bias were identified that evaluated the efficacy of BoNTA versus active controls and provided data on adverse events. One trial compared BoNTA with topiramate,[121] the other compared BoNTA with amitriptyline.[116] Study and patient characteristics have been described with Key Question 1; detailed information is found in Appendix Table F1.

BoNTA vs. Topiramate

One trial compared BoNTA with topiramate.[121] While the topiramate group reported more safety events than the BoNTA group, there were no significant differences between treatment groups in drug-related AEs (RR 0.8, 95% CI 0.6, 1.1), probable/possible drug-related AEs (RR 0.9, 95% CI 0.8, 1.2), and discontinuations related to AEs (RR 0.3, 95% CI 0.1, 1.4), Figure 41. Sample size may have precluded detection of a statistical difference.

Figure 41. Percent of Participants Reporting Safety Events at Long-term Follow-up (36 Weeks), BoNTA versus Topiramate in CM



AEs: adverse events; BoNTA: OnabotulinumtoxinA; CI: confidence interval; CM: chronic migraine; RoB: risk of bias; RR: risk ratio.

There were no statistically significant differences between treatments for individual adverse events. A total of 93 events were reported for BoNTA recipients and a total of 133 for placebo recipients in the one identified trial.[121] Table 23 below summarizes the frequency of definite or probable events as a percent of total events for each treatment group.

Table 23. Summary of Definite or Probable Adverse Events at Long-term Follow-up (36 weeks), BoNTA versus Topiramate in CM*

		Results, n/N (%)*	
Author	**Outcome**	**BoNTA**	**Topiramate**
Mathew 2009 (Moderately High Risk of Bias)	All adverse events	26/26 (100%)	28/29 (96.5%)
	Weakness in eyebrow/eyelids	13/93 (14.0%)	0/133 (0.0%)
	Weakness in forehead/neck	9/93 (9.7%)	0/133 (0.0%)
	Paresthesias	3/93 (3.2%)	25/133 (18.8%)
	Pain in head	4/93 (4.3%)	0/133 (0.0%)
	Sleepiness/fatigue/dizziness	3/93 (3.2%)	4/133 (3.0%)
	Depression/mood disturbance	0/93 (0.0%)	6/133 (4.5%)
	Loss of appetite/weight loss	0/93 (0.0%)	9/133 (6.8%)
	Cognitive deficits	0/93 (0.0%)	15/133 (11.3%)
	Night sweats	0/93 (0.0%)	3/133 (2.3%)
	Dry mouth/thirst	0/93 (0.0%)	4/133 (3.0%)
	Blurred vision/vision problems	0/93 (0.0%)	4/133 (3.0%)

BoNTA, onabotulinumtoxinA; F/U, follow-up; tx, treatment
*With the exception of "all adverse events", the percentages reflect the frequency of individual events over the total number of events for each treatment group; a total of 93 events occurred in the BoNTA group, 133 in the placebo group. It is not clear whether patients could experience more than one event.

BoNTA vs. Amitriptyline

One trial compared BoNTA with amitriptyline.[116] Patient and study characteristics were described in Key Question 1; detailed information is found in Appendix F1.

At longer-term follow-up (12 weeks), adverse events differed between the treatment groups, with participants in the BoNTA group reporting significantly more events of injection site pain (35.0% BoNTA vs 0.0% amitriptyline, RR=not calculable) and edema (14.0% BoNTA vs 0.0% amitriptyline, RR=not calculable). Participants in the amitriptyline group reported significantly greater events of weight gain (11.8% BoNTA vs 58.3% amitriptyline, RR=0.19, 95% CI 0.1, 0.5), somnolence (4.0% BoNTA vs 52.7% amitriptyline, RR=0.1, 95% CI 0.0, 0.4), dry mouth (14.0% BoNTA vs 44.0% amitriptyline, RR=RR 0.3, 95% CI 0.1, 0.8), and constipation (0.0% BoNTA vs 38.8% amitriptyline, RR=not calculable) Table 24.[116]

Table 24. Summary of Adverse Events at 12 weeks: BoNTA versus Amitriptyline in CM

		Results (%)	
Author	**Outcome**	**BoNTA (n = 35)**	**Amytriptyline (n = 37)**
Magalhaes 2010 (Moderately High Risk of Bias)	Weight gain	11.8%	58.3%
	Somnolence	4.0%	52.7%
	Dry mouth	14.0%	44.0%
	Constipation	0.0%	38.8%
	Injection site pain	35.0%	0.0%
	Edema	14.0%	0.0%

BoNTA, onabotulinumtoxinA; F/U, follow-up; tx, treatment

4.3.2.3. Acupuncture versus Active Control for Chronic Migraine

Two RCTs, one with a moderately low and one with a moderately high risk of bias, were identified that evaluated the efficacy of acupuncture versus active controls for treatment of chronic migraine and provided data on adverse events. One trial compared acupuncture with usual care,[170] the other compared acupuncture with topiramate.[180] Study and patient characteristics have been described with Key Question 1; detailed information is found in Appendix Table F2.

Acupuncture vs. Usual Care

No serious adverse events occurred in either the acupuncture or the usual care group as reported by one trial over longer-term follow-up (36 weeks) (Appendix Table H2).[170] In the acupuncture group, four patients (2.5%; 4/161) reported headache following treatment and one patient (0.6%; 1/161) withdrew at 3 months due to adverse effects (no other details were provided). No adverse events were reported in the usual care group.

Acupuncture vs. Topiramate

No serious adverse events or deaths occurred in either the acupuncture or the topiramate group as reported by one trial following treatment (Appendix Table H2).[180] Overall, significantly fewer side effects were seen following acupuncture compared with topiramate: 6% (2/33) vs. 66% (22/33); RR 0.1 (95% CI 0.02, 0.4). In the acupuncture group, all adverse effects were related to the local insertion of the needles (i.e., local pain, local paresthesia, ecchymosis). In the topiramate group, most events were mild and self-limiting and included paresthesia (48.4%), difficulty with memory (36.3%), dyspepsia (36.3%), fatigue (24.2%), dizziness (21.2%), somnolence (18.1%), and nausea (12.1%); three (9%) of these patients withdrew early due to intolerable side effects. No patient in the acupuncture group withdrew early due to needle-related side effects.

4.3.2.4. Manual Therapy/Manipulation versus Active Control for Chronic Migraine

One RCT with a moderately low risk of bias was identified that evaluated the efficacy of spinal manipulation therapy (SMT) versus amitriptyline for treatment of chronic migraine and provided data on adverse events.[129] Study and patient characteristics have been described with Key Question 1; detailed information is found in Appendix Table F4.

Spinal Manipulation Therapy (SMT) vs. Amitriptyline

Adverse events were not well reported in one trial comparing SMT with amitriptyline; the follow-up period was 4 weeks (short-term) (Appendix Table H3).[129] The authors report that 58% (79/136) of patients in either the amitriptyline or the combine amitriptyline plus acupuncture group (the latter was excluded as it does meet the inclusion criteria) experienced medication side effects important enough to document (no further details provided). Adverse effects following SMT were described as "much more benign, infrequent, mild and transitory" (no further details provided). No patient in the SMT group withdrew from the study because of intolerable side effects compared with seven patients in the amitriptyline group (0% [0/77] vs. 10.8% [7/65]; p=0.003).

4.3.2.5. Transcranial Magnetic Stimulation versus Sham for Chronic Migraine

Two RCTs, one with moderately low and one with moderately high risk of bias, were identified that evaluated the efficacy of transcranial magnetic stimulation (TMS) versus sham for the treatment of chronic migraine and provided data on adverse events.[124,165] Study and patient characteristics have been described with Key Question 1; detailed information is found in Appendix Table F3.

One trial with short-term follow-up (4 weeks) compared repetitive high-frequency TMS with sham and reported only minor adverse events which occurred more frequently with TMS (Appendix Table H5).[124] Discomfort during treatment was statistically more frequent with TMS compared with sham (100% [47/47] vs. 14.6% [7/48]; RR 6.9 (95% CI 3.5, 13.6)); mean scores on the Faces Pain Scale were 3.10 ± 0.71 versus 0.14 ± 0.35, respectively, p=0.0001. Additionally, one (2%) patient who received TMS experienced drowsiness for 12 hours following the first session. The authors state that no patient opted to be withdrawn from the study; however, according to their consort diagram it appears that one patient who received TMS did withdraw early due to side effects.

The second trial, which compared repetitive low-frequency TMS with sham, reported a similar frequency of side effects overall in both groups over 8 weeks (short-term); all were considered mild/minor (Appendix Table H5). During treatment, the following side effects were noted, respectively: assessment of visual motor threshold is uncomfortable (36% vs. 31%), sitting is long and uncomfortable (7% vs. 8%), sleepiness (7% vs. 8%), and headache (0% vs. 15%). After treatment, amyostasia and testiness both were experienced by 7% and 8% of the TMS and sham groups, and 7% of the TMS group reported both vigorous dreams and phonophobia. Two patients, one in each group, withdrew early due to adverse effects (no other details provided).

4.3.3. Chronic Tension-type Headache

Summary of results

BoNTA versus Placebo

- At short-term (8 weeks) follow-up in one trial, treatment-related adverse events were more in the BoNTA groups compared to placebo, though the differences were not statistically significant (low evidence) however, the risk of severe adverse events was similar between groups (low evidence) in the same trial.
- At short-term (8 weeks) follow-up in one small trial, there was not difference between groups with regard to injection site pain (insufficient evidence).
- Over the Longer-term, at 12 weeks across two small RCTs, there were no statistical differences between groups with regard to injection site pain (insufficient evidence)
- Vertigo was uncommon across two small RCTs; firm conclusions are not possible (insufficient evidence).

BoNTA versus Active Control

- No studies were identified that met the inclusion criteria.

Acupuncture versus Sham

- Adverse events were not reported by any of the trials included for efficacy.

Acupuncture versus Active Control

- Acupuncture vs. Physiotherapy (1 RCT):
  - Over short- and intermediate follow-up (4-9 weeks), one trial reported that a few patients in the acupuncture group had a slight vasovagal reaction; no other complications were noted and no data was provided (insufficient evidence).
- Acupuncture vs. Physical Training and vs. Relaxation (1 RCT):
  - Adverse events were not reported by the trial included for efficacy.

Manual Therapy/Manipulation versus Sham

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Active Control

- Manual Therapy (MT) vs. Usual Care (1 RCT)
  - Over the longer-term (18 weeks), one trial reported that no adverse events occurred in either the MT or usual care group; however no further data was provided (insufficient evidence).

Massage versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Trigger Point Injection versus Sham

One small trial provided limited evidence regarding safety for this comparison.

- At long-term follow-up (12 weeks), one trial reported that no adverse events occurred in either group; however no further data was provided (insufficient evidence). This same trial also reported a similar frequency of minor side effects between the TPI and the sham group but the sample was small (low strength of evidence).

Trigger Point Injection versus Active Control

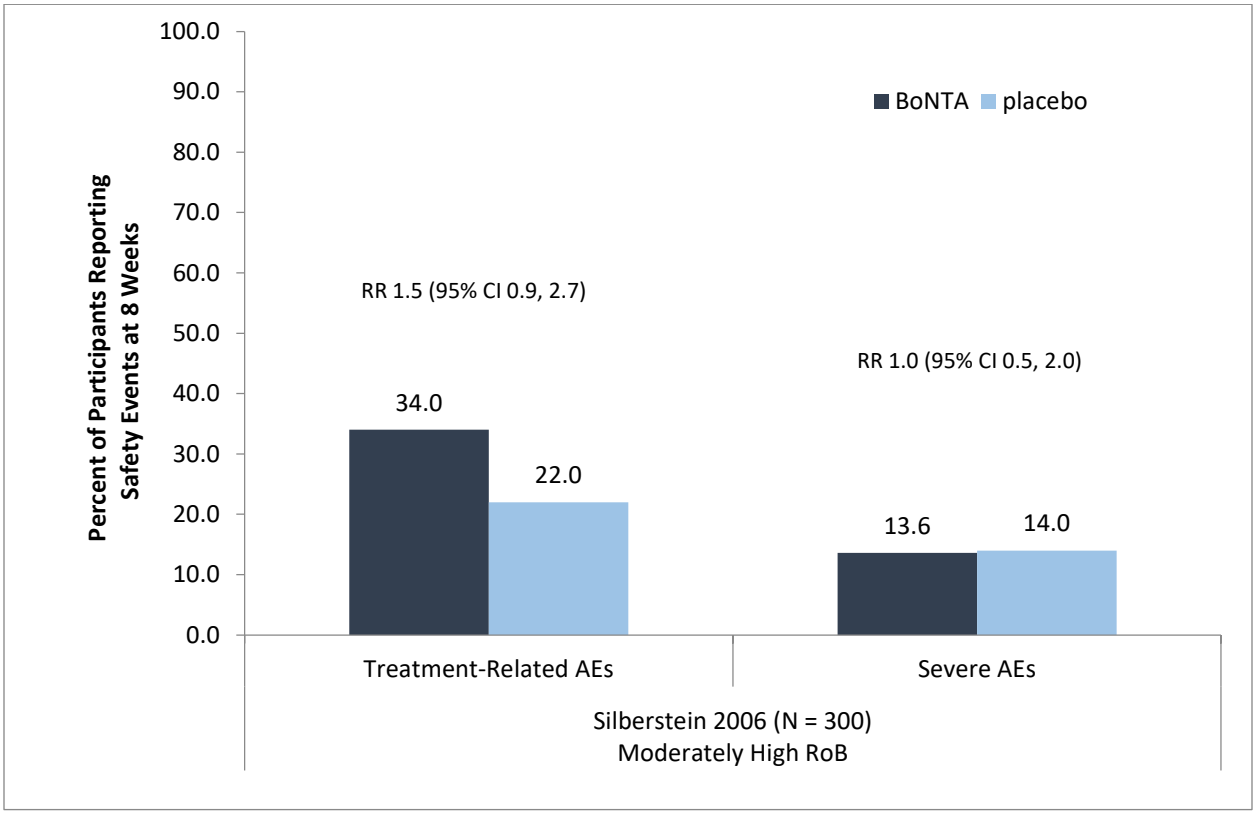
- No studies were identified that met the inclusion criteria.

4.3.3.1. BoNTA versus Placebo for Chronic Tension Type Headache

Five RCTs[82,104,135,147,154] provided varying detail of adverse events. Sample sizes were small (< 60 participants) for all but one trial[154] potentially precluding the identification of rare events and detection of statistical differences between treatments. Detailed information on patient and study characteristics is available in Appendix Table F6. Detailed information on individual adverse events is found in Appendix Table G2.

In the largest trial with a moderately low risk of bias,[154] treatment-related AEs were reported more frequently by participants in the BoNTA groups compared to placebo, though the differences were not significant between the groups (RR 1.5, 95% CI 0.9, 2.7). Serious AEs were similar between the groups over the short-term at 8 weeks (RR 1.0, 95% CI 0.5, 2.0), Figure 42.

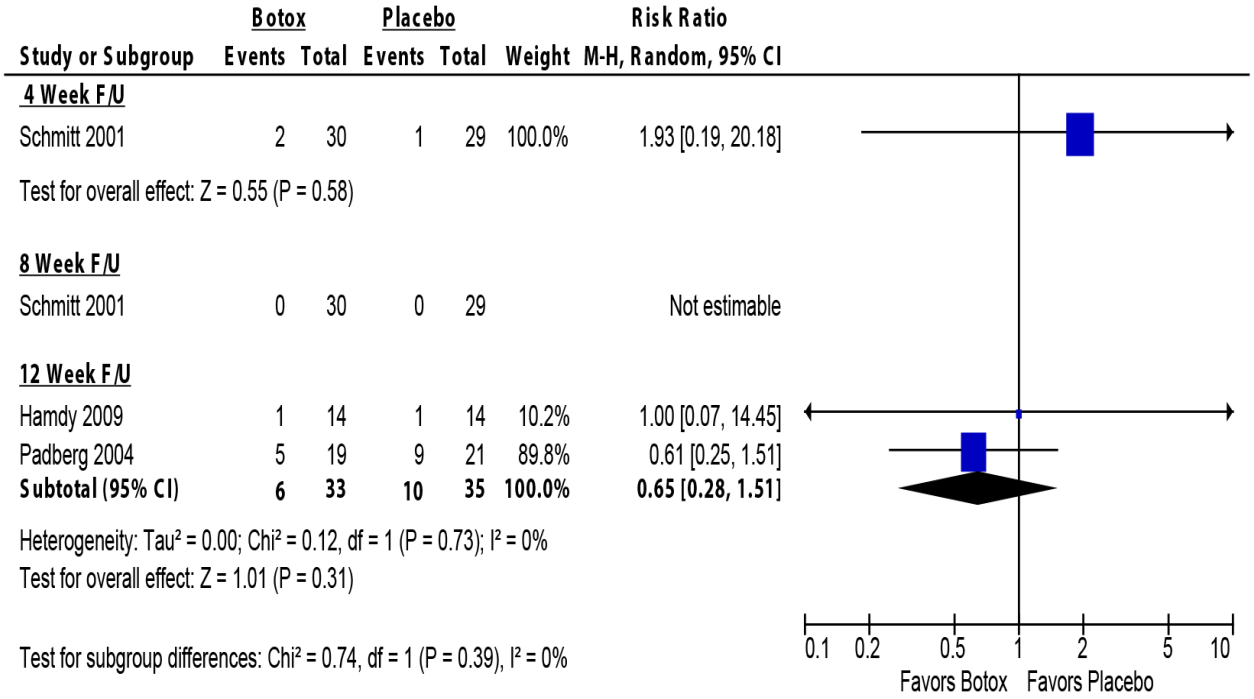
Figure 42. Percent of Participants Reporting Adverse Events in the Short Term (8 weeks), BoNTA versus Placebo in CTTH



AEs: adverse events; BoNTA: OnabotulinumtoxinA; CI: confidence interval; CTTH: chronic tension-type headache; RoB: risk of bias; RR: risk ratio.

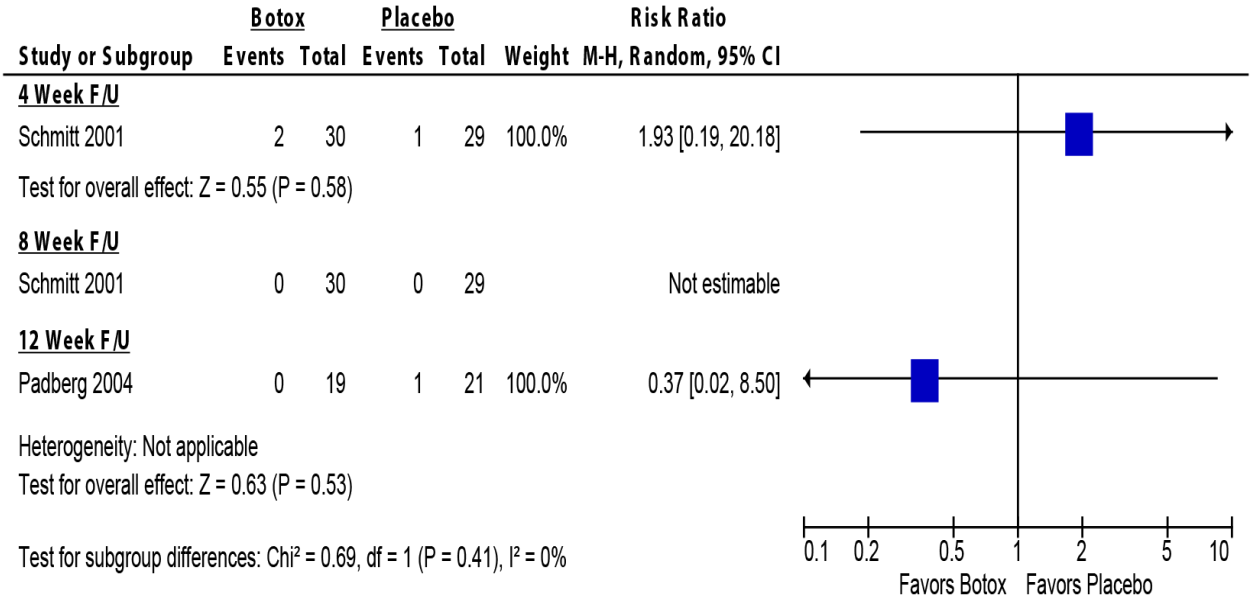
Pain at the injection site was reported in three studies, Figure 43.[82,135,147] At 4 weeks (short-term), there were no significant differences between groups in one trial, RR 1.93 (95% CI 0.19, 20.18).[147] At 8 weeks, participants did not report any events of pain at the injection site the same trial.[147] There also were no significant differences between treatment groups in a pooled analysis at the 12 week (long-term) follow-up, RR 0.65 (95% CI 0.28, 1.51) across two trials.[82,135]

Figure 43. Pooled Analysis of Safety Events: Pain at Injection Site over the Short- (≤8 weeks) and Long-term (≥12 weeks), BoNTA versus Placebo for CTTH



Vertigo was reported in two studies, Figure 44. At short-term follow-up (4 weeks), there were no significant differences between groups in one study, RR 1.93 (95% CI 0.19, 20.18).[147] At 8 weeks, participants did not report any events of dizziness in one study (Schmitt 2001). There also were no significant differences between treatment groups at the 12 week follow-up in one study, RR 0.37 (95% CI 0.02, 8.50).[135] Samples sizes in both trials were small.

Figure 44. Pooled Analysis of Safety Events: Vertigo over the Short- (≤8 weeks) and Long-term (≥12 weeks), BoNTA versus Placebo for CTTH



4.3.3.2. Acupuncture versus Sham for 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.[99,164]

4.3.3.3. Acupuncture versus Active Control for Chronic Tension Type Headache

Of the two RCTs identified that evaluated the efficacy of acupuncture versus an active control for treatment of chronic tension-type headache only one, which compared acupuncture with physiotherapy, provided data on adverse events.[52] Study and patient characteristics have been described with Key Question 1 (and can be found in Appendix Table F7); detailed information on individual adverse events can be found in Appendix Table H2.

Acupuncture vs. Physiotherapy

In one trial comparing acupuncture with physiotherapy,[52] 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).

Acupuncture vs. Physical Training or Relaxation

No safety data was reported by the trial comparing acupuncture with physical training and relaxation.[158,159]

4.3.3.4. Manual Therapy/Manipulation versus Active Control for Chronic Tension Type Headache

One RCT with a moderately low risk of bias was identified that evaluated the efficacy of manual therapy versus usual care for treatment of chronic tension-type headache and provided data on adverse events.[54] Study and patient characteristics have been described with Key Question 1 (and can be found in Appendix Table F8); detailed information on individual adverse events can be found in Appendix Table H3.

Manual Therapy vs. Usual Care

In one trial comparing manual therapy with usual care,[54] the following statement was made related to safety: "No adverse events were reported in both treatment groups." No other information was provided. The follow-up period was 18 weeks post-treatment (longer-term).

4.3.3.5. Trigger Point Injection versus Sham for Chronic Tension Type Headache

One RCT, with a moderately high risk of bias, was identified that evaluated the efficacy of trigger point injections (TPI) versus sham for treatment of chronic tension-type headache and provided data on adverse events.[98] Study and patient characteristics have been described with Key Question 1 (and can be found in Appendix Table F9); detailed information on individual adverse events can be found in Appendix Table H6.

No serious adverse events occurred in either the TPI or the sham group over longer-term (12 weeks) follow-up as reported by one trial.[98] No statistical difference between groups was seen in the frequency of minor side-effects, 29.2% (7/24) vs. 41.7% (10/24), RR 0.7 (95% CI 0.3, 1.5) and included, respectively, injection site/injection pain (13% vs. 17%), dizziness (8% vs. 8%), back pain (8% vs. 13%) and cervical muscle spasm (0% vs. 4%). Small sample size may have precluded detection of a statistical difference.

4.3.4. Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Summary of Results

BoNTA vs. Placebo

Two trials provided information on safety-related outcomes for this comparison.

- At long-term follow-up (24 weeks), treatment-related adverse events were over two-times more common following BoNTA compared with placebo across two RCTs; results were statistically significant (moderate evidence).
- The most common adverse event experienced in BoNTA recipients was muscle weakness (24%) followed by neck pain (19%) and neck rigidity (9.0%). Shoulder/arm pain (5.5%) and Dysphagia (3%) were less common. All of these were significantly more common the BoNTA group compared with placebo. (low evidence for all outcomes)

BoNTA vs. Topiramate

One small RCT provided limited information on safety-related outcomes for this comparison.

- Through longer-term follow-up (12 weeks), nausea was two times more common with BoNTA than with topiramate however both groups experienced similar frequency of mild fatigue in one small RCT (Low evidence).

Acupuncture versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Manual Therapy/Manipulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Massage versus Sham

One small RCT provided limited evidence regarding safety for this comparison.

- Through the intermediate-term (9 weeks), one small trial reported no statistical difference between the massage and the sham group in minor fever, mild soreness, and other discomfort; again, the sample was small (low strength of evidence).

Massage versus Active Control

- No studies were identified that met the inclusion criteria.

Transcranial Magnetic Stimulation versus Sham and versus Active Control

- No studies were identified that met the inclusion criteria.

Trigger Point Injection versus Sham and versus Active Control

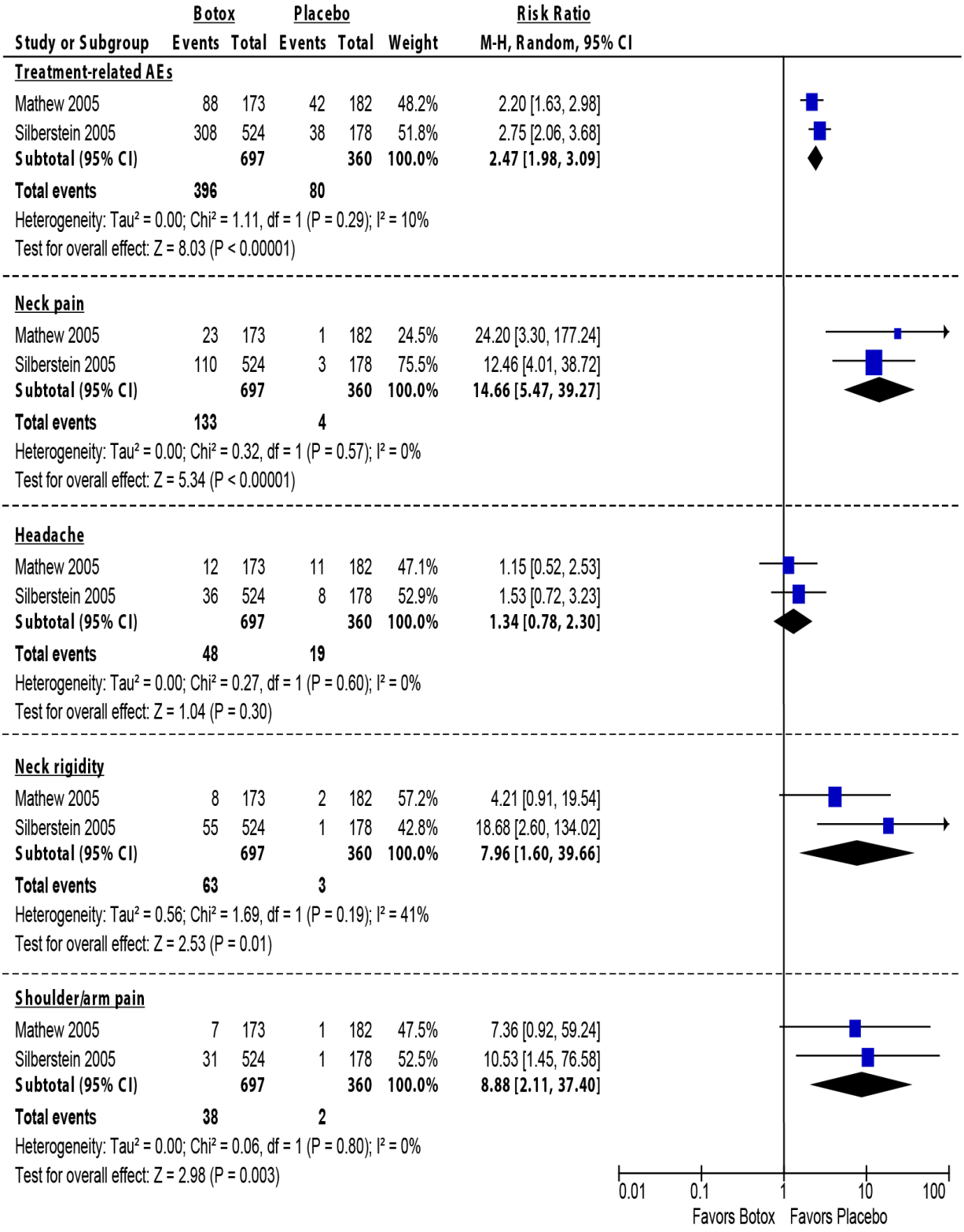
- No studies were identified that met the inclusion criteria.

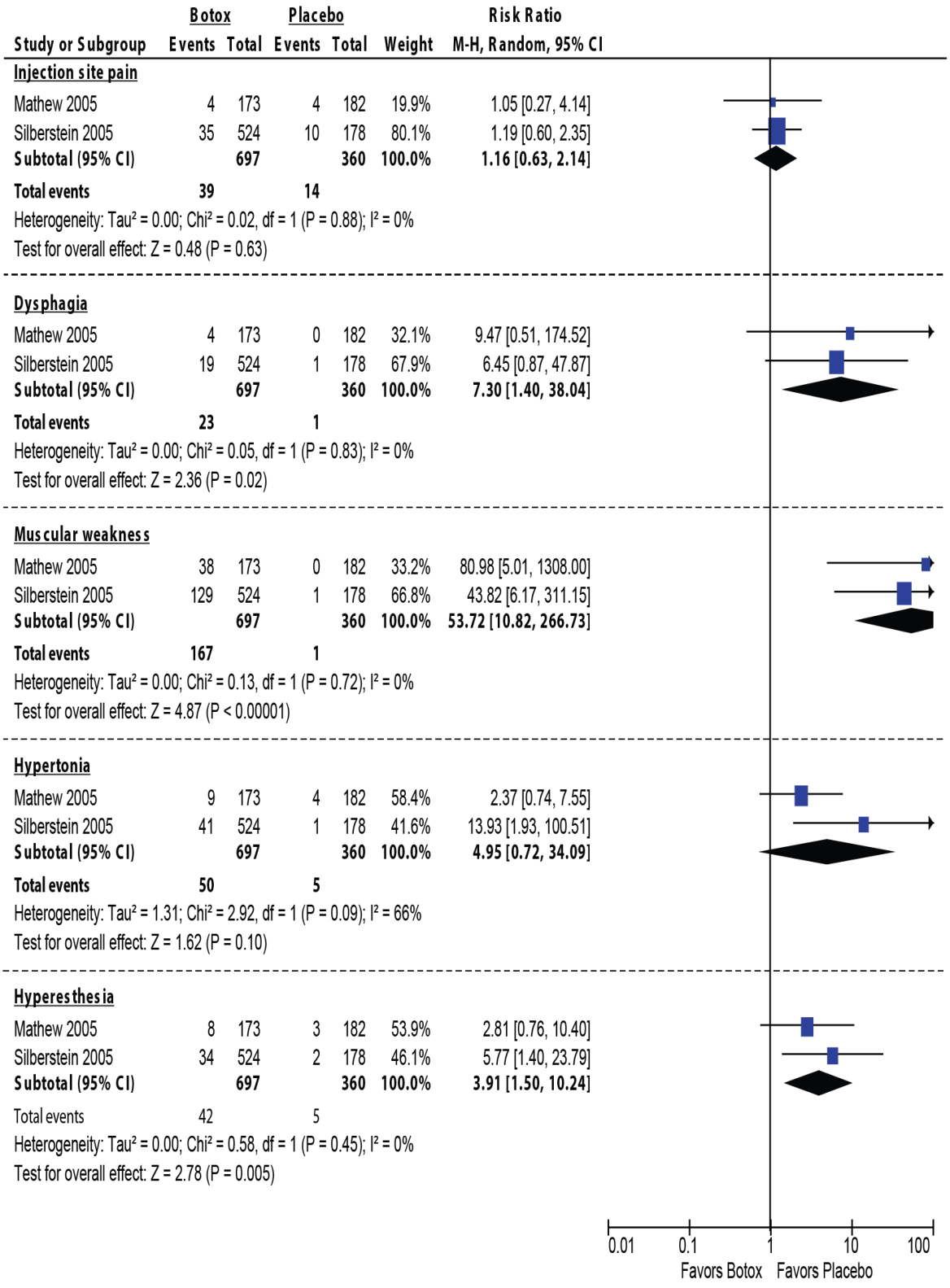
4.3.4.1. BoNTA versus Placebo for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Three RCTs[120,134,155] that enrolled as few as 60 and as many as 702 patients were included. Study descriptions are found with Key Question 1. Detailed information on patient and study characteristics is available in Appendix Table F10. Details regarding invididual adverse events can be found in Appendix Table H1.

Adverse events were reported in two studies with a moderately low risk of bias at longer-term follow-up (24 weeks after initiation of treatment),[120,155] Figure 45. Treatment-related AEs were significantly more common in the BoNTA compared to placebo groups, RR 2.47 (95% CI 1.98, 3.09). Specifically, neck pain, neck rigidity, shoulder/arm pain, dysphagia, muscular weakness, and hyperesthesia were significantly greater in the BoNTA compared to placebo groups, (neck pain RR 14.66 (95% CI 5.47, 39.27), neck rigidity RR 7.96 (95% CI 1.60, 39.66), shoulder/arm pain RR 8.88 (95% CI 2.11, 37.40), dysphagia RR 7.30 (1.40, 38.04), muscular weakness RR 53.72 (95% CI 10.82, 266.73), hyperesthesia RR 3.91 (95% CI 1.50, 10.24). There were no significant differences between groups for headache, injection site pain and hypertonia (headache RR 1.34 (95% CI 0.78, 2.30), injection site pain RR 1.16 (0.63, 2.14), hypertonia RR 4.95 (95% CI 0.72, 34.09).

Figure 45. Pooled Analysis of Safety Events at Long-term Follow-up (24 Weeks), BoNTA versus Placebo in CDH




Botox
Placebo
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
Injection site pain
Mathew 2005 4 173 4 182 19.9% 1.05 [0.27, 4.14]
Silberstein 2005 35 524 10 178 80.1% 1.19 [0.60, 2.35]
Subtotal (95% CI) 697 360 100.0% 1.16 [0.63, 2.14]
Total events 39 14
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Dysphagia
Mathew 2005 4 173 0 182 32.1% 9.47 [0.51, 174.52]
Silberstein 2005 19 524 1 178 67.9% 6.45 [0.87, 47.87]
Subtotal (95% CI) 697 360 100.0% 7.30 [1.40, 38.04]
Total events 23 1
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)
Muscular weakness
Mathew 2005 38 173 0 182 33.2% 80.98 [5.01, 1308.00]
Silberstein 2005 129 524 1 178 66.8% 43.82 [6.17, 311.15]
Subtotal (95% CI) 697 360 100.0% 53.72 [10.82, 266.73]
Total events 167 1
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.87 (P < 0.00001)
Hypertonia
Mathew 2005 9 173 4 182 58.4% 2.37 [0.74, 7.55]
Silberstein 2005 41 524 1 178 41.6% 13.93 [1.93, 100.51]
Subtotal (95% CI) 697 360 100.0% 4.95 [0.72, 34.09]
Total events 50 5
Heterogeneity: Tau² = 1.31; Chi² = 2.92, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 1.62 (P = 0.10)
Hyperesthesia
Mathew 2005 8 173 3 182 53.9% 2.81 [0.76, 10.40]
Silberstein 2005 34 524 2 178 46.1% 5.77 [1.40, 23.79]
Subtotal (95% CI) 697 360 100.0% 3.91 [1.50, 10.24]
Total events 42 5
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
0.01 0.1 1 10 100
Favors Botox Favors Placebo

4.3.4.2. BoNTA versus Topiramate for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

One poor quality RCT[50] with a moderately high risk of bias was included that compared BoNTA to topiramate. The population was 81.7% female, with a mean age of 47 years. Detailed information on patient and study characteristics is available in Appendix Table F10.

By 12 weeks (long-term), participants in the BoNTA group reported a significantly greater frequency of nausea compared to the topiramate group (BoNTA 59.1%, topiramate 27.3%, RR: 2.2, 95% CI 1.0, 4.7). Participants who received BoNTA also reported greater frequencies of mild fatigue (BoNTA 72.7%, topiramate 68.2%, RR: 1.0, 95% CI 0.7, 1.6) and difficulty concentrating (BoNTA 59.1%, topiramate 50.5%, RR: 1.2, 95% CI 0.7, 2.0), though the results were not significantly different between treatment groups. Participants in the topiramate group reported a greater frequency of mood swings, though the results were not significantly different compared to the BoNTA group (BoNTA 18.2%, topiramate 27.3%, RR: 0.7, 95% CI 0.2, 2.0).[50] Additional details are found in Appendix Table H1.

4.3.4.3. Massage versus Sham for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

One RCT with low risk of bias was identified that evaluated the efficacy of traditional Thai massage versus sham ultrasound (US) treatment for chronic daily headache and provided data on adverse events.[59] Study and patient characteristics have been described with Key Question 1 (and in Appendix Table F5).

No statistical differences were noted between the massage and the sham US group in one trial with 9 weeks of follow-up (intermediate-term)[59]: the only adverse effects reported were mild fever, mild soreness, and other discomfort during the treatment period which occurred in 17% (6/36) and 14% (5/36), respectively, RR 1.2 (95% CI 0.4, 3.6) (Appendix Table H4).

4.4. Key Question 3: Differential Efficacy and Harms in Subpopulations

4.4.1. Number of studies retained

For this key question, RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. 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.

Summary of results:

Acupuncture versus Active Control for Chronic Migraine

- Acupuncture vs. Usual Care (1 RCT):
    - 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; all other variables (headache diagnosis, age, sex, chronicity) did not modify the treatment effect (insufficient strength of evidence).
- Acupuncture vs. Topiramate (1 RCT):
    - Baseline headache days (any and moderate/severe) was found to modify treatment effect such that patients with higher (≥20 days/mo.) as compared with lower (<20 days/mo.) frequency showed significantly greater improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect (insufficient strength of evidence).

Manual Therapy versus Usual Care for Chronic Tension Type Headache

- Manual Therapy vs. Usual Care (1 RCT):
    - No differential effect of treatment was seen for the subgroup of patients with comorbid migraine versus without migraine; no formal test for interaction was performed (insufficient strength of evidence).

4.4.2. Chronic Migraine

4.4.2.1. Acupuncture versus Active Control

Acupuncture vs. Usual Care for Chronic Migraine

One RCT included for efficacy reported formal tests for interaction for a number of factors (i.e., age, sex, chronicity, baseline headache score, headache diagnosis); no data was provided for evaluation.[170] Details regarding this study population are available in the section on efficacy and in 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 usual care (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 usual care were much larger for migraine patients (4.9; 95% CI 2.4, 7.5; n=284) than those with tension-type headache (1.1, 95% CI -2.4, 4.5) n=17); the small numbers of patients with tension-type headache likely precluded an effect of acupuncture in this population. Age, sex, and chronicity did not modify the treatment effect.

Acupuncture vs. Topiramate for Chronic Migraine

In a subsequent publication, one RCT included for efficacy that compared acupuncture with topiramate for the treatment of chronic migraine stratified on various patient characteristics in such a way that effect modification could be evaluated and performed formal tests for interaction.[179,180] Details regarding this study population can be found in the section on efficacy and in Appendix Table F2. The baseline number of headache days was the only patient characteristic found to differentially effect 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 and moderate/severe headache days showed significantly greater reduction in mean number of moderate/severe headache days per month following treatment with acupuncture but not with topiramate (Table 25).

Table 25. Changes in Mean Number of Moderate/Severe Headache Days Per 4 Weeks* by Baseline Headache Frequency

	Acupuncture				Topiramate				Interaction
	n	Median	IQR	P	n	Median	IQR	P	P†
Headache days				0.010				NS	0.002
≤20	13	-10	1		13	-9	5		
>20	20	-12	2		20	-8	3.5		
Moderate/severe headache days				0.015				NS	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.[180] 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 SF-36, and reduction in analgesic consumption (Appendix Table G4).

4.4.3. Chronic Tension-Type Headache

4.4.3.1. Manual Therapy/Manipulation versus Active Control for Chronic Tension-Type Headache

One RCT included for efficacy which compared manual therapy (MT) with usual care for the treatment of chronic tension-type headache (CTTH) conducted a subgroup analysis for CTTH participants with co-morbid migraine[54]; 29% of patents randomized to MT and 22% randomized to usual care had comorbid

migraine (see the section on efficacy for more details regarding the study population). The difference between the MT and usual care groups in reduction in headache frequency was 5.1 days (95% CI 1.1, 9.2) for the subgroup with migraine, and 6.3 days (95% CI 4.2, 8.5) for those without migraine, which does not show a differential effect of treatment in these subgroups; no formal test for interaction was performed. There was also no difference between subgroups in the use of pain medication (data not provided).

4.4.4. Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

4.4.4.1. BoNTA versus Placebo for Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache

Two trials comparing BoNTA with placebo provided limited data comparing patients who responded to placebo during the placebo run-in phases.[120,155] Neither trial provides information or data for evaluation with respect to other subgroups (e.g. sex, age).

Silberstein 2005 reported that they examined treatment-by-subgroup interactions for a number of factors (e.g., age, sex, race, time since disease onset, chronic headache subtype, baseline, MIDAS totals days score, and baseline prophylactic treatment).[155] Authors state that there was no statistical interaction between treatment group and placebo response status but do not provide further information. They do not provide information or data on the other subgroups.

Mathew 2005 does not report test for interaction for the evaluation of differential efficacy of BoNTA with respect to placebo response status for any outcome.[120] Authors report that the mean change in mean headache frequency at 180 days was statistically different within the stratum of placebo non-responders (changes reported: BoNTA -6.1 days, placebo -3.1 days, p = 0.013) and within the stratum of placebo responders (BoNTA -9.9 days, placebo -5.6 days, p = 0.004). They do not, however, report a formal test for interaction between the two strata nor do they provide sufficient data to calculate this.

4.5. Key Question 4: Cost effectiveness

4.5.1. Number of studies retained

For the treatment of chronic migraine, three cost utility analyses (CUA) met the inclusion criteria; two compared Botox with placebo[29,146] and one compared acupuncture with usual care.[171]

No economic studies that met our inclusion criteria were identified for the treatment of chronic tension-type headache or chronic daily headache.

4.5.2. Chronic Migraine

4.5.2.1. BoNTA versus Placebo for Chronic Migraine

Study characteristics:
Two cost-utility analyses[29,146] compared OnabotulinumtoxinA (BoNTA) with placebo in patients with chronic migraine (mean 19.9 days/month with headache) using pooled data from the PREEMPT 1 and 2 trials[29] and a cohort of patients from those trials,[146] also included in this report.[67] One study was conducted in the United Kingdom (UK) and was industry-funded (Allergan, Inc.).[29] As well as evaluating all patients enrolled in the PREEMPT trials, this study also presented analyses for two subpopulations: patients who had previously received one or more and three or more oral prophylactic treatments. The other study, conducted in Italy, did not report its source of funding.[146] Study characteristics, results and conclusions are summarized in Table 26.

Both studies employed Markov modeling to determine incremental cost-effectiveness ratios (ICERs) from a healthcare perspective (the UK and Italian National Health Services (NHS)) and used similar methods for transition state modeling. The modeling in the Batty study was somewhat more comprehensive and includes "off-treatment" cycles, accounting for patients to transition in and out of treatment. Authors of the UK study conducted probabilistic sensitivity analysis, varying each model parameter simultaneously. Scenario analyses on administrative costs, stopping rules (positive and negative), time horizon and utility costs. In the Italian study authors state that univariate and multivariate probabilistic sensitivity analysis confirms the robustness of these results, but provide no detail on how analyses were conducted or what parameters were explored.
Both studies reported the clinical effectiveness in terms of quality-adjusted life years (QALY), the values for which were derived from the post-hoc pooled analyses from the PREEMPT trials.[67] The Italian study appears to have used only a subset of the PREEMPT study population and do not provide any demographic data or information on this subset. The UK study authors indicate that a systematic literature search for information on relevant comparators was conducted, but provide no detail. Clinical outcomes included mean number of headache days in a 28 day period, Migraine Specific Quality of Life Questionnaire (MSQ) and death. Utilities were obtained by mapping MQS scores to the EQ-5D, however authors do not report on the reliability of this mapping, providing only a reference.

Costs were reported in 2010 UK pounds and Euros (year not specified). Both studies employed a 24 month time horizon with a 12-week transition cycle length; one discounted costs and QALY at 3.5%[29] and the other study did not report whether discounting was done.[146] Both studies focused on direct

costs. In the UK study, cost data primarily came from the NHS Reference Costs 2010 and other government and published literature. The cost of BoNTA, to include drug cost and initial and subsequent (injection) consultation time, as well as the cost of general practitioner visit, emergency department visits, hospitalizations, and triptan costs were included in the UK study. It is not clear whether these may be underestimated. Costs for medications, hospitalizations, visits to the general practitioner and emergency department were specified in the Italian study, but no data on such costs were provided.

Two reviewers assessed the quality of the CUA using the Quality of Health Economic Study (QHES) metric combined with application of appropriate epidemiologic principles. The UK study was considered to be of poor to moderate quality (QHES score 72) and the Italian study was considered very poor (QHES 25) as they did not provide details of the patient populations, costs, outcomes or model inputs. Given the poor reporting in this study, results and discussion below focus on the higher quality study (Table 21; see Appendix Table E12 for full scoring details).

Primary study limitations for the UK study are outlined in Table 21 below. Briefly, primary limitations include lack of comparison to an active agent such as topiramate, unclear modeling of harms and lack of clear information on long-term (beyond 24 weeks) benefits and harms of BoNTA.

Results

Base Case

For the 2 year time horizon, in the higher quality UK study base case the average cost per patient was £1,680 for the placebo group and £3,077 for the BoNTA group. The QALYs gained were 1.2 with placebo and 1.3 with BoNTA. ICER for BoNTA was £15,028 per QALY gained.

The ICER for the subgroup analysis of patients receiving one or more prior treatments was £14,273 per QALY gained and £17,212 per QALY gained for those who received three or more prior treatments.

Sensitivity Analyses

In the higher quality UK study's probabilistic sensitivity analysis indicated that the likelihood that BoNTA was cost-effective at a willingness-to-pay threshold of £20,000 was 96%. The scenario analyses reveals that the most uncertainty existed around the utility values. In scenarios where the utility values for both BoNTA and placebo were the same for each health state, the ICER increased to £29,157 per QALY gained.

No information on sensitivity analysis was provided by authors of the Italian study.

Conclusions and Limitations

One poor to moderate quality and one very poor quality cost-utility analysis compared BoNTA vs. Placebo. The higher quality UK study suggests that BoNTA may be cost-effective at a willingness to pay threshold of €20,000 to €30,000/QALY). ICERs were higher for patients who had received three or more prior treatments. Based on sensitivity analysis, ICERs ranged from £4945/QALY (if no effect of placebo on # of HA days to £29,175/QALY when utilities for both BoNTA and placebo were the same in a given health state.

Primary limitations include lack of comparison to an active agent such as topiramate, unclear modeling of harms and lack of clear information on long-term (beyond 24 weeks) benefits and harms of BoNTA. Given the chronic nature of CM, it is assumed that continued treatment may needed, however the circumstances for continuation or discontinuation are not clear.

4.5.2.2. Acupuncture versus Usual Care for Chronic Migraine

Study characteristics:
One study from the UK evaluated the cost-effectiveness of acupuncture versus usual care in patients with chronic migraine (mean 15.9 headache days/month).[171] Usual care was described as an "avoid acupuncture" strategy where patients received usual care form their general practitioner but were not referred to acupuncture. Study funding came from the UK National Health Service, Health Technology Assessment Programme. Study characteristics, results and conclusions are summarized in Table 21.

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 was 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 UK central government. The analysis was from both a payer and a societal perspective.

The study reported the clinical effectiveness 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.[170] 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 UK pound. Costs included non-prescription (over-the-counter) drugs and NHS and private healthcare visits (i.e. acupuncture, 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 literatures sources. The cost of prescription drugs, and 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, 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 21; see Appendix Table E12 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 usual care and differences between the UK and US medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.

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 usual care was $189.42 (95% CI $102.24 to $276.61). Compared with usual care, acupuncture yielded an ICER of $9180 (total cost = NHS + 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 OTC 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 of 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 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 increase at later time horizons, RCT data on efficacy and harms only goes to 1 year.

Conclusions and Limitations

One poor to moderate quality CUA 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. 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 needed, however the circumstances for continuation or discontinuation are not clear. Lack of clarity regarding the components of usual care and differences between the UK and US medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.

Table 26. Overview of formal economic studies.

	BOTOX		ACUPUNCTURE
	Batty 2013	**Ruggeri 2014**	**Vickers 2004**
Population	Adult (aged 18-65 years) patients with chronic migraine (mean headache days/month: 19.9): (1) Licensed population, all patients (n=1384) (2) Patients who have previously received ≥1 oral prophylactic treatments (n=983). (3) Patients who have previously received ≥3 oral prophylactic treatments (as considered by NICE) (n=439)	1384 adult (aged 18-65 years) patients with chronic migraine (mean headache days/month: 19.9)	255 adult (aged 16-65 years) patients with chronic migraine (mean headache days/month: 15.9)
Intervention(s)	OnabotulinumtoxinA	OnabotulinumtoxinA	Acupuncture
Comparator(s)	Placebo	Placebo	Usual care (NOS)
Country	UK	Italy	UK and Wales
Funding	Allergan, Inc. (Marlow, Buckinghamshire, UK)	NR	Government (National Health Service, HTA Programme)
Study design	Cost utility	Cost utility	Cost utility
Perspective	Payer (UK NHS)	(a) Payer (Italian NHS) (b) Societal	Payer (UK NHS) and Societal
Time horizon	24 months (12-week cycle length)	24 months (12-week cycle length)	12 months
Analytic model	Markov	Markov	Linear regression model
Effectiveness outcome	QALY	QALY	QALY
Effectiveness outcome components	Headache days/28 days, death	Headache days/28 days, death	SF-36
Source for effectiveness data	Pooled data from 2 RCTs (PREEMPT 1 and 2 trials, Dodick 2010)*, Post hoc analysis	Pooled data from 2 RCTs (PREEMPT 1 and 2 trials, Dodick 2010)*	RCT (Vickers 2014)†
Costing year	2010	NR	2002/2003
Currency	UK £	Euro €	UK £
Cost sources	NHS reference costs 2010, NHS Prescriptions Cost Analysis	NR (payer); ISTAT 2008 (productivity loss)	Published literature (various, including Vickers 2014), Government

	BOTOX		ACUPUNCTURE
	Batty 2013	**Ruggeri 2014**	**Vickers 2004**
Components of cost data	acute headache treatment medications, accident and emergency visits, hospital stays, physician/neurologist visits, cost of onabotulinumtoxinA, and cost of administering onabotulinumtoxinA or placebo	medications, hospitalizations, visits to the general practitioner, emergency department access, costs incurred for productivity losses	Cost of acupuncture treatment
Discounting	Costs and QALYs: 3.5%	NR	None due to short time horizon (in a sensitivity analysis costs and QALYs were discounted at 6% and 1.5%, respectively)
Sensitivity analysis	Scenario‡ Probabilistic§	Probabilistic (uni- and multivariate)	Primarily done around missing values and related imputation; Limited analysis of assumptions
QHES	72	25	71
Results:			
BASE CASE			
Cost / QALY of intervention	(1) £2997 / 1.30 (2) £3024 / 1.26 (3) £2990 / 1.21	(a) €3,274 / 1.34 (b) NR	£403.40 / 0.727
Cost / QALY of comparator	(1) £1630 / 1.20 (2) £1691 / 1.17 (4) £1712 / 1.13	(a) €2,395 / 1.24 (b) NR	£217.20 / 0.708
ICER (intervention vs. comparator)	(1) £15,028/QALY (2) £14,273/QALY (3) £17,212/QALY (BoNTA considered cost-effective at a WTP threshold of €20,000 to €30,000/QALY)	(a) €9,407/QALY (b) €815/QALY (BoNTA considered cost-effective at a WTP threshold of €20,000 to €40,000/QALY)	£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 £4945/QALY (if no effect of placebo on # of HA days to £29,175/QALY when utilities for both BoNTA and placebo were the same in a given health state	NR	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	NR	NR

	BOTOX		ACUPUNCTURE
	Batty 2013	**Ruggeri 2014**	**Vickers 2004**
Probabilistic SA	BoNTA was cost-effective in 96% of occasions at a WTP of £20,000 per QALY and on 98% of occasions at a threshold of £30,000 per QALY.	Data or methods NR, authors state that univariate and multivariate probabilistic sensitivity analysis confirms the robustness of these results	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.
AUTHOR'S CONCLUSION	OnabotulinumtoxinA has been shown to reduce the frequency of headaches in patients with chronic migraine and can be considered a cost-effective use of resources in the UK NHS. The uncertainties in the model relate to the extrapolation of clinical data beyond the 56 week trial.	The incremental cost effectiveness of Botox versus placebo for the prophylaxis of chronic migraine was favorable and below the threshold of acceptability implicitly used by NICE for reimbursement decisions.	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	• Lack of comparison to topiramate (commonly used medication) or other medications/treatments • It is unclear whether costs associated with physician visits, drug administration, and acquisition of BoNTA were underestimated. • The extent to which placebo is representative of usual care is not clear; usual care is not well defined in patients with chronic migraine; the extent of placebo effect cannot be estimated. • Time horizon for which data are available is likely too short, given the chronic nature of the condition; it is assumed that continued treatment would be needed: Long-term effectiveness and harms are not known and it is not clear if BoNTA would be used indefinitely; published RCT data PREEMPT go to 24 weeks.	• Lack of comparison to topiramate (commonly used medication) • Information on study population is not provided • Authors provide no detail on how sensitivity analyses were done or data related to them • Study does not provide detail regarding efficacy or safety outcomes, nor do they provide data on costs, providing only vague references. • Time horizon was limited same limitations for Batty Study)	• The controls group basically 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 is 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 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.

	BOTOX		ACUPUNCTURE
	Batty 2013	**Ruggeri 2014**	**Vickers 2004**
	• The assumption that 24% of patients were able to stop BoNTA and remain largely HA free for 6 months is not well validated • Modeling of adverse events and related discontinuation are not well described		

*Post-hoc analysis of the pooled data from the PREEMPT program.
†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.
‡Scenario analysis was conducted by varying the assumptions around the administration costs, stopping rules, time horizon, and utility scores.
§In the probabilistic analysis, values were randomly sampled from the 95% confidence interval for all parameters (except drug costs), taken from the source publication. Five thousand simulations were performed.

5. Strength of Evidence (SoE) Summary Tables

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

5.1. Strength of Evidence Summary: Chronic Migraine Efficacy Results

Notes:

- Only primary outcomes are were rated for strength of evidence
- 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.

5.1.1. Strength of Evidence Summary: Efficacy of OnabotulinumtoxinA (BoNTA) versus Placebo: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Migraine									
Responders Percent with ≥ 50 % reduction in number of *migraine episodes*	>12 weeks	3 RCTs (Aurora 2011[PREEMPT 1 and 2], Freitag 2008)	N= 1236 and 41 (completers)	No	No	Yes[4] (-1)	No	24 Weeks: 2 RCTs (n=1236), low risk of bias Pooled RR 1.1, 95% CI 1.0, 1.2 Pooled RD 4.7%, 95% CI -0.8%, 10.2%) 16 Weeks: 1 RCT (n=41), moderately high risk of bias RR 2.0, 95% CI 0.6, 6.8 Conclusion: No statistical difference between BoNTA and placebo.	⊕⊕⊕○ MODERATE
Responders Percent with ≥ 50 % reduction in number of	24 weeks	2 RCTs Aurora 2011;PREEMPT 1 and 2	N =1236 (completers)	No	No	Yes[4] (-1)	No	Migraine days: Pooled RR 1.3 95% CI 1.1, 1.5 RD 12.3% (6.9%, 17.8%) Headache days:	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
migraine days, overall number of headache days								Pooled RR 1.3 (95% CI 1.2, 1.5 RD 12.0% (6.5%, 17.4%) Conclusion: More BoNTA participants experienced ≥50% reduction in **number of migraine days** and **overall headache days** compared with placebo; the relative effect size is small; the RD between groups is 12%	
Reduction in mean *HA episodes* per month	24 weeks	2 RCTs (Aurora 2010[PREEMPT 1], Denier 2010 [PREEMPT 2],	N =1384	No	No	Yes[4] (-1)	No	Pooled MD -0.27 (95% CI -1.05, 0.51) Conclusion: There was no statistical difference in mean number of **HA episodes** for BoNTA and placebo	⊕⊕⊕○ MODERATE
Reduction in mean *HA days* per month	16 weeks 24 weeks	3 RCTs (Aurora 2010[PREEMPT 1], Denier 2010 [PREEMPT 2], Freitag 2008)	N= 1420	No	No	Yes[4] (-1)	No	Pooled MD -1.77 (95% CI -2.49, -1.06) Conclusion: A small reduction in the mean number **HA days** favoring BoNTA group compared to placebo was observed.	⊕⊕⊕○ MODERATE
Reduction in mean *migraine episodes* per month	16 weeks 24 weeks	2 RCTs (Aurora 2010[PREEMPT 1], Freitag 2008	N=715	No	Yes[2] (-1)	Yes[4] (-1)	No	Pooled MD -1.29 (95% CI -4.22, 1.64) Conclusion: No statistical difference was observed for the pooled estimate or in the larger trial that was a low risk of bias in the number of **migraine episodes**. The smaller trial at moderately high risk of bias reported a significant decrease in the BoNTA group. The quality rating is based on the larger, low risk of bias trial.	⊕⊕⊕○ MODERATE
Reduction in mean *migraine days* per month	24 weeks	2 RCTs (Aurora 2010[PREEMPT 1], Denier 2010 [PREEMPT 2],	N =1384	No	No	Yes[4] (-1)	No	Pooled MD -1.79 (95% CI -2.61, -0.96) Conclusion: A small reduction in the mean number of **migraine days** favoring BoNTA group compared to placebo was observed.	⊕⊕⊕○ MODERATE
Percentage of Participants with a Severe	24 weeks	2 RCTs (Aurora 2010[PREEMPT 1],	N =1384	No	No	Yes[4] (-1)	No	Pooled RR 0.86 (95% CI 0.81, 0.92)	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
HIT-6 Score (≥60) †		Denier 2010 [PREEMPT						Conclusion: Significantly fewer patients in the BoNTA group still had severe HIT scores at 24 weeks compared to placebo; At baseline, 94% of participants in both groups had a severe score.	
Headache Impact Test-6 (HIT) †	24 weeks	2 RCTs (Aurora 2010[PREEMPT 1], Denier 2010 [PREEMPT	N =1384	No	No	Yes[4] (-1)	No	MD -2.39 (95% CI -3.40, -1.39) Conclusion: Greater reduction in mean HIT scores, suggesting improved function, was seen in the BoNTA group compared to placebo; this may be a clinically important difference.	⊕⊕⊕◯ MODERATE
Migraine Disability Assessment Scale (MIDAS) (0-27[worst])	16 weeks	1 RCT (Frietag 2008)	N = 41	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	Mean change from baseline BoNTA: -11 placebo: +2 Conclusion: Although the mean change in MIDAS scores suggests improved function in the BoNTA group compared to placebo, authors report that the result was not statistically significant.	⊕◯◯◯ IINSUFFICIENT

MIDAS = Migraine Disability Assessment Scale, greater number of days, greater disability, HIT-6 = Headache Impact Test-6 MIQ = Migraine Impact Questionnaire

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers. Authors of the PREEMPT 1 and 2 trials imputed values for missing participants using last observation carried forward for ITT analysis

† Headache Impact Test-6 (HIT) measures the impact headache has on function. Higher scores = higher impact on activities of daily living; Scoring interpretation- Little or no impact: <46, Some impact: 50 – 55, Substantial impact: 56 – 59, Severe impact: 60 –78; a between-group difference in change scores of 2.3 units may be considered clinically significant in patients with ≥ 15 headache days/month.

‡ Results could not be pooled due to differences in data reporting between the trials.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.1.2. Strength of Evidence Summary: Efficacy of OnabotulinumtoxinA (BoNTA) versus Active Control: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Migraine: OnabotulinumtoxinA (BoNTA) versus Topirimate									
Responders Percent with ≥ 50 % reduction in number of *headache days* per month	12, 24, 36 weeks	1 RCT (Mathew 2009)	N=60	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	12 weeks: BoNTA 38.5%, Topiramate 22.7% RR 1.7, 95% CI 0.7, 4.2 24 weeks: BoNTA 58.3%, Topiramate 31.8% RR 1.8, 95% CI 0.9, 3.7 36 weeks: BoNTA 40.9%, Topiramate 42.9% RR 1.0, 95% CI 0.5, 1.9 Conclusion: At 12 and 24 weeks, more BoNTA recipients achieved **≥ 50 reduction in headache days, however,** there were no statistical differences between groups at any time point however this may partly be a function of sample size. There was substantial attrition and differential loss to follow-up: data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks.	12 weeks: ⊕⊕◯◯ LOW 24 and 36 weeks ⊕◯◯◯ INSUFFICIENT
Functional Measures (MIDAS, HIT-6, MIQ)	4- 36 weeks			Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MIDAS: 12 weeks: MD 22.8, 95% CI -2.5, 48.1 24 weeks: MD 35.0, 95% CI -3.2, 73.2 HIT-6 12 weeks: MD 3.2, 95% CI -1.1, 7.5 24 weeks: MD 4.8, 95% CI 0.1, 9.6 36 weeks: MD 5.3, 95% CI 0.8, 9.8 MIQ: 4 weeks: MD -0.2, 95% CI -1.7, 1.3 24 weeks: MD -1.8, 95% CI -3.2, -0.4	12 weeks: ⊕⊕◯◯ LOW 24 and 36 weeks ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
								Conclusion: There were no differences between groups for any functional measure at any time point. As noted above, there was substantial attrition and differential loss to follow-up.	
Chronic Migraine: OnabotulinumtoxinA (BoNTA) versus Amitriptyline									
Responders: Percent of patients with ≥ 50% reduction in the frequency of pain days	12 weeks	1 RCT (Magalhaes 2010)	N=72	Yes[1] (-1)	Unknown	No	Yes (-1)	RR 0.9 (95% CI 0.1, 8.0) Conclusion: There were no differences between groups	⊕⊕◯◯ LOW
Responder: Percent of patients with ≥3 point reduction in pain intensity				Yes[1] (-1)	Unknown	No	Yes (-1)	RR 1.1 (95% CI 0.3, 3.8). Conclusion: There were no differences between groups	⊕⊕◯◯ LOW

MIDAS = Migraine Disability Assessment Scale, greater number of days, greater disability, HIT-6 = Headache Impact Test-6, MIQ = Migraine Impact Questionnaire

* Unless otherwise specified, analyses are based on baseline number of randomized participants.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size.

5.1.3. Strength of Evidence Summary: Efficacy of Acupuncture versus Active Control: Chronic Migraine

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Acupuncture vs. Usual Care									
Responders Proportion with ≥50% reduction in *any, mild, and moderate/ severe headache days* from baseline	36 wks.	1 RCT (Vickers 2004)	301	Yes[1] (-1)	Unknown	Yes[4] (-1)	No	Any headache days: RR 2.0 (95% CI 1.3, 3.2) RD 15.4% (95% CI 6.2%, 24.7%) At least mild headache days: RR 1.9 (95% CI 1.3, 2.9) RD 16.9% (95% CI 7.2%, 26.6%) Moderate/Severe headache days: RR 1.5 (95% CI 1.1, 2.1) RD 12.7% (95% CI 2.2%, 23.2%) Conclusion: Statistically greater improvement with acupuncture vs. usual care for all three measures 36 weeks post-treatment.	⊕⊕◯◯ LOW
Responders Proportion with ≥35% reduction in *headache days* from baseline				Yes[1] (-1)	Unknown	Yes[4] (-1)	No	RR 1.7 (95% CI 1.3, 2.2) RD 21.9% (95% CI 11.0%, 32.8%) Conclusion: Statistically greater improvement with acupuncture vs. usual care 36 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in any, mild or moderate/ severe *headache days* per month (adjusted for baseline score)				Yes[1] (-1)	Unknown	Yes[4] (-1)	No	Any headache days: MD 1.8 (95% CI 0.6, 2.9) At least mild headache days: MD 1.6 (95% CI 0.5, 2.6) Moderate/Severe headache days: MD 1.2 (95% CI 0.4, 2.1) Conclusion: Statistically greater improvement with acupuncture vs. usual	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								care for all three measures 36 weeks post-treatment.	
Chronic Migraine: Acupuncture vs. Topiramate									
Responders Proportion with ≥50% reduction in *any or moderate/ severe headache days* from baseline	4 wks.	1 RCTs (Yang 2011)	66	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Any headache days: RR 4.2 (95% CI 1.8, 9.8) RD 48.5% (95% CI 28.0%, 69.0%) Moderate/Severe headache days: RR 2.5 (95% CI 1.4, 4.3) RD 45.5% (95% CI 24.0%, 66.9%) Conclusion: Statistically greater improvement with acupuncture vs. topiramate for both measures 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *any or moderate/ severe headache days* per month				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Any headache days: MD 2.8 (95% CI 1.2, 4.4) Moderate/Severe headache days: MD 2.7 (95% CI 1.1, 4.3) Conclusion: Statistically greater improvement with acupuncture vs. topiramate for both measures 4 weeks post-treatment.	⊕⊕◯◯ LOW
Migraine Disability Assessment (MIDAS)*				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD 12.6 (95% CI 7.7, 17.5) Conclusion: Statistically greater improvement with acupuncture vs. topiramate 4 weeks post-treatment; it is unclear if this difference is clinically meaningful.	⊕⊕◯◯ LOW

*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 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; Consistency is unknown for single trials

3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.1.4. Strength of Evidence Summary: Efficacy of Manual Therapy/Manipulation versus Active Control: Chronic Migraine

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Spinal Manipulation Therapy (SMT) vs. Amitriptyline									
Responders Proportion with >20%, >40%, and >60% reduction in HI scores* from baseline	4 wks.	1 RCT (Nelson 1998)	108	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	<u>>20% reduction in HI score</u> RR 1.7 (95% CI 1.2, 2.4) RD 30.1% (95% CI 12.4%, 47.9%) <u>>40% reduction in HI score</u> RR 1.7 (95% CI 1.1, 2.6) RD 24.3% (95% CI 6.0%, 42.7%) <u>>60% reduction in HI score</u> RR 1.4 (95% CI 0.6, 3.1) RD 6.4% (95% CI -8.4%, 21.2%) <u>Conclusion</u>: Statistically greater proportion of patients achieved >20% and >40%, but not >60%, reduction in HI scores with SMT vs. amitriptyline 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *<u>percentage of days per month</u>* with headache				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD 3.6% (95% CI -6.8%, 14.0%) <u>Conclusion</u>: No statistical difference between SMT and amitriptyline at 4 weeks post-treatment.	⊕⊕◯◯ LOW

*Headache Index (HI) scores: The weekly sum of each patients headache pain score (rated on a 0-10 scale) on the days they report having a headache.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.1.5. Strength of Evidence Summary: Efficacy of Transcranial Magnetic Stimulation versus Sham: Chronic Migraine

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Transcranial Magnetic Stimulation (TMS) vs. SHAM*									
Responders Proportion with >50% reduction in *migraine attacks* from baseline	4 wks.	1 RCT (Misra 2013)	95	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	RR 2.4 (95% CI 1.3, 3.2) RD 45.4% (95% CI 27.7%, 63.1%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Responders Proportion with >50% improvement in *headache severity†* from baseline				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	RR 2.8 (95% CI 1.7, 4.6) RD 49.5% (95% CI 32.1%, 67.0%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *migraine attacks per month* from baseline				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD -3.7 (95% CI -6.07, -1.33) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in *migraine attacks per 2 weeks* from baseline	8 wks.	1 RCT (Teepker 2010)	27	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD -0.91 (95% CI -4.27, 2.46) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Reduction in *migraine days per 8 weeks*				Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD -3.7 (95% CI -10.1, 2.8) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Functional disability rating of normal or mild§	4 wks.	1 RCT (Misra 2013)	93	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	RR 4.4 (95% CI 2.2., 9.1) RD 49.9% (95% CI 32.7%, 67.1%) Conclusion: Statistically greater improvement with high-frequency TMS vs. sham 4 weeks post-treatment.	⊕⊕◯◯ LOW

*Results could not be pooled due to heterogeneity in patient populations and treatment regimens, variation in the definition of primary outcomes and differences in study quality.

†Headache severity: pain on 0-100 VAS, considering frequency and average severity.

§Functional disability was graded on a 0 to 4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe impairment of activities of daily living (ADL), 4 = inability to perform ADL requiring bed rest) and recorded by the patient in a daily headache diary.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.2. Strength of Evidence Summary: Chronic Tension-Type Headache Efficacy Results

5.2.1. Strength of Evidence Summary: Efficacy of OnabotulinumtoxinA (BoNTA) versus Placebo: 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 : BoNTA vs. Placebo									
Percent of patients with ≥ 25% reduction in pain intensity	4, 8 weeks (short term)	1 RCT (Schmitt 2001)	N = 59	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	4 weeks: BoNTA 36.7%, placebo 27.6%; RR 1.3, 95% CI 0.6, 2.8 8 Weeks: BoNTA 50.0%, placebo 31.0%; RR 1.3, 95% CI 0.6, 2.8 Conclusion: Although more patients the BoNTA experienced **≥ 25% reduction in pain intensity,** results did not reach statistical significance**.** Sample size is small.	⊕○○○ INSUFFICIENT
Percent of patients with ≥ 45% reduction in pain intensity	12 weeks	1 RCT (Padberg 2004)	N = 40	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	12 Weeks: BoNTA 31.6%, placebo 14.3%; RR 1.3, 95% CI 0.6, 2.8 Conclusion: Although more patients the BoNTA experienced **≥ 45% reduction in pain intensity,** results did not reach statistical significance**.** Sample size is small.	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Reduction in % of *HA days* per month	12 weeks	1 RCT (Padberg 2004)	N = 40	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	BoNTA 12±20%, placebo 5±14%; MD: 7.0, 95% CI: -4.0, 18.0 Conclusion: Although the BoNTA group had a greater percent reduction in HA days, statistical significance wasn't reached; small sample size is noted.	⊕○○○ INSUFFICIENT
Reduction in mean *HA days* per month	4 weeks, ≥ 12 weeks	2 RCTs (Hamdy 2009, Kokoska 2004)	N = 68	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	4 weeks: (1 trial, N = 28(MD 3.22 (95% CI -4.84, -1.60 (1 RCT, (n= 28)) 12-24 weeks: Pooled MD-2.98, 95% CI -5.96, -0.01 (2 RCTS N = 68) Conclusion: BoNTA may be associated with fewer HA days; studies were small and at moderately high risk of bias.	⊕○○○ INSUFFICIENT
Functional Measure: Mean HDI Scores†	4, 12 weeks	1 RCTs (Hamdy 2009)	N = 28	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	4 weeks: MD -11.85 (-22.23, -1.47) 12 weeks: MD -18.28 (-31.11, -5.45) Conclusion: Mean HDI scores at 4 and 12 weeks were significantly lower in the BoNTA group, indicating improvement in function compared with placebo. The percent reduction in HDI score was greater in the BoNTA group (40.6%) compared with placebo group (6.6%) at 12 weeks	⊕○○○ INSUFFICIENT

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers.
† HDI = Henry Ford Hospital Headache Disability Inventory, scale 0-100 (worst); 16 point improvement may be considered clinically significant

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.2.2. 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
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	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[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.	⊕◯◯◯ INSUFFICIENT
	52 wks.			Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[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.	⊕◯◯◯ INSUFFICIENT
Reduction in headache *episodes* per month	4-6 wks.	2 RCTs (Tavola 1992, Karst 2000)	69	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	Pooled MD -1.94 (95% CI -6.74, 2.85) <u>Conclusion</u>: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	26-52 wks.	1 RCT (Tavola 1992)	30	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	Authors state that the frequency of headache episodes continued to decrease through 26 and 52 weeks post-	⊕◯◯◯ INSUFFICIENT

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

* 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 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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.2.3. Strength of Evidence Summary: Efficacy 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	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)	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				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] (-1)	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] (-1)	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
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	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								1.73 and median 0.13 (range, 0.00–7.25) (n=30); p=NS Conclusion: Insufficient evidence precludes firm conclusions.	

*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 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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.2.4. Strength of Evidence Summary: Efficacy of Manual Therapy/Manipulation versus Active Control: 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: Manual Therapy (MT)/Manipulation vs. Usual Care									
Responders Proportion with >50% reduction in *headache days per 2 weeks* from baseline	18 wks.	1 RCT (Castien 2011)	82	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	RR 2.0 (95% CI 1.3, 3.0) RD 41.0% (95% CI 21.0%, 61.1%) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Reduction in number of *headache days per 2 weeks*				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD 4.9 (95% CI 2.98, 6.95) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Impact Test (HIT-6)				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD 5.0 (95% CI 1.16, 9.02) Conclusion: Statistically and clinically* greater improvement with MT vs. usual care 18 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Disability Inventory (HDI)				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD 10.1 (95% CI 0.64, 19.5) Conclusion: Statistically greater improvement with MT vs. usual care 18 weeks post-treatment; however, the difference did not meet the author-defined MCID of ≥16 point reduction.	⊕⊕◯◯ LOW

*The Minimal Clinically Important Difference (MCID) as defined by the authors was a >2.3-point decrease on the HIT-6.

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.2.5. Strength of Evidence Summary: Efficacy of Trigger Point Injections versus Sham: 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: Trigger Point Injections (TPI) vs. Sham									
Reduction in number of *headache days* per month	12 wks.	1 RCT (Karadas 2013)	48	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	MD 11.2 (95% CI 9.2, 13.2) Conclusion: Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

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; Consistency is unknown for single trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.3. Strength of Evidence Summary: Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache Efficacy Results

5.3.1. Strength of Evidence Summary: Efficacy of OnabotulinumtoxinA (BoNTA) versus Placebo: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)									
Responders Percent of patients with ≥ 50 % reduction frequency of headache days	24 weeks	1 RCT (Mathew 2005)	N = 355	Yes[1] (-1)	Unknown	Yes[4] (-1)	No	BoNTA 40.3%, Placebo 25.3% RR 1.6, 95% CI 1.1, 2.2) Conclusion: More BoNTA recipients had a ≥ 50 % reduction frequency of headache days compared with placebo.	⊕⊕◯◯ LOW
Change in mean number of headache-free days	24 weeks	2 RCTs (Mathew 2005, Silberstein 2005) †	N = 793	Yes[1] (-1)	Yes	Yes[4] (-1)	No	Pooled MD 0.74 (95% CI -1.51, 2.99). Conclusion: Based on pooled data, there was no difference between groups. A statistically significant difference favoring BoNTA at 24 weeks was reported in Mathew (MD 1.64, 95% CI 0.12, 3.16), however, it did not meet their threshold of 3 days as being clinically significant. There were no differences between treatments at any other time point in this trial. Data from Silberstein were not available at other time frames and data across placebo non-responders and placebo responders could not be pooled.	⊕⊕◯◯ LOW

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers.

† Both trials had a 30 day placebo run-in phase and identified placebo responders and placebo nonresponders. Pooling across these groups was done where data for Mathew, however Silberstein did not provide data on placebo responders, thus the pooled estimate in the table includes only placebo nonresponders for this trial .Placebo nonreponders comprised the majority (>75%) of the study population in the Silberstein trial.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.3.2. Strength of Evidence Summary: Efficacy of OnabotulinumtoxinA (BoNTA) versus Active Control (Topiramate): Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)									
Reduction in frequency of headache days per month	4 and 12 weeks	1 RCT (Cady 2011)	N =59	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[5] (-1)	Means 4 weeks: BoNTA -3.0 Topiramate -4.4 12 weeks: BoNTA -8.0 Topiramate – 8.1 Conclusion: No significant differences between the groups in the reduction of headache days per month; authors do not provide data to calculate effect size.	⊕⊕◯◯ LOW
Function: HIT-6 and MIDAS	12 weeks			Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[5] (-1)	HIT-6: BoNTA -6.3, Topiramate -6.0 MIDAS: BoNTA -38.5, Topiramate -26.7 Conclusion: No significant differences between the groups for either measure; authors do not provide sufficient data for effect size calculation.	⊕⊕◯◯ LOW

* Unless otherwise specified, analyses are based on baseline number of randomized participants versus completers.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.3.3. Strength of Evidence Summary: Efficacy of Massage versus Sham: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Daily Headache: Massage vs. Sham									
Reduction in number of *headache attacks per month* (adjusted for baseline scores)	3-9 wks.	1 RCT (Chatchawan 2014)	72	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	3 weeks: MD 2.6 (95% CI -0.04, 5.2) 9 weeks: MD 0.2 (95% CI -1.1, 0.78) Conclusion: No statistical difference between massage versus sham at 3 and 9 weeks post-treatment.	⊕⊕◯◯ LOW
Headache Disability Index (adjusted for baseline scores)				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	3 weeks: MD 1.9 (95% -6.3, 10.0) 9 weeks: MD 0.4 (95% CI -7.3, 8.0) Conclusion: No statistical difference between massage versus sham at 3 and 9 weeks post-treatment.	⊕⊕◯◯ LOW

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.4. Strength of Evidence Summary: Chronic Migraine Safety and Adverse Events Results

5.4.1. Strength of Evidence Summary: Safety of OnabotulinumtoxinA (BoNTA) versus Placebo: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Migraine									
Treatment-related adverse events (AE)†	24 weeks	2 RCTs (Aurora 2010 [PREEMPT 1], Denier 2010 [PREEMPT 2]	N =1379	No	No	Yes[4] (-1)	No	BoNTA 29.4 %, Placebo 12.7% Pooled RR 2.32 (95% CI 1.85, 2.91) Conclusion: Treatment-related adverse events over were twice as common in the BoNTA group compared to placebo	⊕⊕⊕○ MODERATE
Serious adverse events‡				No	No	Yes[4] (-1)	No	BoNTA 4.8 %, Placebo 2.3 % Pooled RR 2.07 (95% CI 1.15, 3.73) Conclusion: Serious adverse events were significantly more common in the BoNTA group compared to placebo.	⊕⊕⊕○ MODERATE
Treatment-Related Serious Adverse Events‡				No	No	Yes[4] (-1)	Yes[3] (-2)	BoNTA 0.15%, Placebo 0% Pooled RR 3.09 (95% CI 0.13, 75.71 Conclusion: Such events were rare; none were reported in PREEMPT 1 and only one event in the BoNTA reported for PREEMPT 2. There was likely insufficient power to detect such events; firm conclusions are not possible.	⊕○○○ INSUFFICIENT
Discontinuation Related to Adverse Events				No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 3.8%, Placebo 1.2 % Pooled RR 3.19 (95% CI 1.33, 7.05), Conclusion: Discontinuation of treatment related to AEs was 3 times more common for the BoNTA group compared to placebo	⊕⊕○○ LOW

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.
†Treatment-related AEs were defined as events reported by ≥2% of patients. For both Aurora 2010 and Diener 2010, the treatment-related adverse events that occurred at a rate ≥ 5% were neck pain (5.9% in Aurora 2010, 7.5% in Diener 2010) and muscle weakness (5.9% in Aurora 2010, 5.2 in Diener 2010) in the onabotulinumtoxinA group. Other common treatment-related AEs were eyelid ptosis, muscle tightness, and injection-site pain. The treatment-related serious AEs reported in the DoNTA group was migraine requiring hospitalization. No information was given describing what constituted a treatment-related serious adverse event
‡ Aurora 2010 and Diener 2010 did not provide detail on what constituted a serious adverse event

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.4.2. Strength of Evidence Summary: Safety of OnabotulinumtoxinA (BoNTA) versus Active Control: Chronic Migraine

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Drug-related adverse events or possible/probable drug – related adverse events†	36 weeks	1 RCT (Mathew 2009)	N=60	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Drug-related BoNTA 69.2% Topiramate 86.2% RR 0.8, 95% CI 0.6, 1.1 Possible/probable drug-related BoNTA 84.6% Topiramate 89.7% RR 0.9, 95% CI 0.8, 1.2 Conclusion: Although not statistically different, fewer BoNTA patients experienced drug-related AEs compared with topirimate recipients; sample size may preclude detection of statistical differences. Differential attrition between treatment groups and substantial loss to follow-up should be considered when interpreting this finding. Data available for the BoNTA and topiramate groups respectively: 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks.	⊕⊕◯◯ LOW
Discontinuation Related to Adverse Events‡				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	BoNTA 7.7% Topiramate 24.1% RR 0.3, 95% CI 0.1, 1.4 Conclusion: Discontinuation of treatment was not statistically different, however fewer BoNTA recipients discontinued treatment than topiramate recipients; sample size may be a factor.	⊕⊕◯◯ LOW
Chronic Migraine: OnabotulinumtoxinA (BoNTA) versus Amitriptyline									
Injection site pain	12 weeks	1 RCT (Magalhaes 2010)	N = 72	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	BoNTA 35.0% vs amitriptyline 0.0%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
								Conclusion: More BoNTA recipients experienced injection site pain;	
Edema				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	BoNTA 14.0% vs amitriptyline 0.0% Conclusion: More BoNTA recipients experienced injection edema.	⊕⊕◯◯ LOW

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

†The most common (≥3 events) drug-related adverse events reported on the BoNTA group were weakness in eyebrow/eyelids, weakness in forehead/neck, paresthesias, pain in head, and sleepiness (including tiredness and fatigue) and dizziness. Adverse events reported in the topiramate group were sleepiness (including tiredness and fatigue) and dizziness, depression/mood disturbance, appetite/weight loss, cognitive deficits, night sweats, dry mouth/thirst, blurred vision/vision problems

‡ Mathew 2009 did not provide information on what constituted AEs that caused discontinuation

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.4.3. Strength of Evidence Summary: Safety of Acupuncture versus Active Control: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Acupuncture vs. Usual Care									
Serious adverse events	36 wks.	1 RCT (Vickers 2004)	301	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	No serious adverse events occurred in either group; 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				Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	0.6% (1/161) vs. 0% (0/140) Conclusion: Although no statistical difference between groups, it is unclear whether there was sufficient sample size to detect a statistical difference.	⊕◯◯◯ INSUFFICIENT
Headache				Yes[1] (-1)	Unknown	Yes[4] (-1)	No	2.5% (4/161) vs. 0% (0/140) Conclusion: No statistical difference between groups; it is unclear whether sample size played a role.	⊕⊕◯◯ LOW
Chronic Migraine: Acupuncture vs. Topiramate									
Serious adverse events	4 wks.	1 RCTs (Yang 2011)	66	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	No serious adverse events occurred in either group; 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
Death				Yes[1] (-1)	Unknown	No	Yes[3] (-2)	No deaths occurred in either group.	⊕◯◯◯

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								Conclusion: Small sample size makes the detection of rare events difficult; insufficient evidence preclude firm conclusions.	INSUFFICIENT
Discontinuation due to adverse events				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	0% (0/33) vs. 9% (3/33) Conclusion: No statistical difference between groups; small sample size may have precluded detection of a statistical difference.	⊕⊕◯◯ LOW
Any side effect				Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RR 0.1 (95% CI 0.02, 0.4) • Acupuncture: 6% (2/33); all due to local insertion of needles (pain, paresthesia, ecchymosis) • Topiramate: 66% (22/33); to include paresthesia (48%), difficulty with memory (36%), dyspepsia (36%), fatigue (24%), dizziness (21%), somnolence (18%), and nausea (12%) Conclusion: Statistically fewer side-effects occurred following acupuncture versus topiramate.	⊕⊕◯◯ LOW

*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 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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.4.4. Strength of Evidence Summary: Safety of Manual Therapy/Manipulation versus Amitriptyline: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Spinal Manipulation Therapy (SMT) vs. Amitriptyline									
Discontinuation due to adverse events	4 wks.	1 RCT (Nelson 1998)	108	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	0% (0/77) vs. 11% (7/65) Conclusion: Lower frequency of withdrawal from study due to adverse events in the SMT versus amitriptyline group.	⊕⊕◯◯ LOW
Any adverse event				Yes[1] (-1)	Unknown	No	Yes[3] (-2)	Authors report that 58% (79/136) of patients who received amitriptyline (alone or in combination with acupuncture)† experienced medication side effects important enough to document (no further details provided); adverse effects following SMT were much more benign/mild, infrequent, and transitory (no further details provided). Conclusion: Lack of comparative data limits ability to draw conclusions.	⊕◯◯◯ INSUFFICIENT

*Author does not provided information on what constituted adverse events that caused discontinuation; specifics regarding any adverse events were not reported.

†The combination group (amitriptyline plus acupuncture) was excluded because it did not meet the inclusion criteria.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.4.5. Strength of Evidence Summary: Safety of Transcranial Magnetic Stimulation versus Sham: Chronic Migraine

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Chronic Migraine: Transcranial Magnetic Stimulation (TMS) vs. SHAM†									
Discontinuation due to adverse events	4 wks.	1 RCT (Misra 2013)	95	No	Unknown	Yes[4] (-1)	Yes[3] (-2)	2.1% (1/47) vs. 0% (0/48) Conclusion: Although no statistical difference between groups, it is unclear whether there was sufficient sample size to detect a statistical difference.	⊕○○○ INSUFFICIENT
Discomfort during treatment				No	Unknown	Yes[4] (-1)	Yes[3] (-1)	100% (47/47) vs. 15% (7/48) RR 6.9 (95% CI 3.5, 13.6) Conclusion: More patients receiving high-frequency TMS experienced discomfort during treatment (no to mild pain)‡ compared with sham.	⊕⊕○○ LOW
Discontinuation due to adverse events	8 wks	1 RCT (Teepker 2010)	27	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	7.1% (1/14) vs. 7.7% (1/13) RR 0.9 (95% CI 0.1, 13.4) Conclusion: No difference between groups; however evidence is insufficient to draw a firm conclusion	⊕○○○ INSUFFICIENT
Minor adverse events §				Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	• Assessment of visual motor threshold is uncomfortable: 35.7% (5/14) vs. 30.8% (4/13); RR 1.1 (95% CI 0.4, 3.4) • Headache: 0% (0/14) vs. 15.4% (2/13) • Vigorous dreams: 7.1% (1/14) vs. 0% (0/13) • Phonophobia: 7.1% (1/14) vs. 0% (0/13) • One event was reported in each group for the following: ○ Sitting is long-lasting and uncomfortable ○ Sleepiness ○ Amyostasia ○ Testiness	⊕○○○ INSUFFICIENT

Outcome*	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								7.1% (1/14) vs. 7.7% (1/13); RR 0.9 (95% CI 0.1, 13.4) Conclusion: No statistical differences between group; however, insufficient evidence precludes firm conclusions.	

*Authors do not provide information on what constituted adverse events that caused discontinuation; specifics regarding any adverse events were not reported.
†Results could not be pooled due to heterogeneity in patient populations and treatment regimens, variation in the definition of primary outcomes and differences in study quality.
‡Mean scores on the Faces Pain Scale were 3.10 ± 0.71 versus 0.14 ± 0.35, respectively, p=0.0001.
§It was unclear if patients could have more than one event.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.5. Strength of Evidence Summary: Chronic Tension-Type Headache Safety and Adverse Events Results

5.5.1. Strength of Evidence Summary: Safety of OnabotulinumtoxinA (BoNTA) versus Placebo: 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									
Treatment-related adverse events†	8 weeks	1 RCT (Silberstein 2006)	N=200	Yes[1] (-1)	Unknown	Yes[4] (-1)	No	BoNTA 34% , placebo 22.0% RR 1.5, 95% CI 0.9, 2.7 Conclusion: Treatment-related AEs were more in the BoNTA groups compared to placebo, though the differences were not statistically significant.	⊕⊕◯◯ LOW
Severe Adverse events‡	8 weeks	1 RCT (Silberstein 2006)	N=200	Yes[1] (-1)	Unknown	Yes[4] (-1)	No	BoNTA 13.6% , placebo 14.0% RR 1.0, 95% CI 0.5, 2.0 Conclusion: The frequency of severe AEs was similar between groups	⊕⊕◯◯ LOW
Pain at injection site	4, 8 , 12 weeks	3 RCTs (Schmitt 2001, Hamdy 2009, Padberg 2004)	N= 127	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	4 weeks: (1 RCT n =59) BoNTA 6.7% , placebo 3.4% RR 1.9, 95% CI 0.2, 20.2 8 Weeks: (1 RCT n =59) BoNTA 0 %, placebo 0 %; 12 weeks: (2 RCTS n = 68) BoNTA 18.1% , placebo 28.6% RR 0.65, 95% CI 0.3, 1.5 Conclusion: There were no statistical differences at any time.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Vertigo	4, 8 , 12 weeks	2 RCTs (Schmitt 2001, Padberg 2004)	N = 59 N= 40	Yes[1] (-1)	Unknown§	Yes[4] (-1)	Yes[3] (-1)	4 weeks: (1 RCT n =59) BoNTA 6.7% , placebo 3.4% RR 1.9, 95% CI 0.2, 20.2 8 Weeks: (1 RCT n =59) BoNTA 0 %, placebo 0 %; 12 weeks: (1 RCT n = 40) BoNTA 0%% , placebo 4.8% (n = 1) <u>Conclusion</u>: Vertigo was uncommon; firm conclusions are not possible given small samples sizes	⊕◯◯◯ INSUFFICIENT

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.
† The relationship of an adverse event to the treatment was assessed by the investigator. The most frequently reported treatment-related adverse events across all groups were neck pain and muscular weakness. Additional treatment-related adverse events reported in ≥ 3% of patients in any treatment group were neck rigidity, headache, pain dizziness, injection-site pain, dysphagia, paraethesia, asthenia, hypertonia, nausea, pharyngitis, and burning at the injection site.
‡ Serious adverse events were defined as an event that was fatal, life threatening, permanently disabling, resulted in hospitalization, or resulted in prolongation of existing hospitalization. Silberstein 2006 did not give details of specific serious adverse events that occurred in subjects.

§Data were only available from one study at 4 and 8 weeks (Schmitt) and one study at 12 weeks (Padberg); consistency across studies cannot be assessed.
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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.5.2. 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] (-1)	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

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.5.3. Strength of Evidence Summary: Safety of Manual Therapy/Manipulation 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: Manual Therapy (MT)/Manipulation vs. Usual Care									
Any adverse events	18 wks.	1 RCT (Castien 2011)	82	No	Unknown	Yes[4] (-1)	Yes[3] (-2)	No adverse events occurred in either treatment group; no other information was 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

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.5.4. Strength of Evidence Summary: Trigger Point Injections versus Sham: 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: Trigger Point Injections (TPI) vs. Sham									
Serious adverse events*	12 wks.	1 RCT (Karadas 2013)	48	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	No serious adverse events occurred in either group; 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
Minor side effects†				Yes[1] (-1)	Unknown	Yes[4] (-1)	No	• Injection site/injection pain: 12.5% (3/24) vs. 16.7% (4/24); RR 0.8 (95% CI 0.2, 3.0) • Dizziness: 8.3% (2/24) vs. 8.3% (2/24); RR 1.0 (95% CI 0.2, 6.5) • Back pain: 8.3% (2/24) vs. 12.5% (3/24); RR 0.7 (95% CI 0.1, 3.6) • Cervical muscle spasm: 0% (0/24) vs. 4.2% (1/24) • Any event: 29.2% (7/24) vs. 41.7% (10/24); RR 0.7 (95% CI 0.3, 1.5) Conclusion: No statistical difference between the groups; small sample size	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Outcome
								may have precluded detection of a statistical difference.	

*Authors do not provided information on what constituted a serious adverse event.

†It was unclear if patients could have more than one event.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care are considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.6. Strength of Evidence Summary: Chronic Daily Headache/Co-existent Chronic Migraine and Tension Headache: Safety and Adverse Events Results

5.6.1. Strength of Evidence Summary: Safety of OnabotulinumtoxinA (BoNTA) versus Placebo: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)									
Treatment-related adverse events †	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	No	BoNTA 56.8% , placebo 22% RR 2.47, 95% CI 1.98, 3.09 Conclusion: Treatment-related AEs over two times more common in the BoNTA groups compared to placebo.	⊕⊕⊕◯ MODERATE
Dyspahgia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 3.3% , placebo 0.3% RR 7.30 (1.40, 38.04) Conclusion: Dysphagia occurred in 3.3% of BoNTA recipients; it was significantly more common with BoNTA than placebo.	⊕⊕◯◯ LOW
Neck Pain	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 19.1% , placebo 1.1% RR 14.66 (95% CI 5.47, 39.27) Conclusion: Neck pain occurred in 19% of BoNTA recipients and was more common compared with placebo	⊕⊕◯◯ LOW
Neck Rigidity	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 9.0 % , placebo 0.8% RR 7.96 (95% CI 1.60, 39.66 Conclusion: Neck rigidity occurred in 9.0% of BoNTA recipients ; it was significantly more common with BoNTA than placebo	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Shoulder/arm pain	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 5.5% , placebo 0.5 % RR 8.88 (95% CI 2.11, 37.40 Conclusion: Shoulder or arm pain occurred in 5.5% of BoNTA recipients; it was significantly more common with BoNTA than placebo.	⊕⊕◯◯ LOW
Muscle Weakness	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 24% , placebo 0.3% RR 53.72 (95% CI 10.82, 266.73), Conclusion:Muscle weakness occurred in 24% of BoNTA patients; it was significantly more common with BoNTA than placebo	⊕⊕◯◯ LOW
Hyperesthesia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	BoNTA 6.0% , placebo 1.4% RR 3.91 (95% CI 1.50, 10.24 Conclusion: Hyperesthesia occurred in 6.0% of BoNTA recipients and was more common compared with placebo.	⊕⊕◯◯ LOW
Headache, Injection site pain, hypertonia	24 weeks	2 RCT (Mathew 2005, Silberstein 2005)	N= 1057	No	No	Yes[4] (-1)	Yes[3] (-1)	Headache: BoNTA 6.9 % , placebo 5.3% RR 1.34, 95% CI 0.78, 2.30 Injection site pain: BoNTA 5.6% , placebo 3.9% RR 1.16 (0.63, 2.14) Hypertonia: BoNTA 7.2% , placebo 1.4 % RR 4.95 (95% CI 0.72, 34.09) Conclusion: There were no statistical differences between groups for these adverse events	⊕⊕◯◯ LOW

* Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† In Mathew 2005, the most frequently reported adverse events for the BoNTA group were muscular weakness, neck pain, headache, and blepharoptosis. The most frequently reported adverse events for the placebo group were headache and injection-site hemorrhage. Additional treatment-related adverse events reported by ≥ 3 patients in either group were neck rigidity, shoulder/arm pain, injection site pain, pain, face pain, dysphagia, muscular weakness, hypertonia, hyperesthesia, dizziness, pharyngitis, skin tightness, and visual disturbance. In Silberstein 2005, the relationship of adverse events to the study treatment was assessed by the investigator. The most frequently reported treatment related AEs in the BoNTA group were muscular weakness (in areas of injection sites), neck pain, neck rigidity, injection pain, hypertonia, headache, shoulder/arm pain, and hypesthesia. The most frequently reported adverse events in the placebo group were injection-site pain and headache. Additional treatment related AEs reported by ≥ 3% of patients in either treatment group were blepharoptosis, dysphagia, asthenia, back pain, injection-site stinging, and migraine

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.6.2. Strength of Evidence Summary: Safety of OnabotulinumtoxinA (BoNTA) versus Topirimate: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)									
Nausea†	12 weeks	1RCT (Cady 2011)	N= 59	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	BoNTA 59.1% , topiramate 27.3% RR: 2.2, 95% CI 1.0, 4.7 Conclusion: Nausea was two times more common with BoNTA than with topirimate	⊕⊕◯◯ LOW
Mild fatigue	12 weeks	1RCT (Cady 2011)	N= 59	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	BoNTA 72.7%, topiramate 68.2%, RR: 1.0, 95% CI 0.7, 1.6 Conclusion: There was no difference between groups.	⊕⊕◯◯ LOW

*Safety events were reported based on numbers of events and denominators provided by authors; patient may have experienced more than 1 event.

† The most frequently reported adverse events for both groups were mild fatigue, nausea, difficulty concentrating or with memory, and mood swings. Cady 2011 did not give details on additional adverse events.

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.6.3. Strength of Evidence Summary: Safety of Massage versus Sham: Chronic Daily Headache (Co-existent Chronic Migraine and Tension-Type Headache)

Outcome	Follow-up	RCTs	N*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion*	Quality
Chronic Daily Headache: Massage vs. Sham									
Minor fever, mild soreness, and other discomfort	3-9 wks.	1 RCT (Chatchawan 2014)	72	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	17% (6/36) vs. 14% (5/36) RR 1.2 (95% CI 0.4, 3.6) Conclusion: No statistical difference between the massage and the sham ultrasound group.	⨁⨁◯◯ LOW

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 for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harms and/or wide confidence intervals noted. If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice.
4. Comparisons of an intervention to placebo or usual care is considered indirect;
5. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.7. Strength of Evidence Summary: Differential Efficacy and Harms

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 diagnosis; Age; Sex; Chronicity	Headache score	36 wks.	1 RCT (Vickers 2004)	301	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	Yes (-1)[5]	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). Improvements following acupuncture compared with usual care were larger for patients with a migraine (4.9; 95% CI 2.4, 7.5; n=284) versus a CTTH (1.1, 95% CI -2.4, 4.5); n=17) diagnosis; however no interaction was seen and the small number of CTTH patients may have precluded an effect in this population. Age, sex and chronicity did not modify the treatment effect.	⊕○○○ INSUFFICIENT
Chronic Migraine: Acupuncture versus Topiramate											
Baseline headache days; various other demographic and headache characteristics	≥50% reduction from baseline in moderate/ severe headache days	36 wks.	1 RCT (Yang 2013)	66	Yes[4] (-1)	No	No	Yes[3] (-1)	Yes (-1)[5]	Baseline headache days (any and moderate/severe) was found to modify treatment effect such that patients with higher (≥20 days/mo.) as compared with lower (<20 days/mo.) frequency showed significantly greater	⊕○○○ INSUFFICIENT

Exposure	Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HTE-related	Conclusion	Quality
										improvement with acupuncture but not with topiramate; all other variables explored did not modify the treatment effect	
Chronic Tension Type Headache: Manual Therapy versus Usual Care											
Comorbid migraine	Headache days	18 wks.	1 RCT (Castien 2011)	82	No	No	Yes[4] (-1)	Yes[3] (-1)	Yes (-1)[6]	No differential effect of treatment was seen for the subgroup of patients with comorbid migraine versus without migraine: mean difference in reduction in headache frequency was 5.1 days (95% CI 1.1, 9.2) versus 6.3 days (95% CI 4.2, 8.5), respectively; no formal test for interaction was performed.	⊕◯◯◯ INSUFFICIENT

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 for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Comparisons of an intervention to placebo or usual care is considered indirect.

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

5. Subgroup analysis not preplanned or unknown
6. Statistical test for homogeneity or interaction not performed

5.8. Strength of Evidence Summary: Cost Effectiveness

BoNTA versus Placebo for Chronic Migraine

One poor to moderate quality and one very poor quality cost-utility analysis compared BoNTA vs. Placebo. The higher quality UK study suggests that BoNTA may be cost-effective at a willingness to pay threshold of €20,000 to €30,000/QALY). ICERs were higher for patients who had received three or more prior treatments. Based on sensitivity analysis, ICERs ranged from £4945/QALY (if no effect of placebo on # of HA days to £29,175/QALY when utilities for both BoNTA and placebo were the same in a given health state.

Primary limitations include lack of comparison to an active agent such as topiramate, lack of consideration of indirect costs (e.g., absenteeism, lost productivity, emergency department visit), unclear modeling of harms and lack of clear information on long-term (beyond 24 weeks) benefits and harms of BoNTA. Given the chronic nature of CM, it is assumed that continued treatment may needed, however the circumstances for continuation or discontinuation are not clear.

Acupuncture versus Usual Care for Chronic Migraine

One poor to moderate quality CUA 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. 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, lack of consideration of indirect costs (e.g., absenteeism, lost productivity, emergency department visit), 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 needed, however the circumstances for continuation or discontinuation are not clear. Lack of clarity regarding the components of usual care and differences between the UK and US medical systems make it difficult to generalize this study's finding to the U.S. healthcare system.

References

1. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

2. PubChem Compound Database, CID=8223. National center for Biotechnology Information.

3. Summary Health Statistics, National Interview Survery, 2015 Table A-5a. National Center for Health Statistics: CDC.

4. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia : an international journal of headache 1988;8 Suppl 7:1-96.

5. Aura. National Headache Foundation, 2007.

6. Coexisting Migraine and Tension-Type Headaches. National Headache Foundation, 2007.

7. In: Heath CAfDaTi, ed. Ottawa (ON): Canadian Agency for Drugs and Technologies in Heath 2015 Jul.

8. Brain Stimulation Therapies. National Institute of Health, 2016.

9. The International Classification of Headache Disorders 3rd Edition (Beta version). International Headache Society; 2016.

10. The Latest on Headache Relief. Preston, J. Oregon Health and Science University 2016. Available at: http://www.ohsu.edu/health/for-healthcare-professionals/newsletter/migraine-or-headache.php.

11. Physical Therapy and Migraine Headaches. Michigan Headahce and Neurological Institute, 2017.

12. Repetitve Transcranial Magnetic Stimulation (rTMS). King's College London; 2017.

13. Tension Migraine. Health Union, LLC, 2017.

14. Triptans Medications for Migraines: An Introduction. Health Union, LLC, 2017.

15. Administration USFaD. De Novo Classification Request for Cerena Transcranial Magnetic Stimulator (TMS) Device. In: Administration USFaD, ed.2013.

16. Administration USFaD. BOTOX Cosmetic Prescribing Information. In: Administration USFaD, ed.2015.

17. Administration USFaD. Botox Prescribing Information In: Administration USFaD, ed.2016.

18. Administration USFaD. Medication Guide: BOTOX and BOTOX Cosmetic for Injection. In: Administration USFaD, ed.2016.

19. Ahmed F, Parthasarathy R, Khalil M. Chronic daily headaches. Annals of Indian Academy of Neurology 2012;15:S40-50.

20. Alvarez DJ, Rockwell PG. Trigger points: diagnosis and management. American family physician 2002;65:653-60.

21. Andree C, Vaillant M, Barre J, et al. Development and validation of the EUROLIGHT questionnaire to evaluate the burden of primary headache disorders in Europe. Cephalalgia : an international journal of headache 2010;30:1082-100.

22. Andree C, Vaillant M, Rott C, Katsarava Z, Sandor PS. Development of a self-reporting questionnaire, BURMIG, to evaluate the burden of migraine. The journal of headache and pain 2008;9:309-15.

23. Ashkenazi A, Blumenfeld A, Napchan U, et al. Peripheral nerve blocks and trigger point injections in headache management - a systematic review and suggestions for future research. Headache 2010;50:943-52.

24. Aurora SK, Dodick DW, Diener HC, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta neurologica Scandinavica 2014;129:61-70.

25. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia : an international journal of headache 2010;30:793-803.

26. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache 2011;51:1358-73.

27. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Annals of neurology 2006;59:652-61.

28. Barron R, Carlsen J, Duff SB, Burk C. Estimating the cost of an emergency room visit for migraine headache. Journal of Medical Economics 2003;6:43-53.

29. Batty AJ, Hansen RN, Bloudek LM, et al. The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK. J Med Econ 2013;16:877-87.

30. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry 1961;4:561-71.

31. Beithon J GM, Johnson K, Kildahl P, Krenik J, Liebow M, Linbo L, Myers C, Peterson S, Schmidt J, Swanson J. Diagnosis and Treatment of Headache. 11th ed: Institute for Clinical Systems Improvement 2013.

32. Bendtsen L. Drug and Nondrug Treatment in Tension-type Headache. Therapeutic advances in neurological disorders 2009;2:155-61.

33. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. European journal of neurology 2010;17:1318-25.

34. Bendtsen L, Jensen R. Tension-type headache. Neurologic clinics 2009;27:525-35.

35. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical care 1981;19:787-805.

36. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. Neurology 2006;66:545-50.

37. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression (or for chronic daily headaches)--clinical lessons. Headache 2006;46 Suppl 3:S144-6.

38. Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. Neurology 2007;68:1851-61.

39. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 2008;48:1157-68.

40. Biondi DM. Physical treatments for headache: a structured review. Headache 2005;45:738-46.

41. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. Headache 2010;50:1406-18.

42. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A. Procedures for administering botulinum toxin type A for migraine and tension-type headache. Headache 2003;43:884-91.

43. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. Jama 2004;291:965-73.

44. Bronfort G, Nilsson N, Haas M, et al. Non-invasive physical treatments for chronic/recurrent headache. The Cochrane database of systematic reviews 2004:Cd001878.

45. Bryans R, Descarreaux M, Duranleau M, et al. Evidence-based guidelines for the chiropractic treatment of adults with headache. Journal of manipulative and physiological therapeutics 2011;34:274-89.

46. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache 2015;55:21-34.

47. Burke A, Upchurch DM, Dye C, Chyu L. Acupuncture use in the United States: findings from the National Health Interview Survey. Journal of alternative and complementary medicine 2006;12:639-48.

48. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 2012;52:1456-70.

49. Cabyoglu MT, Ergene N, Tan U. The mechanism of acupuncture and clinical applications. The International journal of neuroscience 2006;116:115-25.

50. Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011;51:21-32.

51. Calandre EP, Hidalgo J, Garcia-Leiva JM, Rico-Villademoros F. Trigger point evaluation in migraine patients: an indication of peripheral sensitization linked to migraine predisposition? European journal of neurology 2006;13:244-9.

52. Carlsson J, Augustinsson LE, Blomstrand C, Sullivan M. Health status in patients with tension headache treated with acupuncture or physiotherapy. Headache 1990;30:593-9.

53. Castells ET, Delgado EV, Escoda CG. Use of amitriptyline for the treatment of chronic tension-type headache. Review of the literature. Med Oral Patol Oral Cir Bucal 2008;13:E567-72.

54. Castien RF, van der Windt DA, Grooten A, Dekker J. Effectiveness of manual therapy for chronic tension-type headache: a pragmatic, randomised, clinical trial. Cephalalgia : an international journal of headache 2011;31:133-43.

55. Cathcart S, Winefield AH, Lushington K, Rolan P. Stress and tension-type headache mechanisms. Cephalalgia : an international journal of headache 2010;30:1250-67.

56. Chaibi A, Russell MB. Manual therapies for primary chronic headaches: a systematic review of randomized controlled trials. The journal of headache and pain 2014;15:67.

57. Chaibi A, Saltyte Benth J, Tuchin PJ, Russell MB. Chiropractic spinal manipulative therapy for migraine: a study protocol of a single-blinded placebo-controlled randomised clinical trial. BMJ open 2015;5:e008095.

58. Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. The journal of headache and pain 2011;12:127-33.

59. Chatchawan U, Eungpinichpong W, Sooktho S, Tiamkao S, Yamauchi J. Effects of Thai traditional massage on pressure pain threshold and headache intensity in patients with chronic tension-type and migraine headaches. Journal of alternative and complementary medicine 2014;20:486-92.

60. WHO Official Position. Chmielnicki, Bartosz, 2014.

61. Clouse JC, Osterhaus JT. Healthcare resource use and costs associated with migraine in a managed healthcare setting. The Annals of pharmacotherapy 1994;28:659-64.

62. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. J Clin Epidemiol 2006;59:374-80.

63. Derogatis LR. The psychosocial adjustment to illness scale (PAIS). Journal of psychosomatic research 1986;30:77-91.

64. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia : an international journal of headache 2010;30:804-14.

65. Dodick DW. Clinical practice. Chronic daily headache. The New England journal of medicine 2006;354:158-65.

66. Dodick DW, Mauskop A, Elkind AH, et al. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 2005;45:315-24.

67. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50:921-36.

68. Dommerholt J, Mayoral del Moral O, Grobli C. Trigger Point Dry Needling. The Journal of Manual and Manipulative therpay 2006;14:E70-E87.

69. Ernst E. The safety of massage therapy. Rheumatology 2003;42:1101-6.

70. Estemalik E, Tepper S. Preventive treatment in migraine and the new US guidelines. Neuropsychiatric disease and treatment 2013;9:709-20.

71. Fernandez-de-Las-Penas C, Courtney CA. Clinical reasoning for manual therapy management of tension type and cervicogenic headache. The Journal of manual & manipulative therapy 2014;22:44-50.

72. Fernandez-de-las-Penas C, Cuadrado ML, Arendt-Nielsen L, Simons DG, Pareja JA. Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia : an international journal of headache 2007;27:383-93.

73. Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. The International journal of neuroscience 2005;115:1397-413.

74. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache 2008;48:201-9.

75. Fumal A, Schoenen J. Tension-type headache: current research and clinical management. The Lancet Neurology 2008;7:70-83.

76. Garza I, Schwedt TJ. Diagnosis and management of chronic daily headache. Seminars in neurology 2010;30:154-66.

77. Gazerani P, Staahl C, Drewes AM, Arendt-Nielsen L. The effects of Botulinum Toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization. Pain 2006;122:315-25.

78. Giggins OM, Persson UM, Caulfield B. Biofeedback in rehabilitation. Journal of neuroengineering and rehabilitation 2013;10:60.

79. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743-800.

80. Groppa S, Oliviero A, Eisen A, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2012;123:858-82.

81. Guy W. ECDEU Assessment Manual for Psychopharmacology Rockville, Maryland: U.S. Department of Health, Education, and Welfare; 1976.

82. Hamdy SM, Samir H, El-Sayed M, Adel N, Hasan R. Botulinum toxin: could it be an effective treatment for chronic tension-type headache? The journal of headache and pain 2009;10:27-34.

83. Hamel E. Serotonin and migraine: biology and clinical implications. Cephalalgia : an international journal of headache 2007;27:1293-300.

84. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-5.

85. Hamilton M. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry 1960;23:56-62.

86. Hao XA, Xue CC, Dong L, Zheng Z. Factors associated with conflicting findings on acupuncture for tension-type headache: qualitative and quantitative analyses. Journal of alternative and complementary medicine 2013;19:285-97.

87. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

88. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://handbook.cochrane.org.2011.

89. Holroyd KA, Stensland M, Lipchik GL, Hill KR, O'Donnell FS, Cordingley G. Psychosocial correlates and impact of chronic tension-type headaches. Headache 2000;40:3-16.

90. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Archives of internal medicine 1999;159:813-8.

91. Ibanez-Garcia J, Alburquerque-Sendin F, Rodriguez-Blanco C, et al. Changes in masseter muscle trigger points following strain-counterstrain or neuro-muscular technique. Journal of bodywork and movement therapies 2009;13:2-10.

92. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. Jama 2012;307:1736-45.

93. Jacobson GP, Ramadan NM, Aggarwal SK, Newman CW. The Henry Ford Hospital Headache Disability Inventory (HDI). Neurology 1994;44:837-42.

94. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. The Lancet Neurology 2008;7:354-61.

95. Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. Headache 1998;38:295-302.

96. Jones LN. Strain and Counter-Strain. Amercain Acadamey of Osteopathy; 1981.

97. Kaniecki RG. Tension-type headache. Continuum 2012;18:823-34.

98. Karadas O, Inan LE, Ulas U, Odabasi Z. Efficacy of local lidocaine application on anxiety and depression and its curative effect on patients with chronic tension-type headache. European neurology 2013;70:95-101.

99. Karst M, Rollnik JD, Fink M, Reinhard M, Piepenbrock S. Pressure pain threshold and needle acupuncture in chronic tension-type headache--a double-blind placebo-controlled study. Pain 2000;88:199-203.

100. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Current pain and headache reports 2012;16:86-92.

101. Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain 1985;23:345-56.

102. Kim M, Danielsson A, Ekelund A, et al. Botulinum toxin type A for Prophylactic Treatment of Chronic Migraine: Västra Götalandsregionen, Sahlgrenska universitetssjukhuset, HTA-centrum; 2014.

103. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. The Lancet Neurology 2003;2:145-56.

104. Kokoska MS, Glaser DA, Burch CM, Hollenbeak CS. Botulinum toxin injections for the treatment of frontal tension headache. The journal of headache and pain 2004;5:103-9.

105. Headache. Clevelend Clinic Foundation, 2010.

106. Kwek AB, Tan EK, Luman W. Dysphagia as a side effect of botulinum toxin injection. The Medical journal of Malaysia 2004;59:544-6.

107. Lefaucheur JP. Methods of therapeutic cortical stimulation. Neurophysiologie clinique = Clinical neurophysiology 2009;39:1-14.

108. Legatt AD, Emerson RG, Epstein CM, et al. ACNS Guideline: Transcranial Electrical Stimulation Motor Evoked Potential Monitoring. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2016;33:42-50.

109. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of tension-type headache. The Cochrane database of systematic reviews 2016;4:Cd007587.

110. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for migraine prophylaxis. The Cochrane database of systematic reviews 2009:CD001218.

111. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. Neurology 2009;72:S3-7.

112. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. The Lancet Neurology 2010;9:373-80.

113. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML. Impact of NSAID and Triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2013;53:1548-63.

114. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology 2011;77:1465-72.

115. Lo MY, Lin JG, Wei Ong M, Sun WZ. Cerebral hemodynamic responses to acupuncture in migraine patients: a systematic review. Journal of traditional and complementary medicine 2013;3:213-20.

116. Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical neurology and neurosurgery 2010;112:463-6.

117. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. Neurology 2011;76:711-8.

118. Marcus DA, Scharff L, Mercer S, Turk DC. Nonpharmacological treatment for migraine: incremental utility of physical therapy with relaxation and thermal biofeedback. Cephalalgia : an international journal of headache 1998;18:266-72; discussion 42.

119. Martelletti P, Jensen RH, Antal A, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. The journal of headache and pain 2013;14:86.

120. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 2005;45:293-307.

121. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache 2009;49:1466-78.

122. Meissner K, Fassler M, Rucker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA internal medicine 2013;173:1941-51.

123. Millea PJ, Brodie JJ. Tension-type headache. American family physician 2002;66:797-804.

124. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. Journal of neurology 2013;260:2793-801.

125. Mizusawa H, Sakai F, Tsuj S. Clinical Practice Guideline for Chronic Headache 2013. Japanese Society of Neurology; 2013.

126. National Institute for Health and Care Excellence (NICE). Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Technology appraisal guidance. June 2012. Avaialble at: https://www.nice.org.uk/guidance/ta260.

127. National Institute for Health and Care Excellence (NICE). Diagnosis and management of headaches in young people and adults. Clinical Guideline 150. Methods, evidence and recommendations. September 2012. Accessed at: https://www.guideline.gov/summaries/summary/38444/headaches-diagnosis-and-management-of-headaches-in-young-people-and-adults.

128. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia : an international journal of headache 2010;30:599-609.

129. Nelson CF, Bronfort G, Evans R, Boline P, Goldsmith C, Anderson AV. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. Journal of manipulative and physiological therapeutics 1998;21:511-9.

130. NICE. Transcranial Magnetic Stimulation for Treating and Preventing Migraine: National Insitute for Health and Care Excellence; 2014.

131. Nicholson RA. Chronic headache: the role of the psychologist. Current pain and headache reports 2010;14:47-54.

132. Niere K, Quin A. Development of a headache-specific disability questionnaire for patients attending physiotherapy. Manual therapy 2009;14:45-51.

133. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. European journal of neurology 2012;19:155-62.

134. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia : an international journal of headache 2004;24:60-5.

135. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia : an international journal of headache 2004;24:675-80.

136. Petrusic I, Zidverc-Trajkovic J. Cortical spreading depression: origins and paths as inferred from the sequence of events during migraine aura. Functional neurology 2014;29:207-12.

137. Posadzki P, Ernst E. Spinal manipulation: an update of a systematic review of systematic reviews. The New Zealand medical journal 2011;124:55-71.

138. Posadzki P, Ernst E. Spinal manipulations for tension-type headaches: a systematic review of randomized controlled trials. Complementary therapies in medicine 2012;20:232-9.

139. Posadzki P, Ernst E. The safety of massage therapy: an update of a systematic review. Focus on Alternative and Complementary Therapies 2013;18:27-32.

140. Quinn C, Chandler C, Moraska A. Massage therapy and frequency of chronic tension headaches. American journal of public health 2002;92:1657-61.

141. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the

prophylaxis of episodic migraine headaches. Cephalalgia : an international journal of headache 2007;27:492-503.

142. Robbins MS, Kuruvilla D, Blumenfeld A, et al. Trigger point injections for headache disorders: expert consensus methodology and narrative review. Headache 2014;54:1441-59.

143. Robbins MS, Lipton RB. The epidemiology of primary headache disorders. Seminars in neurology 2010;30:107-19.

144. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2009;120:2008-39.

145. Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology 2007;68:484-8.

146. Ruggeri M. The cost effectiveness of Botox in Italian patients with chronic migraine. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2014;35 Suppl 1:45-7.

147. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 2001;41:658-64.

148. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 1998;50:466-70.

149. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and Management of Headache in Adults: A national clinical guideline. 2008 November. Available at: http://www.sign.ac.uk/pdf/sign107.pdf.

150. Shamliyan TA, Kane RL, Taylor FR. Migraine in Adults: Preventive Pharmacologic Treatments. Comparative Effectiveness Review No. 103. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I) AHRQ Publication No. 13-EHC068-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2013. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

151. Shan WS, Chi Ho CV. Acupuncture: filling the effectiveness gaps in Western medicine? The British journal of general practice : the journal of the Royal College of General Practitioners 2011;61:374-5.

152. Sherman KJ, Hogeboom CJ, Cherkin DC, Deyo RA. Description and validation of a noninvasive placebo acupuncture procedure. Journal of alternative and complementary medicine 2002;8:11-9.

153. Silberstein S, Diener HC, Lipton R, et al. Epidemiology, risk factors, and treatment of chronic migraine: a focus on topiramate. Headache 2008;48:1087-95.

154. Silberstein SD, Gobel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia : an international journal of headache 2006;26:790-800.

155. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clinic proceedings 2005;80:1126-37.

156. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:1818-26.

157. Snaith RP. The Hospital Anxiety And Depression Scale. Health and quality of life outcomes 2003;1:29.

158. Soderberg E, Carlsson J, Stener-Victorin E. Chronic tension-type headache treated with acupuncture, physical training and relaxation training. Between-group differences. Cephalalgia : an international journal of headache 2006;26:1320-9.

159. Soderberg EI, Carlsson JY, Stener-Victorin E, Dahlof C. Subjective well-being in patients with chronic tension-type headache: effect of acupuncture, physical training, and relaxation training. The Clinical journal of pain 2011;27:448-56.

160. Common Headache Disorders: Diagnosis and Management, Part II. AHC Media, 2009.

161. Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Anxiety and Depression in Tension-Type Headache: A Population-Based Study. PloS one 2016;11:e0165316.

162. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P. Headache disorders are third cause of disability worldwide. The journal of headache and pain 2015;16:58.

163. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology 2001;56:S20-8.

164. Tavola T, Gala C, Conte G, Invernizzi G. Traditional Chinese acupuncture in tension-type headache: a controlled study. Pain 1992;48:325-9.

165. Teepker M, Hotzel J, Timmesfeld N, et al. Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia : an international journal of headache 2010;30:137-44.

166. Toro-Velasco C, Arroyo-Morales M, Fernandez-de-Las-Penas C, Cleland JA, Barrero-Hernandez FJ. Short-term effects of manual therapy on heart rate variability, mood state, and pressure pain sensitivity in patients with chronic tension-type headache: a pilot study. Journal of manipulative and physiological therapeutics 2009;32:527-35.

167. Toward Optimized Practice (TOP) Headache Working Group. Primary care management of headache in adults: clinical practice guideline: 2nd edition. Edmonton AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org/cpgs/10065. 2016 September.

168. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. Jama 1994;271:1609-14.

169. Vernon H, Lawson G. Development of the headache activities of daily living index: initial validity study. Journal of manipulative and physiological therapeutics 2015;38:102-11.

170. Vickers AJ, Rees RW, Zollman CE, et al. Acupuncture for chronic headache in primary care: large, pragmatic, randomised trial. Bmj 2004;328:744.

171. Vickers AJ, Rees RW, Zollman CE, et al. Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis. Health Technol Assess 2004;8:iii, 1-35.

172. Vo AH, Satori R, Jabbari B, et al. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviation, space, and environmental medicine 2007;78:B113-8.

173. Waldie KE, Buckley J, Bull PN, Poulton R. Tension Headaches.

174. Wang Y, Xue CC, Helme R, Da Costa C, Zheng Z. Acupuncture for Frequent Migraine: A Randomized, Patient/Assessor Blinded, Controlled Trial with One-Year Follow-Up. Evidence-based complementary and alternative medicine : eCAM 2015;2015:920353.

175. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992;30:473-83.

176. Ware JE, Keller SD, Kosinski M. SF-36: Physical and mental health summary scales: A user's manual: Health Assessment Lab; 1994.

177. Weatherall MW. The diagnosis and treatment of chronic migraine. Therapeutic advances in chronic disease 2015;6:115-23.

178. Winter. Associations of socioeconomic status with migraine and non-migraine headache. Available at: http://journals.sagepub.com/doi/pdf/10.1177/0333102411430854 2011.

179. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical journal of pain 2013;29:982-7.

180. Yang CP, Chang MH, Liu PE, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. Cephalalgia : an international journal of headache 2011;31:1510-21.

181. Yin P, Gao N, Wu J, Litscher G, Xu S. Adverse events of massage therapy in pain-related conditions: a systematic review. Evidence-based complementary and alternative medicine : eCAM 2014;2014:480956.