Washington State Health Care Authority

Order of Scheduled Presentations:

Treatment of chronic migraine and chronic tension-type headache

	Name
1	
2	
3	

No requests to provide public comment on this technology review were received.

Washington State Health Care Authority

Agency medical director comments

Chronic migraines and chronic tension-type headaches

Shana Johnson, MD
HCA Medicaid Medical Director
Health Care Authority
May 19, 2017

Chronic headache

- Headache disorders are a leading cause of disability and diminished quality of life
- Common reason for patient visits in primary care, neurology, and emergency departments
- Variety of interventions may be used to manage chronic tension-type headache and migraines

2

Chronic migraine and chronic tension-type headache

What is the clinical effectiveness of interventions for chronic headaches?

- OnabotulinumtoxinA injection (BoNTA)
- Trigger point injections
- Transcranial magnetic stimulation
- Manipulation
- Acupuncture
- Massage

3

Chronic pain

Considerations when considering the clinical effectiveness of treatment options in chronic pain disorders

- Clinical significance of change in pain measure outcomes
- Functional outcomes
- Long-term follow-up; sustainability
- Impact of social and psychological stress
- Optimizing treatment for social and psychological stress

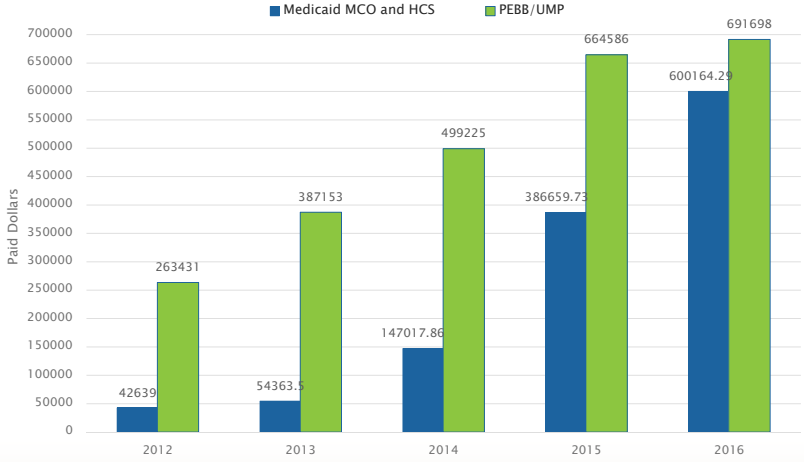
4

Agency medical director concerns

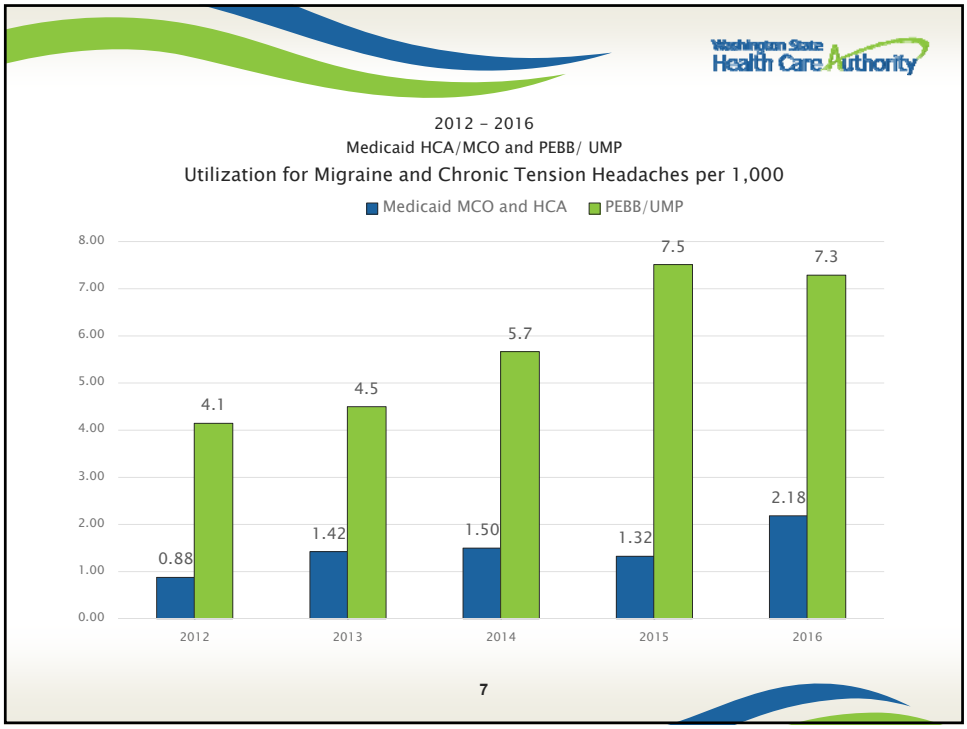
- Safety = Medium/High
- Efficacy = Medium/High
- Cost = Medium/High

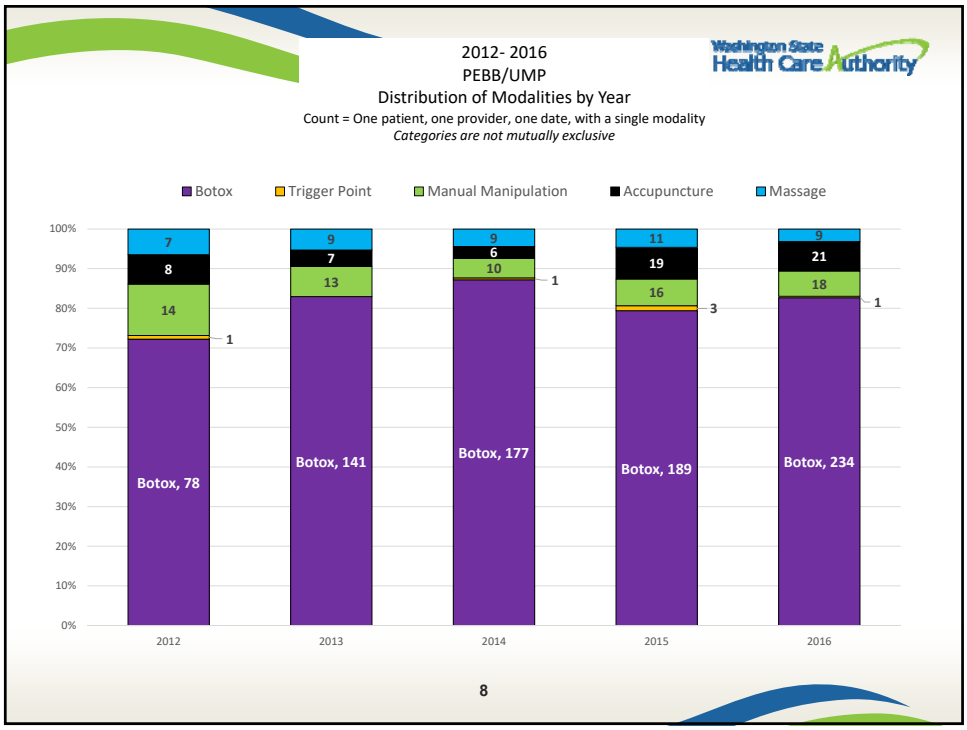
5

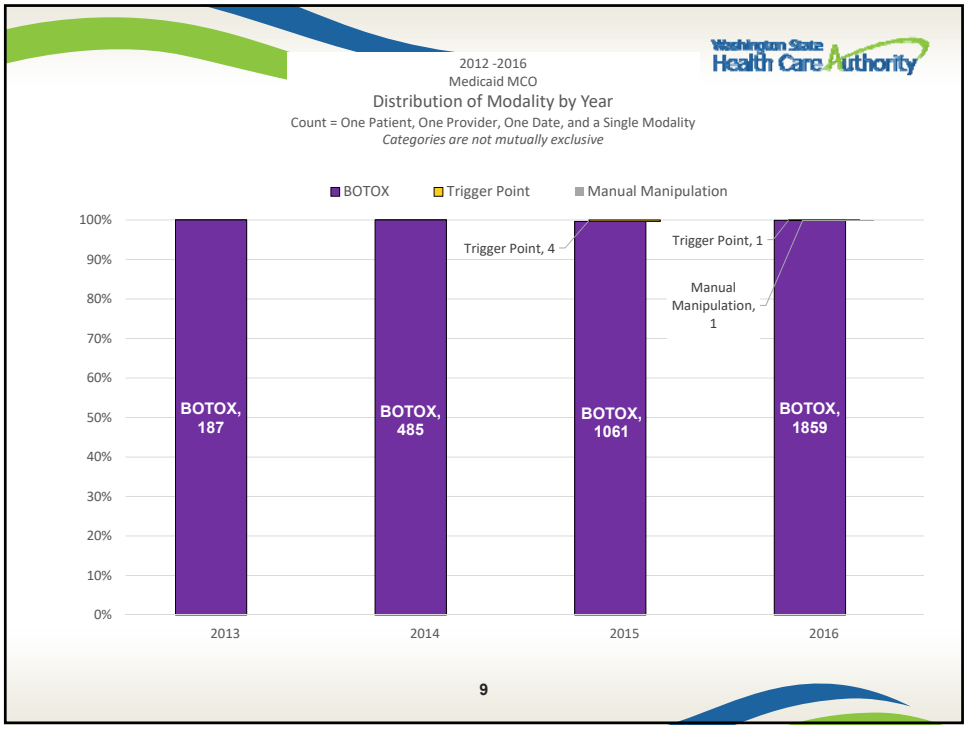
2012 – 2016
Medicaid MCO and HCA and PEBB/UMP
Chronic Migraine and Chronic Tension Headaches
Total Paid Dollars by Year

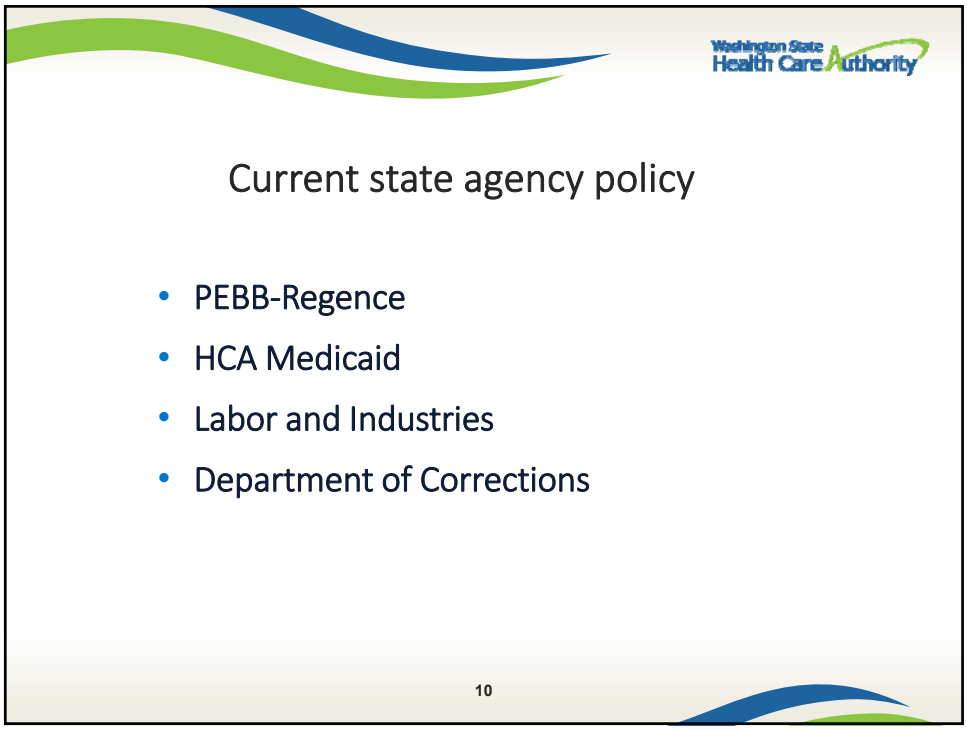


6


2012 – 2016
Medicaid HCA/MCO and PEBB/ UMP
Utilization for Migraine and Chronic Tension Headaches per 1,000
Medicaid MCO and HCA
PEBB/UMP
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.88
4.1
1.42
4.5
1.50
5.7
1.32
7.5
2.18
7.3
2012
2013
2014
2015
2016
7


2012- 2016
PEBB/UMP
Distribution of Modalities by Year
Count = One patient, one provider, one date, with a single modality
Categories are not mutually exclusive
Botox
Trigger Point
Manual Manipulation
Accupuncture
Massage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
7
8
14
1
Botox, 78
9
7
13
Botox, 141
9
6
10
1
Botox, 177
11
19
16
3
Botox, 189
9
21
18
1
Botox, 234
2012
2013
2014
2015
2016
8


2012 -2016
Medicaid MCO
Distribution of Modality by Year
Count = One Patient, One Provider, One Date, and a Single Modality
Categories are not mutually exclusive
BOTOX
Trigger Point
Manual Manipulation
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
BOTOX, 187
BOTOX, 485
Trigger Point, 4
BOTOX, 1061
Trigger Point, 1
Manual Manipulation, 1
BOTOX, 1859
2013
2014
2015
2016
9


Current state agency policy
PEBB-Regence
HCA Medicaid
Labor and Industries
Department of Corrections
10

PEBB-Regence

PEBB	Chronic migraine	Chronic tension-type headache
OnabotulinumtoxinA (onaBoNT-A, Botox)	Covered with conditions; PA	Not covered
Trigger point injections	Covered with conditions; PA	Covered with conditions; PA
Transcranial Magnetic Stimulation(TMS)	Investigational	Investigational
Manipulation/Manual therapies	Covered; Visit limit per year	Covered; Visit limit per year
Massage	Covered; Visit limit per year	Covered; Visit limit per year
Acupuncture	Not covered	Not covered

11

HCA Medicaid

HCA MEDICAID	Chronic migraine	Chronic tension-type headache
OnabotulinumtoxinA (onaBoNT-A, Botox)	Covered with conditions; PA	Not covered
Trigger point injections	Covered	Covered
Transcranial Magnetic Stimulation (TMS)	Covered with limits	Covered with limits
Manipulation/Manual therapies	Adult chiropractic not covered	Adult chiropractic not covered
Massage Non-covered WAC 182-531-0150-	Not Covered by massage therapists Some codes covered by rehab providers	Not Covered by massage therapists Some codes covered by rehab providers
Acupuncture Non-covered WAC 182-531-0150-	Not covered	Not covered

12

Labor and Industries

LABOR AND INDUSTRIES	Chronic migraine	Chronic tension-type headache
OnabotulinumtoxinA (onaBoNT-A, Botox)	Covered with conditions; PA	Not covered
Trigger point injections	Covered with limits; PA	Covered with limits; PA
Transcranial Magnetic Stimulation (TMS)	Case by case	Case by case
Manipulation/Manual therapies	Covered	Covered
Massage	Covered	Covered
Acupuncture	Not covered	Not covered

13

Department of Corrections

Department of Corrections	Chronic migraine	Chronic tension-type headache
OnabotulinumtoxinA (onaBoNT-A, Botox)	PA	PA
Trigger point injections	PA	PA
Transcranial Magnetic Stimulation (TMS)	PA	PA
Manipulation/Manual therapies	PA	PA
Massage	PA	PA
Acupuncture	Not covered	Not covered

14

Centers for Medicare Medicaid Services (CMS)

No national coverage determination (NCD)

- BoNTA for chronic migraine
- Trigger points
- Manipulation (LCD)
- Massage
- TMS

NCD acupuncture

- Not medically necessary

15

Chronic migraine and BoNTA

Preempt1 and Preempt2, moderate quality studies

- Exclusion criteria: moderate depression, fibromyalgia, psychiatric disorders, other primary or secondary HA disorders
- Clients had been inadequately treated by available medical therapies

Outcomes (PREEMPT1/PREEMPT 2)

- Pain measure: decrease in mean HA days per month -1.4/-2.3 days; clinical significance
- Functional measures:
  - *Headache Impact Test (HIT) -6 score reduction -2.3/-2.5; clinically significant difference of -2.3*
  - *% with severe HIT-6 score reduction -10.2/-11%*
- No change in acute medication use; post-hoc analysis with decreased triptan intake
- More serious AE BoNTA group compared to placebo

16

Transcranial magnetic stimulation

- Misra, 2013, Low quality, short-term (4 weeks) study
  - *Improvement in HA frequency and severity >50%*
  - *Functional measures reported not pre-specified, not validated measures*
  - *Analgesic use--no difference between groups*
- Promising results

Chronic tension type headache manual therapy

- Castien, 2011, Low quality study
  - Intervention included manual therapy and physical therapy
  - Manual therapy consisted of: mobilization, muscle exercises, and posture correction. Manipulation and physical exercise.

17

Limited and/or low quality data limits valid determination of efficacy:

- *Acupuncture*
- *Massage*
- *Trigger point injections*

18

Agency Recommendations

CHRONIC MIGRAINES

Covered with conditions-OnabotulinumtoxinA injections

- Treatment of comorbid psychiatric conditions and other primary or secondary headache disorders
- Inadequately treated by available prophylactic medical therapies

Non-covered due to insufficient evidence supporting efficacy

- Trigger point injections
- Transcranial magnetic stimulation
- Manipulation
- Acupuncture
- Massage

19

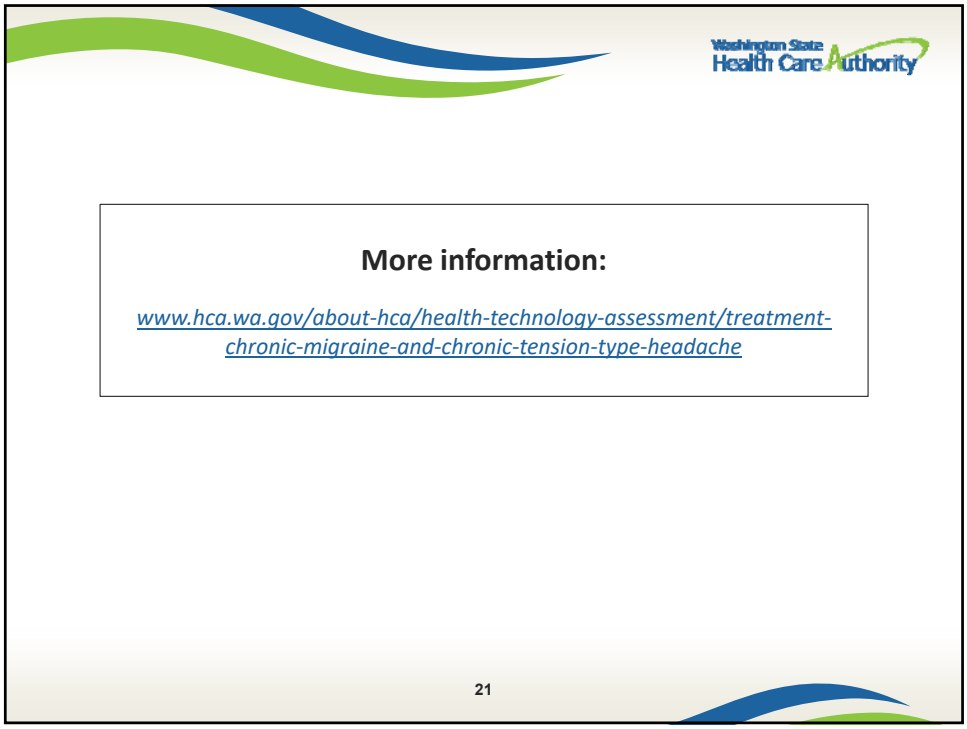
Agency Recommendations

CHRONIC TENSION HEADACHES

Non-covered due to insufficient evidence supporting efficacy

- OnabotulinumtoxinA
- Trigger point injections
- Transcranial magnetic stimulation
- Manipulation
- Acupuncture
- Massage

20


Washington State Health Care Authority
More information:
www.hca.wa.gov/about-hca/health-technology-assessment/treatment-chronic-migraine-and-chronic-tension-type-headache
21

Treatment of chronic migraine and chronic tension-type headache

Presentation to
Washington State Health Care Authority
Health Technology Clinical Committee
Andrea C. Skelly, PhD, MPH
May 19, 2017

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

1

Background

Burden of Disease and Epidemiology

- Headache disorders combined are third highest cause of years lost to disability
- In 2015, 17.9% of Americans reported migraine or severe headache in past 3 months
- Prevalence:
  - Chronic migraine: 1.4%–2.2%
  - Chronic tension-type headache: 0.9%–2.2%
  - Chronic daily headache: ~4%
- Usual care = pharmacological and nonpharmacological treatments including trigger management, physical therapy, and psycho-behavioral training
- **Focus for chronic headache:** preventative treatment

2

Background – General Headache Classification

Primary vs. Secondary

✓ **Primary:** are not caused by an underlying disease; tension-type headache and migraine are the most common

Secondary: are a result of a recognized disease process or other medical condition (e.g. from musculoskeletal disorders)

Frequency:

✓ **Chronic:** ≥ 15 days per month or ≥ 180 days per year

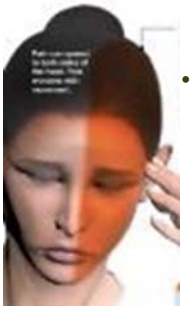
Episodic: 0-15 days per month

Diagnosis of 1° HA: Combination of clinical history, headache diary, exclusion of causes for secondary headache

International Classification of Headache Disorders 3rd edition

3

Background – Characteristics



Chronic Migraine

- Recurrent unilateral pulsatile; lasts 4- 72 hours; nausea, vomiting, light and sound sensitivity are frequent
- Common migraine (without aura); classic (with aura or neurological symptoms)

Chronic Tension-Type

- Dull, non-pulsatile, diffuse, band-like/vice-like) pain; intensity is mild to moderate in head, scalp or neck.
- No clear cause; has been associated with muscle contraction and stress.

- **Chronic Daily HA:** Coexistent CM and TT (as defined for this report); one of the most common clinical presentations

4

Background – OnabotulinumtoxinA (BoNTA)

BoNTA is the only botulinum toxin with FDA approval for headaches, exclusively for chronic migraine:

Indications

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

Contraindications

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

spectrumresearch

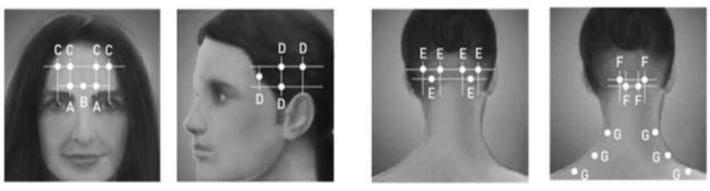
5

Background: FDA BoNTA Administration

Doses

- 155 Units injected into 31 sites across the head and neck; Each injection 0.1 mL (5 Units)
- From FDA labeling: Do not exceed a total dose of 360 units administered every 12 to 16 weeks or at longer intervals

FDA fixed sites:

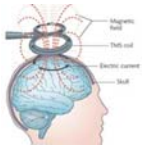


spectrumresearch

6

Background – Other Treatments

- **Acupuncture:** solid, filiform needle insertion at acupuncture points (including trigger points)
- **Manual therapies:** involve passive movement of joints and soft tissues by hands or equipment
- **Massage:** manual manipulation of soft body tissues, including trigger points usually with the hands
- **Transcranial Magnetic Stimulation**: device used to induce pulses of magnetic fields to excite neural tissue; Two FDA approved devices for treatment of pain associated with migraine with aura (Cerena TMS device, Spring TMS)



- **Trigger Point Injections:** injection of local anesthetic or other injectate into contracted muscles (trigger points)

spectrumresearch

7

Key Questions

In adults with chronic migraine or chronic tension type headache, for the comparisons of interventions listed with usual treatment options, placebo, sham waitlist or no treatment:

1. What is the evidence of short-and long-term efficacy?
2. What is the evidence related to of short- and long-term safety
3. What is the evidence of differential efficacy or safety issues amongst special populations?
4. What is the evidence of cost effectiveness?

spectrumresearch

8

PICO Scope: Inclusion Criteria

Population - Patients with

- Patients with chronic migraine, chronic tension headache, chronic daily headache

Interventions:

- Botulinum toxin injection, acupuncture, manipulation/manual therapy, massage, transcranial magnetic stimulation (TMS), trigger point injection (TPI) or dry needling

Comparator(s)

- Placebo, sham, usual care/treatments, waitlist, no treatment

Study design

- RCTs; observational studies (for safety only), full economic studies; focus on studies with least potential for bias

Publication

- Full-length studies published in English in peer-reviewed journals, FDA reports (no meeting abstracts, proceedings)

spectrumresearch

9

Inclusion Criteria

Primary outcomes:

- **Efficacy**
  - Treatment responders ("success"): Proportion of patients achieving a threshold (e.g. ≥50%) for improvement
  - Reduction in number of episodes (specify HA type)
  - Reduction in number of HA days/HA-free days (specify type)
  - Validated Function/Disability Measures
- **Adverse events or complications**
- **ICER/other measures of cost-effectiveness**

Follow-up definitions:

Short-term: ≤ 8 weeks
Intermediate-term: > 8 to 12 weeks
Longer-term: ≥12 weeks

spectrumresearch

10

Strength of Evidence (SoE)

SoE for overall body of evidence for primary outcomes was assessed based on:

- **Risk of bias**: the extent to which the included studies protect against bias
  - Appropriate randomization
  - Allocation concealment
  - Intention to treat analysis
  - Blind assessment of outcomes
  - Co-interventions applied equally
  - Adequate follow-up (≥80%) and <10% follow-up difference between groups
  - Controlling for confounding
- **Consistency**: degree to which estimates are similar in terms of range and variability.
- **Directness**: whether the evidence is directly related to patient health outcomes. NOTE: Placebo- or sham-controlled trials are considered indirect.
- **Precision**: level of certainty surrounding the effect estimates.
- **Publication/report bias**: selective reporting or publishing.

spectrumresearch

11

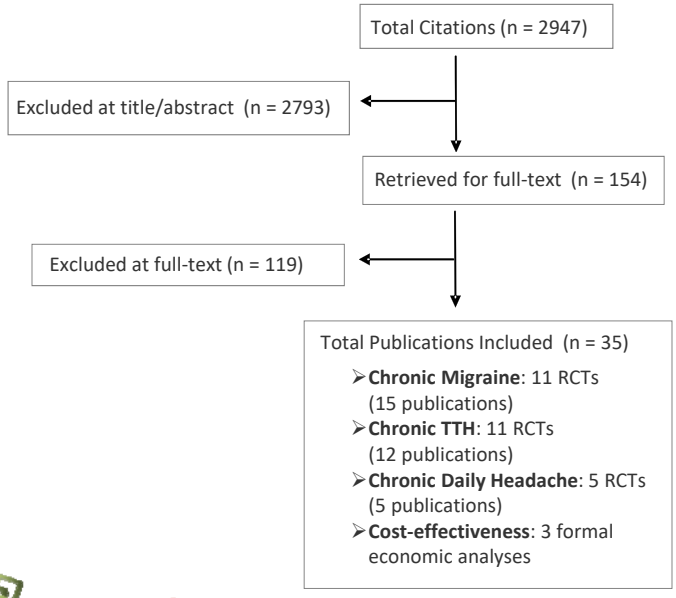
Evaluating Strength of Evidence

AHRQ/GRADE Methods ***Strength of Evidence (SOE)*** approach based on risk of bias, consistency of results across studies, directness of the evidence linking the intervention and health outcomes, and precision of the effect estimate

Strength of Evidence Ratings	
High	Very confident that effect is true.
Moderate	Moderately confident.
Low	Limited confidence.
Insufficient	No evidence or no confidence in effect.

spectrumresearch

Literature Search Results



spectrumresearch

13

Chronic Migraine (CM)

Evidence Base

OnabotulinumtoxinA (BoNTA) vs. Placebo	4 RCTs
OnabotulinumtoxinA (BoNTA) vs. Active Control	
• OnabotulinumtoxinA (BoNTA) vs. Topiramate	1 RCT
• OnabotulinumtoxinA (BoNTA) vs. Amitriptyline	1 RCT
Acupuncture vs. Sham	0 RCTs
Acupuncture vs. Active Control	
• Acupuncture vs. Usual Care	1 RCT
• Acupuncture vs. Topiramate	1 RCT
Spinal Manipulation Therapy vs. Sham	0 RCTs
Spinal Manipulation Therapy vs. Active Control (Amitriptyline)	1 RCT
Massage vs. Sham and vs. Active Control	0 RCTs
Transcranial Magnetic Stimulation vs. Sham	2 RCTs
Transcranial Magnetic Stimulation vs. Active Control	0 RCTs
Trigger Point injection vs. Sham and vs. Active Control	0 RCTs

spectrumresearch

14

Overview of PREEMPT Trial Publications

	Publication	Randomized Phase	Open-label Phase*	Comments
PREEMPT 1	**Aurora 2010**	N=679	N=607	• Index Trial (56 sites – US, Canada) • **Primary outcome**: mean Δ from baseline in headache *episodes*
PREEMPT 2	**Diener 2010**	N=705	N=629	• Index Trial (66 sites – North America, Europe) • **Primary outcome:** mean Δ from baseline in headache *days*
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) • Primary endpoint same as PREEMPT 2
	Lipton 2011	N=1384	NR	• Pooled results at 24 week follow-up; Only HIT-6 (disability) and MSQ v2.1 (HRQoL)
	Aurora 2011	N=1384	N=1236	• Pooled results through 56 week follow-up); including RCT phase (24 weeks, 2 injection cycles) and open-label phase (3 injection cycles); OL phase BoNTA only.
	Aurora 2014	N=1384	N=1005	• Pooled results at 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 of BoNTA

15

Chronic Migraine: Outcomes reported

Headache

Measure	MCID
HA, Migraine *days* (responders, mean Δ)	3 days* (mean Δ)
HA, Migraine *episodes* (responders, mean Δ)	NR
HA intensity/pain (responders)	NR

* based on Mathew 2005

Function/Disability

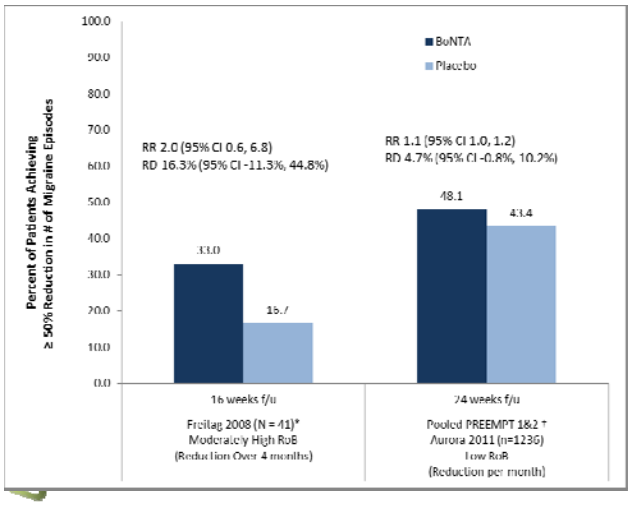
Measure*	MCID
HIT-6 (scale 36-78) (mean Δ)	2.3 points
% w/ HIT-6 score ≥60 (severe)	NA
MIDAS (scale 0-27) (mean Δ)	NR
Functional Disability† (scale 0-4), % w/ none or mild (score 0 or 1)	NA

*Higher score = worse function/disability
†Not a validated measure (Misra 2013)

16

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Placebo

Responders: ≥ 50% reduction of *migraine episodes* longer term (≥ 12 weeks)



Difference between BoNTA and placebo is not statistically significant.

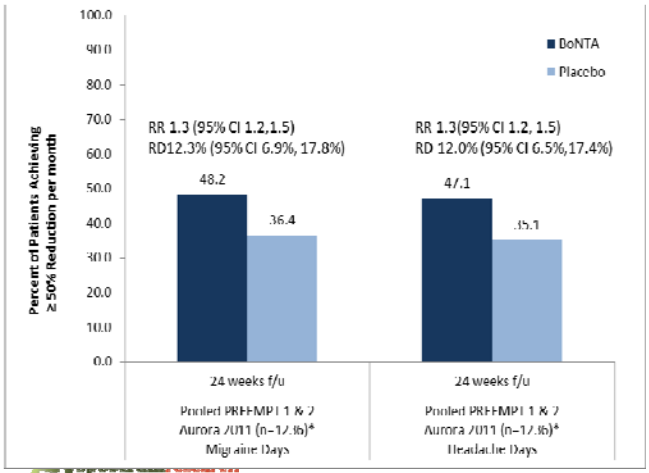
Moderate evidence

† PREEMPT: Only pooled, "observed" data were available. Baseline medication overuse: 64.8%, BoNTA 66.1% placebo

17

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Placebo

Responders: ≥ 50% reduction of *migraine days, headache days* longer term (≥ 12 weeks)



Significantly more BoNTA responders vs. placebo; the relative effect size is small.

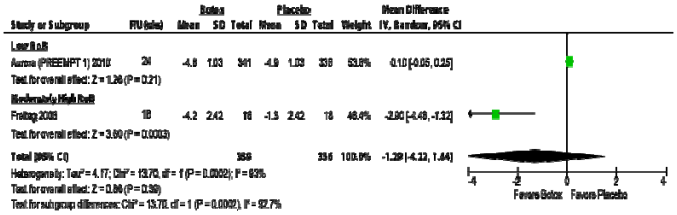
Moderate evidence

* PREEMPT: Only pooled, "observed" data were available. Baseline medication overuse: 64.8%, BoNTA 66.1% placebo

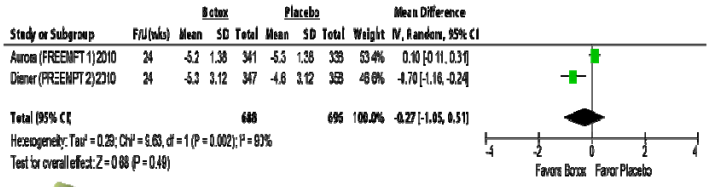
18

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Placebo

Reduction in mean *migraine episodes* longer term



Reduction in mean *headache episodes* longer term



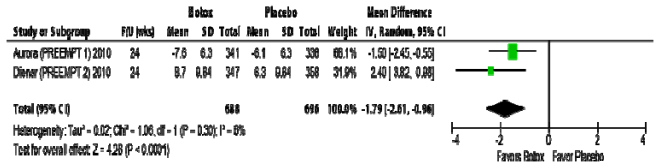
Pooled difference was not statistically significant for either outcome; substantial heterogeneity

Moderate evidence

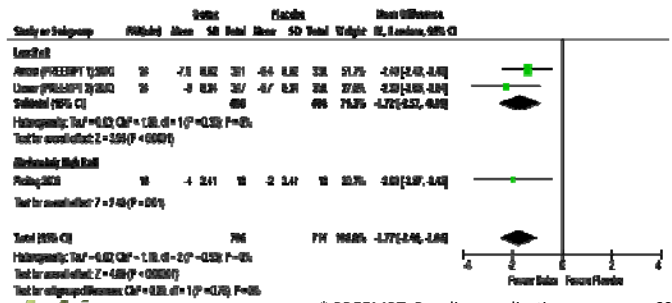
* PREEMPT: Baseline medication overuse:> 60%

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Placebo

Reduction in mean *migraine days* longer term



Reduction in mean *headache days* longer term



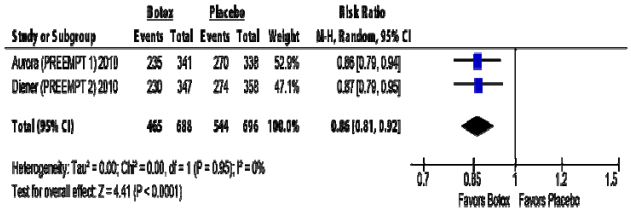
Small reduction (< 2 days) in both outcomes with BoNTA vs. placebo; clinical significance unclear

Moderate evidence

* PREEMPT: Baseline medication overuse: > 60%

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Placebo

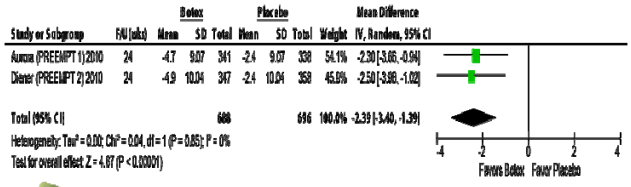
Proportion (%) with severe HIT-6 Score (≥60) longer term



Moderate evidence:

Significantly fewer BoNTA recipients had a severe HIT-6 score by 24 weeks

Reduction in mean HIT-6 scores longer term



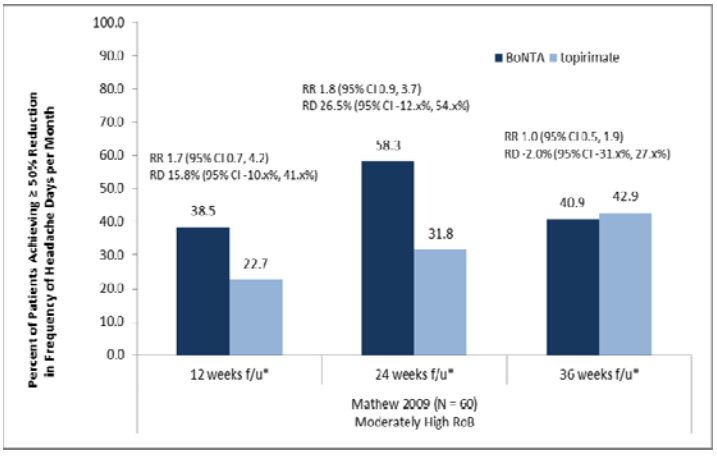
Significantly lower mean HIT scores following BoNTA by 24 weeks; may be clinically significant

spectrumresearch

* PREEMPT: Baseline medication overuse:> 60%

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Topiramate

Responders: ≥ 50% reduction in ***headache days*** longer term



No statistically significant difference

Substantial and differential loss to follow-up

Low evidence 12 weeks

Insufficient 24, 36 weeks

spectrumresearch

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Topiramate

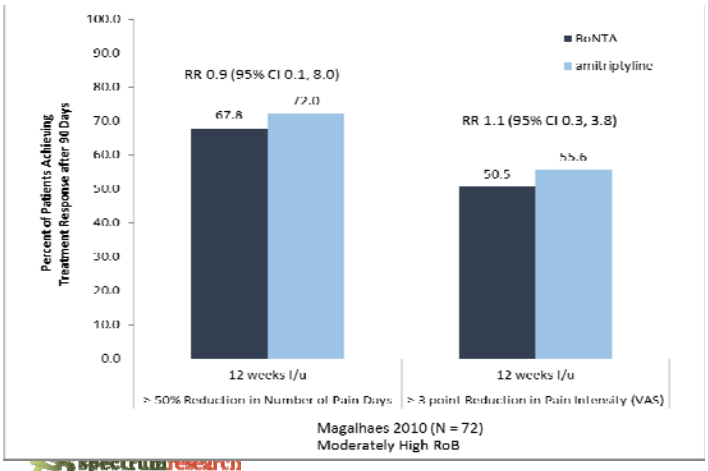
Functional Measures longer term

Outcome	RCTs N	Down Grade	Conclusion	Quality
Functional Measures (MIDAS, HIT-6, MIQ)	1 (Matthew 2009) N = 60 (randomized)	Risk of bias (-1) Imprecision (-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: 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**; substantial attrition, differential loss to follow-up.	12 weeks ⊕⊕◯◯ LOW 24 and 36 weeks ⊕◯◯◯ INSUFFICIENT

*F/u 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks

KQ 1: Efficacy Results
Chronic Migraine: BoNTA vs. Amitriptyline

Responders, longer term: ≥ 50% reduction in pain days, ≥ 3 point reduction in pain

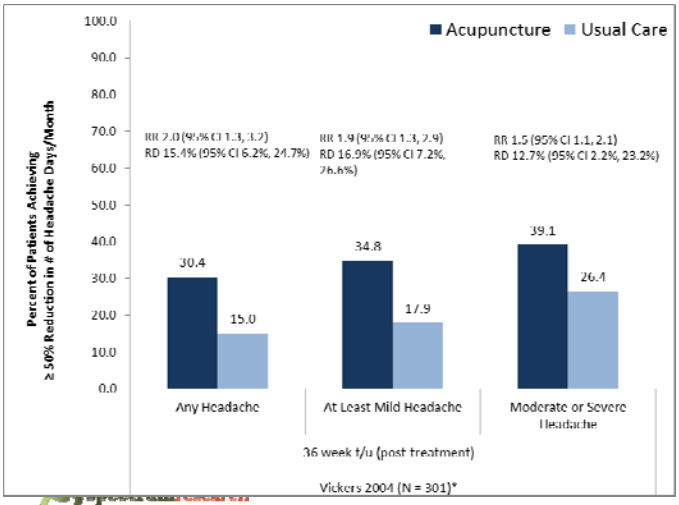


No statistically significant difference

Low evidence

KQ 1: Efficacy Results
Chronic Migraine: Acupuncture vs. Usual Care

Responders: ≥ 50% reduction in number of *headache days*



Statistically significant improvement with acupuncture

1 moderately high RoB trial. Relative effect size small.

Low evidence

25

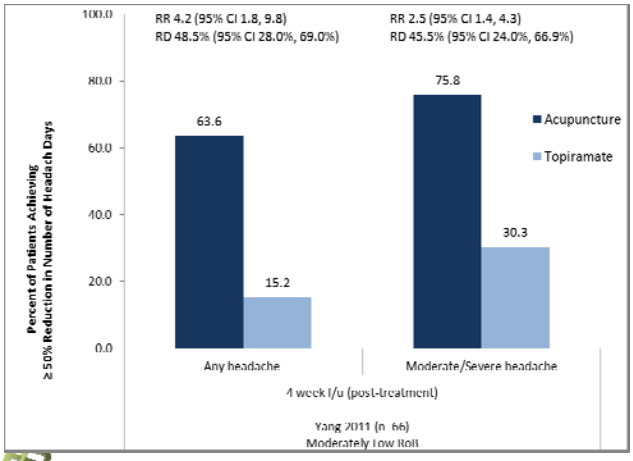
KQ 1: Efficacy Results
Chronic Migraine: Acupuncture vs. Usual Care

Other outcomes at longer term

Outcome	F/U	RCTs	Down Grade	Conclusion	Quality
≥35% reduction in *headache days* from baseline	36 wks.	1 RCT (Vickers 2004) N = 301	Risk of Bias (-1) Indirect(-1)	RR 1.7 (95% CI 1.3, 2.2) RD 21.9% (95% CI 11.0%, 32.8%) **Statistically significant improvement with acupuncture vs. usual care;**	⊕⊕◯◯ LOW
Reduction in *headache days* per month (adjusted for baseline score)				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) **Small but statistically significant improvement with acupuncture vs. usual care.** **Clinical significance of reduction in mean HA days is unclear**	⊕⊕◯◯ LOW

KQ 1: Efficacy Results
Chronic Migraine: Acupuncture vs. Topiramate

Responders: ≥ 50% reduction in number of *headache days* – short term



More in acupuncture group had ≥ 50% reduction; effect size moderate to large

Low evidence

spectrumresearch

27

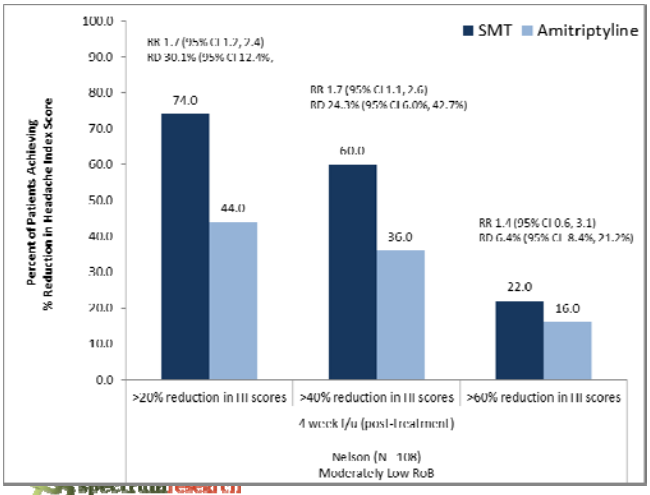
KQ 1: Efficacy Results
Chronic Migraine: Acupuncture vs. Topiramate

Other outcomes – short term

Outcome	F/U	RCTs N	Down Grade	Conclusion	Quality
Reduction in mean any or moderate/ severe *headache days* per month	4 wks.	1 RCTs (Yang 2011) N =66	Risk of Bias (-1) Imprecise (-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 significant improvement with acupuncture** vs. topiramate for both measures 4 weeks post-treatment.	⊕⊕◯◯ LOW
Migraine Disability Assessment (MIDAS)*			Risk of Bias (-1) Imprecise (-1)	MD 12.6 (95% CI 7.7, 17.5) **Conclusion: Statistically significant improvement with acupuncture** vs. topiramate 4 weeks post-treatment; **it is unclear if this difference is clinically meaningful.**	⊕⊕◯◯ LOW

KQ 1: Efficacy Results
Chronic Migraine: Spinal Manipulation Therapy vs. Amitriptyline

Responders: > 20%, 40%, 60% reduction in headache intensity scores; Short term



Responders: More achieved >20%, 40% reduction with SMT; >60% reduction NS

Low evidence

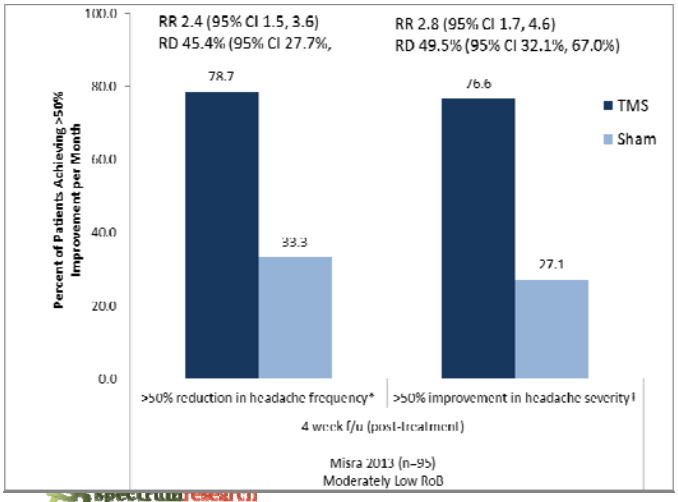
Authors also report reduction in *percent* of headache days/month, p=NS: MD 3.6% (95% CI -6.8%, 14%)

Low evidence

29

KQ 1: Efficacy Results
Chronic Migraine: Transcranial Magnetic Stimulation vs. Sham

Responders: ≥ 50% reduction in headache intensity scores – Short term



More in TMS group had ≥ 50% reduction in frequency and severity with TMS

Low evidence

30

KQ 1: Efficacy Results
Chronic Migraine: Transcranial Magnetic Stimulation vs. Sham

Outcome	F/U	RCTs N	Down Grade	Conclusion	Quality
Reduction in migraine attacks per month from baseline	4 wks.	1 RCT (Misra 2013) N = 95	Indirect Imprecise	MD -3.7 (95% CI -6.07, -1.33) **Conclusion: Statistically significant improvement with high-frequency TMS vs. sham**	⊕⊕◯◯ LOW
Reduction in migraine attacks per 2 weeks from baseline	8 wks.	1 RCT (Teepker 2010) N = 27	Risk of Bias Indirect Imprecise	MD -0.91 (95% CI -4.27, 2.46) **Conclusion: Insufficient evidence precludes firm conclusions.**	⊕◯◯◯ INSUFFICIENT
Reduction in migraine days per 8 weeks			Risk of Bias Indirect Imprecise	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) N = 93	Indirect Imprecise	RR 4.4 (95% CI 2.2., 9.1) RD 49.9% (95% CI 32.7%, 67.1%) **Conclusion: Statistically significant improvement with high-frequency TMS**	⊕⊕◯◯ LOW

31

KQ 1: Efficacy Results
Chronic Daily Headache (CDH)

Evidence Base

OnabotulinumtoxinA (BoNTA) vs. Placebo	3 RCTs
OnabotulinumtoxinA (BoNTA) vs. Active Control (Topiramate)	1 RCT
Acupuncture vs. Sham and vs. Active Control	0 RCTs
Manual Therapy/Manipulation vs. Sham and vs. Active Control	0 RCTs
Massage vs. Sham	1 RCT
Massage vs. Active Control	0 RCTs
Transcranial Magnetic Stimulation vs. Sham and vs. Active Control	0 RCTs
Trigger Point Injections vs. Sham and vs. Active Control	0 RCTs

spectrumresearch

32

CDH: Outcomes reported

Headache

Measure	MCID
HA *days* (responders, mean Δ)	3 days* (mean Δ)
HA *episodes* (mean Δ)	NR
HA-free days (mean Δ)	NR

*Chronic Migraine population (Mathew 2005)

Function/Disability

Measure*	MCID
HIT-6 (scale 36-78) (mean Δ)	2.3 points
HDI (scale 0-100) (mean Δ)	16 points†
MIDAS (scale 0-27) (mean Δ)	NR

*Higher score = worse function/disability
†CTTH population (Castien 2011)

spectrumresearch

33

KQ 1: Efficacy Results
CDH: BoNTA vs. Placebo

Responders: ≥ 50% reduction in *headache days* longer term

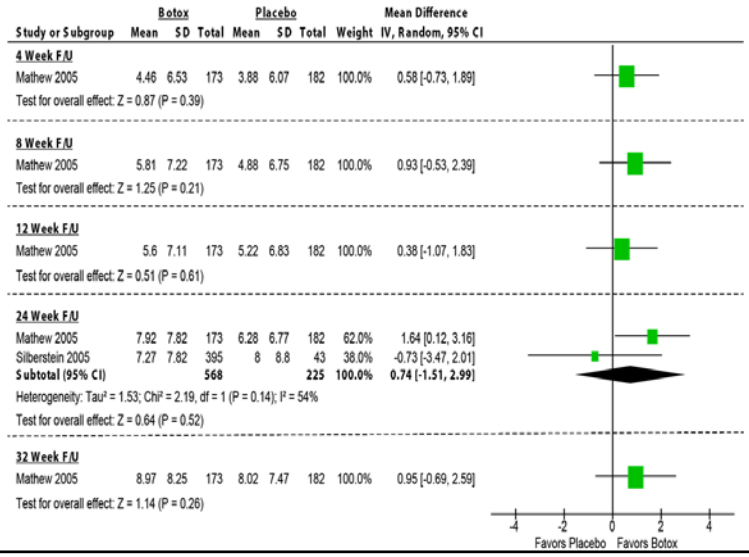
Outcome	F/U	RCTs	Down Grade	Conclusion*	Quality
≥ 50 % reduction frequency of headache days	24 wks	1 RCT (Mathew 2005) N = 355	Risk of Bias (-1) Indirect (-1)	BoNTA 40.3%, Placebo 25.3% RR 1.6, 95% CI 1.1, 2.2) RD 15.2% (95% CI 5.5%,24.9%) **Conclusion: More BoNTA recipients had a ≥ 50 % reduction frequency of headache days compared with placebo. Relative effect size is small**	⊕⊕◯◯ LOW

spectrumresearch

34

KQ 1: Efficacy Results
CDH: BoNTA vs. Placebo

Change in mean *headache-free days* per month (short to longer term)



No difference between groups at any time point

Low evidence

35

KQ 1: Efficacy Results
CDH: BoNTA vs. Topiramate

Reduction in mean *headache days* per month and *function* measures

Outcome	F/U	RCTs	Down Grade	Conclusion*	Quality
Reduction in frequency of headache days per month	4 and 12 wks	1 RCT (Cady 2011) N =59	Risk of Bias Imprecision	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 wks			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

36

KQ 1: Efficacy Results
CDH: Massage vs. Sham

Reduction in mean *headache attacks* per month and HDI

Outcome	F/U	RCTs	Down Grade	Conclusion	Quality
Reduction in number of headache attacks per month (adjusted for baseline scores)	3, 9 wks.	1 RCT (Chatchawan 2014) N = 72	Indirectness (-1) Imprecision (-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)				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

37

KQ 1: Efficacy Results
Chronic Tension-type Headache (CTTH)

Evidence Base

OnabotulinumtoxinA (BoNTA) vs. Placebo	5 RCTs
OnabotulinumtoxinA (BoNTA)vs. Active Control	0 RCTs
Acupuncture vs. Sham	2 RCTs
Acupuncture vs. Active Control	
• Acupuncture vs. Physical Training and vs. Relaxation	1 RCT
• Acupuncture vs. Physiotherapy	1 RCT
Manual Therapy/Manipulation vs. Sham	0 RCTs
Manual Therapy/Manipulation vs. Usual Care	1 RCT
Transcranial Magnetic Stimulation vs. Sham and vs. Active Control	0 RCTs
Trigger Point Injections vs. Sham	1 RCT
Trigger Point Injections vs. Active Control	0 RCTs

spectrumresearch

38

CTTH: Outcomes reported

Headache		Function/Disability	
Measure	**MCID**	**Measure***	**MCID**
HA *days, *episodes*** (responders, mean Δ)	3 days* (mean Δ)	**HIT-6** (scale 36-78) (mean Δ)	2.3 points
HA-free *days*, *periods* (mean Δ)	NR	**HDI** (scale 0-100) (mean Δ)	16 points†
HA intensity/pain (responders)	NR	**SIP** (scale 0-100) (mean Δ)	NR
Headache Index (HI) (responders)	NR		

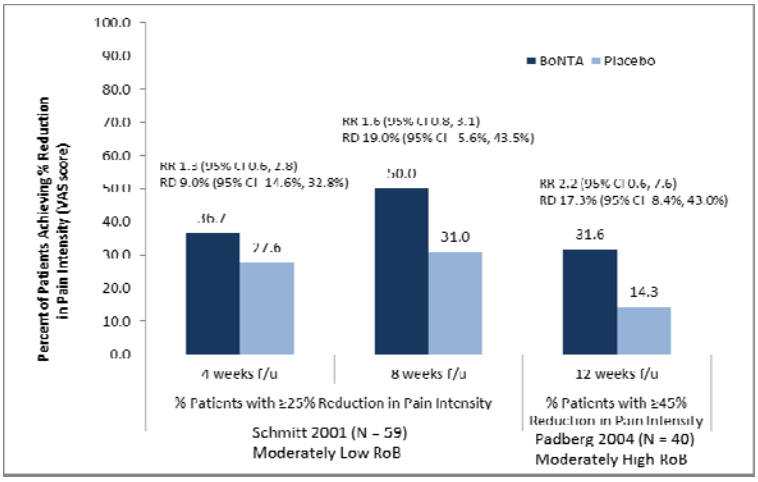
*Chronic Migraine population (Mathew 2005)

*HIT-6, HDI: higher score=worse function/disability;
SIP: higher score=better outcome
†CTTH population (Castien 2011)

39

KQ 1: Efficacy Results
CTTH: BoNTA vs. Placebo

Responders: ≥ 25% and ≥ 45% reduction in pain intensity – short, intermediate, and longer term



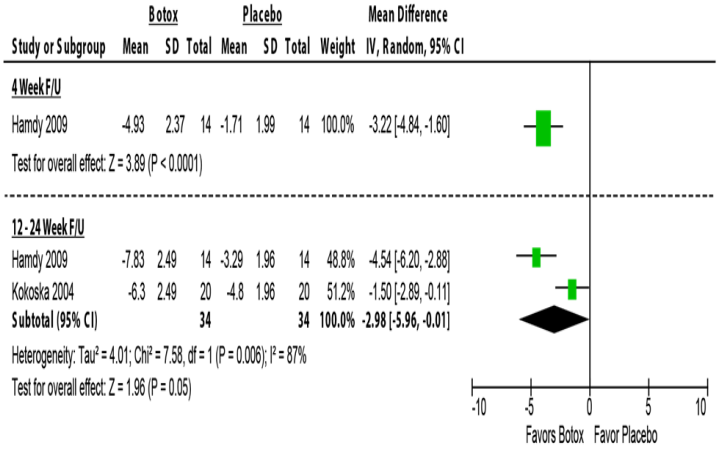
No difference between groups; small sample sizes

Insufficient evidence – all time frames

40

KQ 1: Efficacy Results
CTTH: BoNTA vs. Placebo

Reduction in mean *headache days* per month – short term, longer term



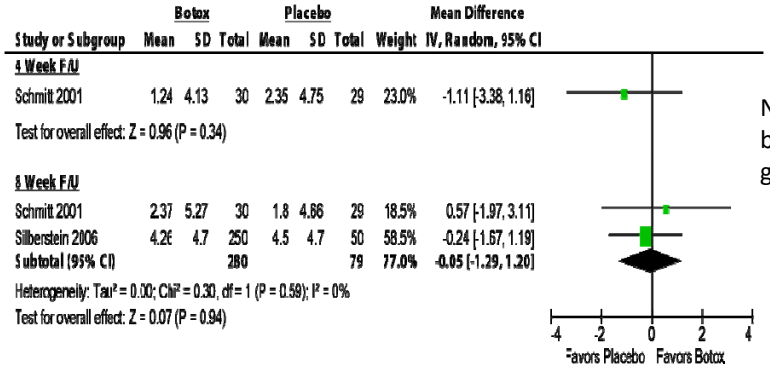
Reduction in mean frequency was significantly greater in the BoNTA group

Substantial heterogeneity , small sample noted.

Insufficient evidence

KQ 1: Efficacy Results
Chronic tension-type headache: BoNTA vs. Placebo

Increase in mean pain-free days per month
(short, intermediate term)



No difference between groups

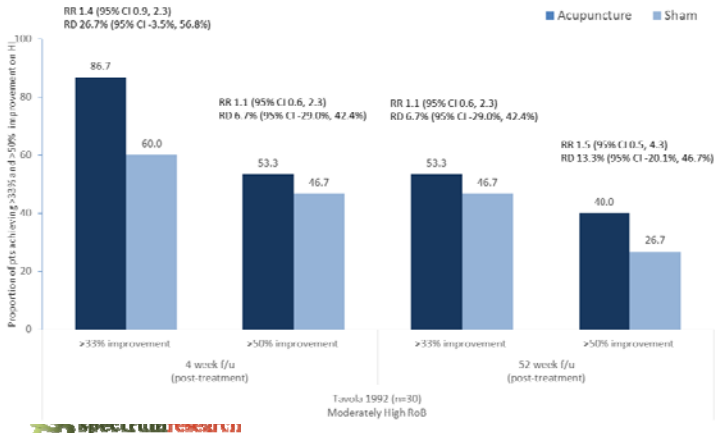
KQ 1: Efficacy Results
CTTH: BoNTA vs. Placebo

Reduction in % of *headache days* per month and in HDI

Outcome	Follow-up	RCTs	Down Grade	Conclusion*	Quality
Reduction in % of headache days per month	12 wks	1 RCT (Padberg 2004 N = 40)	Risk of Bias Indirect Imprecise	BoNTA 12 ± 20%, placebo 5 ± 14%; MD: 7.0, 95% CI: -4.0, 18.0 Conclusion: Statistical significance wasn't reached; insufficient evidence to draw a conclusion.	⊕◯◯◯ INSUFFICIENT
Functional Measure: Mean HDI Scores†	4, 12 wks	1 RCTs (Hamdy 2009) N = 28	Risk of Bias Indirect Imprecise	4 weeks: MD -11.85 (-22.23, -1.47) 12 weeks: MD -18.28 (-31.11, -5.45) Conclusion: Significantly lower scores with BoNTA, suggest improved function; [Percent reduction in HDI score was also greater with BoNTA (40.6%) vs. placebo (6.6%) at 12 wks;]	⊕◯◯◯ INSUFFICIENT

KQ 1: Efficacy Results
CTTH: Acupuncture vs. Sham

Responders: > 33% and > 50% improvement on Headache Index – short term, longer term

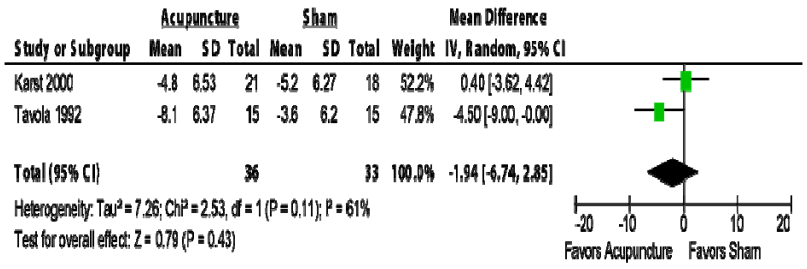


No difference between groups; small sample size

Insufficient evidence – all time frames

KQ 1: Efficacy Results
CTTH: Acupuncture vs. Sham

Reduction in mean ***headache episodes*** per month – short term



Insufficient evidence precludes drawing firm conclusions; small sample sizes noted

spectrumresearch

45

KQ 1: Efficacy Results
CTTH: Acupuncture vs. Active Treatments

There is insufficient evidence to draw conclusions

	F/U	Outcome	Results
vs. Physical Training/ Exercise* 1 RCT (n=60) Moderately High RoB	Longer-term (12-26 wks.)	• **Headache-free periods per week**	No diff
		• **Headache-free days per week**	No diff
vs. Physiotherapy 1 RCT (n=62) Moderately High RoB	Short-, Intermediate-term (4-9 wks.)	• **Reduction in headache *episodes***	Unclear
		• **Sickness Impact Profile**	Unclear
vs. Relaxation Training* 1 RCT (n=60) Moderately High RoB	Longer-term (12-26 wks.)	• **Headache-free *periods* per week**	No diff
		• **Headache-free days per week**	No diff

*Same trial. This trial included 3 arms: acupuncture, physical training, and relaxation.

spectrumresearch

46

KQ 1: Efficacy Results
CTTH: Manipulation vs. Usual Care

Responders and reduction in *headache days*

Outcome	F/U	RCTs	Down Grade	Conclusion	Quality
>50% reduction in headache days per 2 weeks from baseline	18 wks	1 RCT (Castien 2011) N = 82	Indirect (-1) Imprecise (-1)	RR 2.0 (95% CI 1.3, 3.0) RD 41.0% (95% CI 21.0%, 61.1%) **Conclusion: Statistically significant improvement with MT**	⊕⊕◯◯ LOW
Reduction in number of headache days per 2 weeks				MD 4.9 (95% CI 2.98, 6.95) **Conclusion: Statistically significant improvement with MT**	⊕⊕◯◯ LOW

spectrumresearch

47

KQ 1: Efficacy Results
CTTH: Manipulation vs. Usual Care

Headache Impact Test and Headache Disability Index

Outcome	F/U	RCTs	Down Grade	Conclusion	Quality
Headache Impact Test (HIT-6)	18 wks.	1 RCT (Castien 2011) N = 82	Indirect (-1) Imprecise (-1)	MD 5.0 (95% CI 1.16, 9.02) **Conclusion:** Statistically and clinically* significant improvement with MT *author defined as >2.3 point decrease	⊕⊕◯◯ LOW
Headache Disability Inventory (HDI)			Indirect (-1) Imprecise (-1)	MD 10.1 (95% CI 0.64, 19.5) **Conclusion**: Statistically significant improvement with MT however, the difference did not meet the author-defined MCID of ≥16 point reduction.	⊕⊕◯◯ LOW

spectrumresearch

48

KQ 1: Efficacy Results
CTTH: Trigger Point Injection (lidocaine) vs. Sham

Outcome	F/U	RCTs	Down Grade	Conclusion	Quality
↓ in *headache days* per month	12 wks.	1 RCT (Karadas) N = 48	Risk of Bias (-1) Indirect (-1) Imprecise (-1)	MD 11.2 (95% CI 9.2, 13.2) **Conclusion:** Statistically significant improvement with TPI. **Insufficient evidence precludes firm conclusions.**	⊕⊕⊕◯ INSUFFICIENT

- MODERATELY HIGH risk of bias violating every criterion for a good quality RCT except for blind assessment of outcomes (double-blind, placebo controlled trial).

spectrumresearch

49

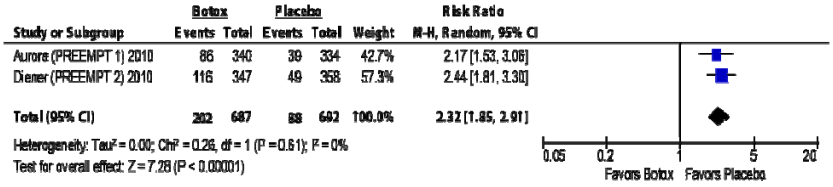
KQ 2: Harms and Complications

spectrumresearch

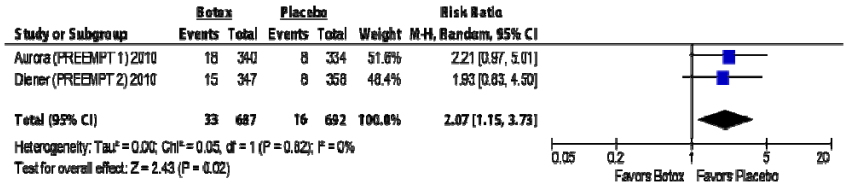
50

KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Placebo

Treatment-related adverse events longer term (24 weeks)



Serious adverse events longer term (24 weeks)

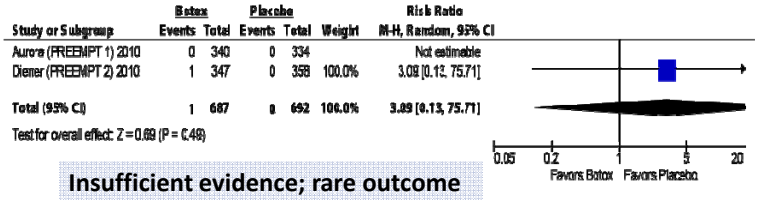


More AEs with BoNTA vs. Placebo
Moderate evidence for both outcomes

51

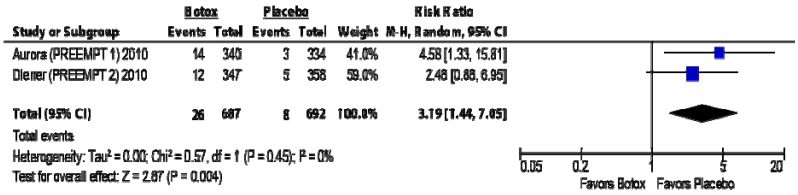
KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Placebo

Treatment-related serious AE longer term (24 weeks)



Insufficient evidence; rare outcome

Discontinuation related to AE longer term (24 weeks)



Discontinuation more common with BoNTA
Moderate evidence

52

KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Placebo

Summary of individual adverse events longer term (24 weeks)

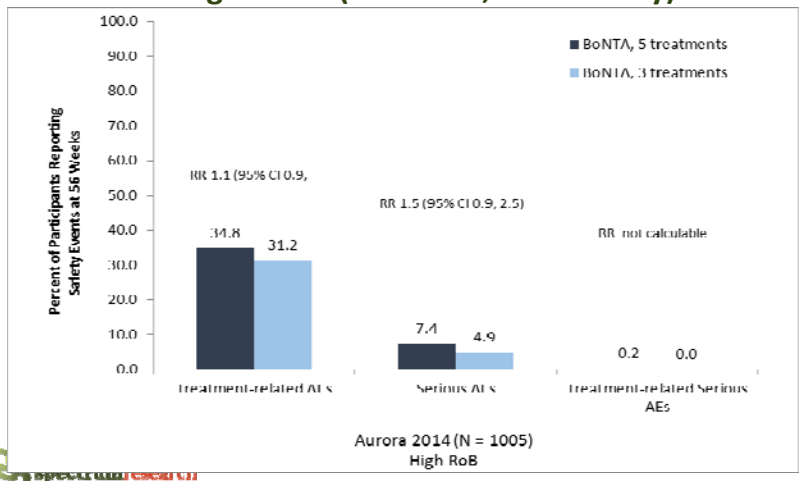
		Results, n/N (%)	
Author	Outcome	BoNTA	Placebo
Aurora 2011 (PREEMPT 1 & 2) (Low Risk of Bias)	All adverse events	429/687 (62.4%)	358/692 (51.7%)
	Death	0 (0.0%)	0 (0.0%)
	Neck pain	46/687 (6.7%)	15/692 (2.2%)
	Muscular weakness	38/687 (5.5%)	2/692 (0.3%)
	Eyelid ptosis	23/687 (3.3%)	2/692 (0.3%)
	Musculoskeletal 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%)

spectrumresearch

53

KQ 2: Safety Results
Chronic Migraine: BoNTA *(Open Label)*

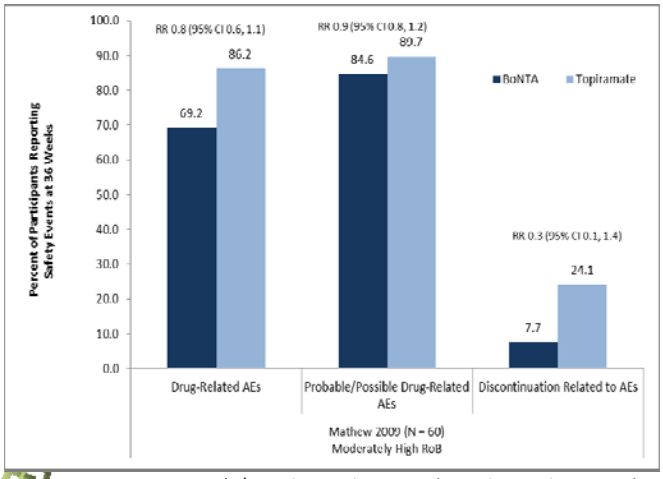
Adverse events – PREEMPT 1 & 2 Open-label phase longer term (56 weeks, BoNTA only)



spectrumresearch

54

KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Topiramate
Adverse events – longer term (to 36 weeks)



No statistically significant difference

Substantial and differential loss to follow-up

Timing of events not reported

Low evidence (all outcomes)

*F/u 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks

55

KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Topiramate
Adverse events – longer term (36 weeks)

		Results, n/N (%)*	
Author	**Outcome**	**BoNTA (n/N) %**	**Topiramate (n/N) %**
Mathew 2009 (Moderately High Risk of Bias)	**All adverse events**	26/26 (100%)	28/29 (96.5%)
		events/total events	
	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%)

*F/u 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks

56

KQ 2: Safety Results
Chronic Migraine: BoNTA vs. Amitriptyline

Summary of Adverse Events – longer term (12 weeks)

		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%**

Low Evidence (Injection site pain, edema)

spectrumresearch

57

KQ 2: Safety Results
Chronic Migraine: Acupuncture, Spinal Manipulation
Limited data on adverse outcomes were reported

Acupuncture vs. Usual Care

- No serious AE; NS differences between groups for discontinuation due to AEs or headache to 36 weeks (Insufficient, 1 RCT, N = 301)

Acupuncture vs. Topiramate

- No serious AE (undefined by authors) or deaths occurred to 4 weeks; data not provided; Conclusions are not possible (Insufficient, 1 RCT, N = 66)

Spinal Manipulation vs. Amitriptyline

- Discontinuation due to AEs less common with SMT (0% vs. 11%); Authors report 58% of amitriptyline group experienced side effects to 4 weeks. (LOW, 1 RCT, N = 108)

spectrumresearch

58

KQ 2: Safety Results
Chronic Migraine: TMS vs. Sham

Limited data on adverse outcomes were reported

Transcranial Magnetic Stimulation vs. Sham

- Discomfort during treatment: Significantly more TMS (high frequency) patients experienced this to 4 weeks (100% vs. 15%, RR 6.9, 95% CI 3.5, 13. 6); LOW evidence, 1 RCT, N = 95

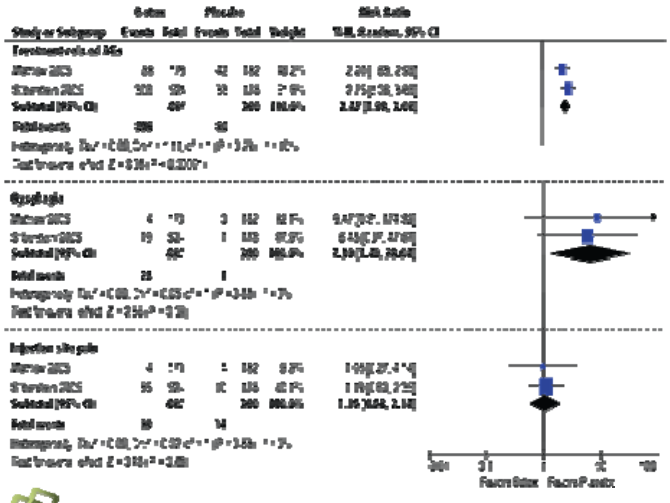
- Discontinuation due to AEs; neither available trial described events leading to withdrawal; INSUFFICIENT evidence:
  - High frequency TMS: 2.1% vs. 0% (1 RCT, N=95)
  - Low frequency TMS: 7.1% vs. 7.7% (1 RCT, N = 27); this trial lists minor AEs only.

spectrumresearch

59

KQ 2: Safety Results
Chronic Daily Headache: BoNTA vs. Placebo

Adverse Events longer-term (through 24 weeks);



Significantly more common with BoNTA:

- Treatment-related AEs
- Dysphagia (wide CI)

No difference for injection-site pain

LOW evidence

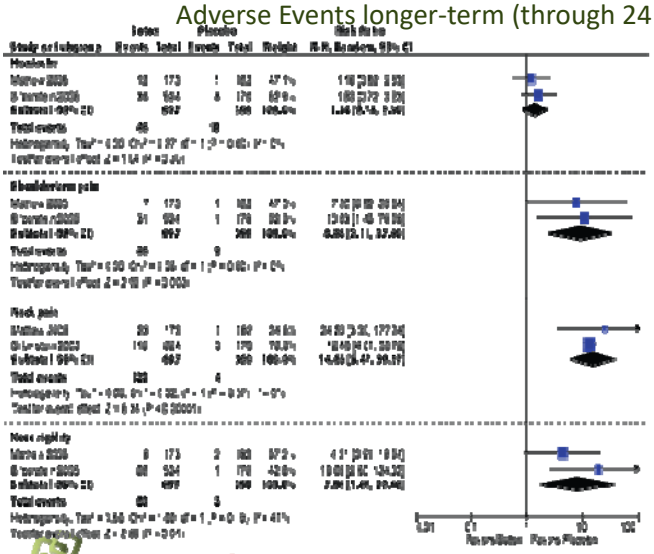
spectrumresearch

60

KQ 2: Safety Results

Chronic Daily Headache: BoNTA vs. Placebo

Adverse Events longer-term (through 24 weeks)



No difference in headache

With BoNTA: Significantly more

- Shoulder pain
- Neck pain and
- Neck rigidity

Wide CIs for most LOW evidence

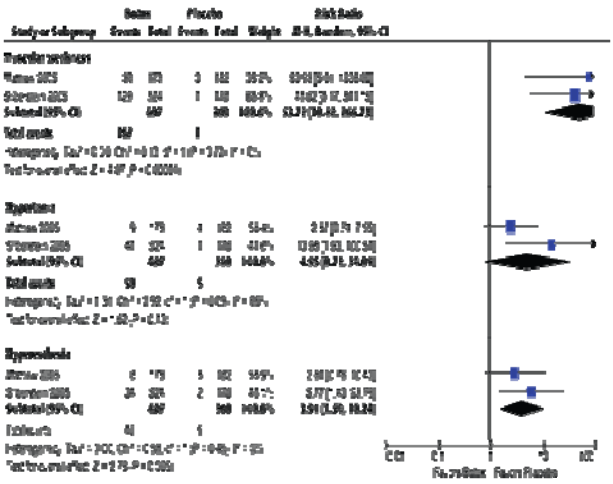
spectrumresearch

61

KQ 2: Safety Results

Chronic Daily Headache: BoNTA vs. Placebo

Adverse Events longer-term (through 24 weeks); LOW evidence



With BoNTA Significantly more muscle weakness

No difference in hypertonia

With BoNTA Significantly more Hyperesthesia

Wide CIs for all LOW evidence

spectrumresearch

62

KQ 2: Safety Results

Chronic Daily Headache: BoNTA vs. Topiramate

Adverse Events longer-term (through 24 weeks)

Outcome	Follow-up	RCTs	Down Grade	Conclusion	Quality
Nausea	12 wks	1RCT (Cady 2011) N= 59	Risk of Bias Imprecise	BoNTA 59.1% , topiramate 27.3% RR: 2.2, 95% CI 1.0, 4.7 **Conclusion:** Nausea was more common with BoNTA vs. topirimate	⊕⊕◯◯ LOW
Mild fatigue			Risk of Bias Imprecise	BoNTA 72.7%, topiramate 68.2%, RR: 1.0, 95% CI 0.7, 1.6 **Conclusion**: No difference	⊕⊕◯◯ LOW

spectrumresearch

63

KQ 2: Safety Results

Chronic Daily Headache: Massage vs. Sham (ultrasound)

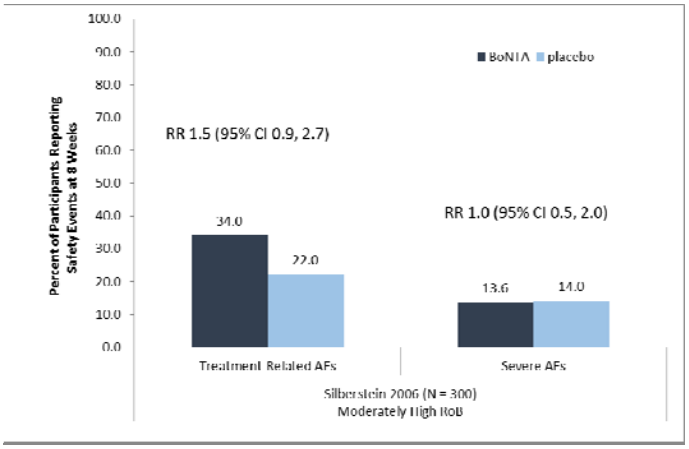
Adverse Events, short to intermediate term (3-9 weeks)

Outcome	Follow-up	RCTs	Down Grade	Conclusion*	Quality
Minor fever, mild soreness, and other discomfort	3-9 wks.	1 RCT (Chatchawan 2014) N = 72	Indirect Imprecise	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

spectrumresearch

64

KQ 2: Safety Results
CTTH: BoNTA vs. Placebo
Adverse events intermediate-term (8 weeks, 1 RCT)



No statistically significant difference between group for treatment-related or severe AEs

LOW evidence

spectrumresearch

65

KQ 2: Safety Results
CTTH: BoNTA vs. Placebo
Other adverse events: all time frames

Outcome	F/U	RCTs	Down Grade	Conclusion*	Quality
Pain at injection site	4, 8 , 12 wks	3 RCTs (Schmitt 2001, Hamdy 2009, Padberg 2004	Risk of Bias Indirect Imprecise	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: No differences at any time.**	⊕◯◯◯ INSUFFICIENT
Vertigo	4, 8 , 12 wks	2 RCTs (Schmitt 2001, N = 59) Padberg 2004, N= 40	Risk of Bias Indirect Imprecise	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

spectrumresearch

66

KQ 2: Safety Results
CTTH: Acupuncture, Manual Therapy/Manipulation

There is insufficient evidence to draw conclusions

	F/U	Outcome	Results
Acupuncture vs. Physiotherapy 1 RCT (n=62) Moderately High RoB	Short-, Intermediate-term (4-9 wks.)	• **Vasovagal reaction**	Unclear
Manual Therapy vs. Usual Care 1 RCT (n=82) Moderately Low RoB	Longer-term (18 wks.)	• **Any adverse events**	No diff

spectrumresearch

67

KQ 2: Safety Results
CTTH: Trigger Point Injections vs. Sham

Adverse events – longer term (12 weeks)

		Results, n/N (%)	
Author	**Outcome**	**TPI w/ lidocaine** (n/N) %	**Sham** (n/N) %
Karadas 2013 (Moderately High Risk of Bias)	**Serious adverse events**	0/24 (0%)	0/24 (0%)
	Any minor adverse event	7/24 (29.2%)	10/24 (41.7%)
	Injection site/injection pain	3/24 (12.5%)	4/24 (16.7%)
	Dizziness	2/24 (8.3%)	2/24 (8.3%)
	Back pain	2/24 (8.3%)	3/24 (12.5%)
	Cervical muscle spasm	0/24 (0%)	1/24 (4.2%)

INSUFFICIENT Evidence

LOW Evidence

spectrumresearch

68

KQ 2: Safety Results
CTTH: Transcranial Magnetic Stimulation vs. Sham

Minor adverse events – short term (8 weeks)

		Results, n/N (%)	
Author	**Outcome**	**TMS** (n/N) %	**Sham** (n/N) %
Teepker 2010 (Moderately High Risk of Bias)	**Assessment of visual motor threshold is uncomfortable**	5/14 (35.7%)	4/13 (30.8%)
	Headache	0/14 (0%)	2/13 (15.4%)
	Vigorous dreams	1/14 (7.1%)	0/13 (0%)
	Phonophobia	1/14 (7.1%)	0/13 (0%)
	Sitting is long-lasting and uncomfortable	1/14 (7.1%)	1/13 (7.7%)
	Sleepiness	1/14 (7.1%)	1/13 (7.7%)
	Amyostasia	1/14 (7.1%)	1/13 (7.7%)
	Testiness	1/14 (7.1%)	1/13 (7.7%)

All **INSUFFICIENT** evidence

spectrumresearch

69

KQ 3: Differential Effectiveness or Safety
Chronic Migraine

Acupuncture vs. Usual care (1 RCT, N=301, longer term):

Insufficient Evidence

- Patients with more severe baseline symptoms had greater improvement with acupuncture vs. usual care (interaction p-value 0.004, no data provided)
- No interaction observed
  - Headache type (CM vs. CTTH)
  - Age
  - Sex
  - Chronicity

spectrumresearch

70

KQ 3: Differential Effectiveness or Safety
Chronic Migraine

Acupuncture vs. Topiramate (1 RCT, N=66, longer term):

Insufficient evidence

- Authors report modification by baseline headache days and moderate/severe headache days (≥20 days vs. <20 days/month); In patients with more HA days or more moderate/severe HA days showed more improvement following acupuncture
- No interaction observed: other characteristics including demographic factors, baseline functional measures, headache characteristics or treatment expectations

spectrumresearch

71

KQ 3: Differential Effectiveness or Safety
Chronic Tension-Type Headache

Manual Therapy vs. Usual Care (1 RCT, N=82, longer term):

Insufficient Evidence

- No differential effect of treatment is observed for the subgroup of patients with comorbid migraine versus without migraine for reduction of mean headache days based on consideration of point estimates and overlap of confidence intervals (no formal test for interaction)

spectrumresearch

72

KQ 4: Economic studies

Chronic Migraine: BoNTA vs. Placebo

	Batty 2013 (QHES Score = 72)	Ruggeri 2014 (QHES , 25)
Population	Adult (aged 18-65 years), N =1384 PREEMPT 1 & 2	
Time horizon	24 months (12-week cycle length)	
Funding	Allergan, Inc. (Marlow, Buckinghamshire, UK)	NR
ICER	Base: £15,028/QALY	€815/QALY to €9,407/QALY
One-way SA	**ICERs ranged: £4945/QALY to £29,175/QALY**	NR
AUTHOR'S CONCLUSION	**BoNTA cost-effective at WTP £20,000 to £30,000/QALY and on 98% of occasions £30,000 per QALY; Model uncertainties relate to extrapolation beyond the 56 week trial.**	Incremental cost effectiveness of BoNTA is favorable.

spectrumresearch

73

KQ 4: Economic studies

Chronic Migraine: BoNTA vs. Placebo

	Batty 2013 (QHES Score = 72)	Ruggeri 2014 (QHES , 25)
STUDY LIMITATIONS	• No comparison to other medications/treatments • Unclear if some costs were underestimated. • The extent to which placebo is representative of usual care is not clear; the extent of placebo effect unclear. • Time horizon too short, given chronic nature of the condition; PREEMPT data go to 24 weeks (randomized phase). • The assumption that 24% of patients were able to stop BoNTA and remain largely HA free for 6 months is not well validated • Adverse events, related discontinuation not well described	• Lack of comparison to commonly used medications • No detail on outcomes, costs • No detail on sensitivity analyses • Time horizon limited

spectrumresearch

74

KQ 4: Economic studies

Chronic Migraine: Acupuncture vs. Usual Care

	Vickers 2004 (QHES Sore 71)
Population	255 adult (aged 16-65 years); Vickers RCT
Funding	Government (National Health Service, HTA Programme)
ICER	**£ 9,951/QALY (UK NHS perspective) £ 9,180/QALY(societal)**
SA ICERs range	£801/QALY (for a 10 year time horizon) to £12,333/QALY if GP provided the service (Payer); Cost-effective on 84% to 92% of the time at ceiling of £30,000
AUTHOR'S CONCLUSION	**Incremental cost-effectiveness favorable and below the WTP threshold; Estimated improvement in QOL correlates with observed reductions in headache severity and frequency.**
STUDY LIMITATIONS	• **Controls group: "usual care to avoid acupuncture", no detail provided; no comparison to more active treatments** • **Generalizability across settings and health systems is unclear** • **Limited time horizon (1 year)** • **The need for continued or periodic treatment: unclear** • **Limited sensitivity analyses for economic model inputs** • **Lack of long term follow-up data for benefits and harms.**

75

SUMMARY Efficacy: Chronic Migraine

BoNTA vs. Placebo – headache outcomes

		Strength of Evidence		
		LOW	MOD	HIGH
Longer term (16-24 wks.)	Responders (≥50% ↓ in migraine *episodes*)		3 RCTs	
	Responders (≥50% ↓ in migraine, HA *days*)		2 RCTs	
	↓ in mean migraine, HA *episodes* per month		2 RCTs	
	↓ in mean migraine, HA *days* per month*		3 RCTs	

Favors intervention – mod. to large effect

Favors intervention – small effect

No difference

Favors control

*unclear if change is clinically significant

76

SUMMARY Efficacy: Chronic Migraine (cont.)
BoNTA vs. Placebo – functional measures

		Strength of Evidence		
		LOW	MOD	HIGH
Longer term (24 wks.)	% with severe HIT-6 (≥60)		2 RCTs	
	↓ in mean HIT-6 score		2 RCTs	
	↓ in mean MIDAS score		1 RCTs	

Favors intervention – mod. to large effect
Favors intervention – small effect
No difference
Favors control

spectrumresearch

77

SUMMARY Efficacy: Chronic Migraine (cont.)
BoNTA vs. Active Controls

Longer term (12 wks.):		Strength of Evidence		
		LOW	MOD	HIGH
Topiramate*	Responders (≥50% ↓ in HA days)	1 RCT		
	Mean function scores (HIT-6, MIDAS, MIQ)	1 RCT		
Amytriptyline	Responders (≥50% ↓ in frequency of pain days)	1 RCT		
	Responders (≥3 point ↓ in VAS pain intensity)	1 RCT		

Favors intervention – mod. to large effect
Favors intervention – small effect
No difference
Favors control

*Insufficient evidence for all outcomes at 24 and 36 weeks

spectrumresearch

78

SUMMARY Efficacy: Chronic Migraine (cont.)
Acupuncture vs. Active Controls

			Strength of Evidence		
			LOW	MOD	HIGH
Acupuncture vs. Usual Care	Longer-term (36 wks.)	Responders (≥50% & ≥35% ↓ in HA days)	1 RCT		
		↓ in mean HA days	1 RCT		
Acupuncture vs. Topiramate	Short-term (4 wks.)	Responders (≥50%↓ in HA days)	1 RCT		
		↓ in mean HA days	1 RCT		
		Function (MIDAS)	1 RCT		

Favors intervention – mod. to large effect
Favors intervention – small effect
No difference
Favors control

spectrumresearch

79

SUMMARY Efficacy: Chronic Migraine (cont.)
Manual Therapy/Manipulation vs. Amitriptyline

		Strength of Evidence		
		LOW	MOD	HIGH
Short-term (4 wks.)	Responders (>20%, >40%, and >60% ↓ in HI scores)	1 RCT		
	↓ in % of days per month with HA	1 RCT		

Favors intervention – mod. to large effect
Favors intervention – small effect
No difference
Favors control

spectrumresearch

80

SUMMARY Efficacy: Chronic Migraine (cont.)
TMS vs. Sham

		Strength of Evidence LOW	MOD	HIGH
Short term (4 wks.)	Responders (>50% ↓ in migraine *attacks*)	1 RCT		
	Responders (>50% ↓ in HA severity)	1 RCT		
	↓ in mean migraine *attacks* per month	1 RCT		
	Functional disability rating normal/mild (%)	1 RCT		

- Favors intervention – mod. to large effect
- Favors intervention – small effect
- No difference
- Favors control

spectrumresearch

81

SUMMARY Efficacy: Chronic Daily Headache
BoNTA vs. Placebo, Topiramate

			Strength of Evidence LOW	MOD	HIGH
BoNTA vs. Placebo	Longer term (24 wks.)	Responders (≥50% ↓ in HA days)	1 RCT		
		↑ in HA free days	2 RCTs		
BoNTA vs. Topiramate	Short term (4 wks.)	↓ in mean HA days	1 RCT		
	Longer term (12 wks.)	↓ in mean HA days	1 RCT		
		Function (HIT-6, MIDAS)	1 RCT		

- Favors intervention – mod. to large effect
- Favors intervention – small effect
- No difference
- Favors control

spectrumresearch

82

SUMMARY Efficacy: Chronic Daily Headache (cont.)
Massage vs. Sham

		Strength of Evidence		
		LOW	MOD	HIGH
Short and Intermediate term (3, 9 wks.)	Reduction in number of HA attacks per month	1 RCT		
	Function (HDI)	1 RCT		

Favors intervention mod. to large effect
Favors intervention small effect
No difference
Favors control

spectrumresearch

83

SUMMARY Efficacy: Chronic Tension-Type Headache
Manual Therapy/Manipulation vs. Usual Care

		Strength of Evidence		
		LOW	MOD	HIGH
Longer-term (18 wks.)	Responders (>50% ↓ in HA *days* per 2 weeks)	1 RCT		
	Mean ↓ in HA *days* per 2 weeks*	1 RCT		
	Function (HIT-6*, HDI)	1 RCT		

Favors intervention – mod. to large effect
Favors intervention – small effect
No difference
Favors control

*May be clinically significant. One trial [Mathew 2005] considered a mean change from baseline of ≥3 headache days to be clinically significant; MD here is 4.9 days (95% CI 3.0, 7.0). For the HIT-6 MCID as defined by the authors was a >2.3 points; MD is 5.0 (95% CI 1.2, 9.0).

spectrumresearch

84

SUMMARY Efficacy: Chronic Tension-Type Headache (cont.)
All other comparisons, *Insufficient Evidence**

	F/U	Outcome	Results
BoNTA vs. Placebo 2 RCTs (n= 40, 59)	Short-, longer-term (4-8, 12 wks.)	• **Responders (≥25%, >45% ↓ in pain intensity)** • **↓ in HA *days* per mo.** • **mean HDI scores**	No diff + BoNTA + BoNTA
Acupuncture vs. Sham 2 RCTs (n= 30, 69)	Short-, longer-term (4-6, 26-52 wks.)	• **Responders (>33%, >50% ↑ on Headache Index)** • **↓ in HA *episodes* per mo.**	No diff No diff
Acupuncture vs. Exercise and vs. Relaxation 1 RCT (n=90)	Longer-term (12-26 wks.)	• **HA-free *periods* per wk.** • **HA-free *days* per wk.**	No diff No diff
Acupuncture vs. Physiotherapy 1 RCT (n=62)	Short-, Intermediate-term (4-9 wks.)	• **↓ in HA *episodes* per mo.** • **Sickness Impact Profile**	Unclear Unclear
TPI vs. Sham 1 RCT (n=48)	Longer-term (12 wks.)	• **↓ in HA *days* per mo.**	+ TPI

spectrumresearch ***All trials at MODERATELY HIGH risk of bias**

85

SUMMARY Safety: BoNTA vs. Placebo

Outcome	CM	CDH	CTTH
Treatment-related AEs	**↑ BoNTA (2-fold)** (2 RCTs)	**↑ BoNTA (2-fold)*** (2 RCTs)	**NS** (1 RCT)
Serious AE	**↑ BoNTA (2-fold)** (2 RCTs)	**↑ BoNTA (2-fold)** (2 RCTs)	**NS** (1 RCT)
Treatment-related severe AEs	**Rare, No conclusion** (2 RCTs)	---	---
Discontinuation due to AEs	**↑ BoNTA (3-fold)** (2 RCTs)	---	---

Moderate evidence Low evidence Insufficient evidence

spectrumresearch

86

SUMMARY Safety: BoNTA vs. Active Control

All *LOW* Strength of Evidence

Chronic Migraine

vs. Topiramate (1 RCT):

- ↓ drug-related, possible/probable drug-related AEs with BoNTA (NS)
- ↓ discontinuation due to AEs with BoNTA

vs. Amitriptyline (1 RCT):

- injection site pain and edema with BoNTA (NR for control)

Chronic Daily Headache

vs. Topiramate (1 RCT):

- ↑ Nausea (2-fold) with BoNTA (marginally sig.)
- Mild fatigue, no difference b/w groups

spectrumresearch

87

SUMMARY Safety: Acupuncture

3 RCTs (2 in CM, 1 in CTTH) compared Acupuncture with an Active Control and reported limited data on adverse events:

LOW evidence of :

- Any side effect: significantly less common with acupuncture vs. topiramate (1 RCT, CM)
- NS difference for discontinuation due to AEs (vs. topiramate, 1 RCT, CM)
- NS difference between groups for headache (vs. usual care, 1 RCT, CM)

INSUFFICIENT evidence:

- No Serious AEs or deaths reported (2 RCT, vs. usual care and vs. topiramate, CM)
- NS difference in discontinuation (vs. usual care, 1 RCT, CM)
- Vasovagal reaction - "a few" in the acupuncture group (vs. physiotherapy, 1 RCT, CTTH)

spectrumresearch

88

SUMMARY Safety: Manipulation/Manual Therapy

Spinal Manipulation vs. Amitriptyline (1 RCT, CM):

LOW evidence:

- ↓ Discontinuation due to AEs with SMT
- 58% of amitriptyline users reported some AE

Manual Therapy vs. Usual Care (1 RCT, CTTH):

INSUFFICIENT evidence:

- No adverse events reported in either group

spectrumresearch

89

SUMMARY Safety: Transcranial Magnetic Stimulation

TMS vs. Sham for Chronic Migraine (2 RCTs)

LOW evidence:

- Discomfort with high frequency TMS in 100% of TMS, 15% of sham (1 RCT)

INSUFFICIENT evidence:

- NS difference between groups for:
  - Discontinuation due to AEs for high (1 RCT) or low frequency (1 RCT) TMS (small samples)
  - Minor events, with low frequency TMS but sample size likely precluded detection (1 RCT)

spectrumresearch

90

SUMMARY Safety: Massage, Trigger Point Injections

Massage vs. Sham for CDH (1 RCT)

LOW evidence:

- NS differences between groups: mild fever, mild soreness, other discomforts; small N

TPI vs. Sham for CTTH (1 RCT)

LOW evidence:

- NS difference in injection site pain, dizziness, back pain, cervical muscles spasm or any adverse event; small N

INSUFFICIENT evidence:

- No serious AEs reported; small N

spectrumresearch

91

SUMMARY: Differential Efficacy or Harm

Chronic Migraine

- **Greater improvement with Acupuncture vs. Active Controls in patients with the following baseline characteristics:**
  - **More severe symptoms (not specified further)** (versus Usual Care, 1 RCT)
  - **More HA days (≥ 20 vs. < 20 days)** (versus Topiramate, 1 RCT)
- **No modification by other factors in either trial**
- **All evidence INSUFFICIENT**

spectrumresearch

92

SUMMARY: Cost-Effectiveness

Chronic Migraine, BoNTA vs. Placebo

1 poor to moderate study, 1 very poor study

- European studies based on PREEMPT trials;
- Suggests that BoNTA may be cost-effective; study limitations include lack of active comparator, short time horizon and unknown benefit/safety long term;

Chronic Migraine, Acupuncture vs. Usual care

1 poor to moderate quality study (UK):

- Suggests cost-effectiveness of acupuncture is favorable; limitations no active treatment comparator, limited time horizon, limited sensitivity analyses

spectrumresearch

93

Considerations

- Medication overuse at baseline and prior prophylactic medications common; the impact on outcomes is not clear
- Data beyond 24 weeks are limited; the implications/needs for continued treatment, benefits and harms longer term are unclear.
- Limited data on interventions vs. common active comparators
- Impact of co-existent headache types on outcomes is not clear
- Placebo effect in treatment of headache may be substantial
- Regression to the mean possible for some outcomes
- General quality of studies across interventions is low.
- Nomenclature related to CDH/CM has evolved

spectrumresearch

94

Appendices

KQ 1: Efficacy Results
Comparison of CM and CDH : BoNTA vs. Placebo

Outcome	CM	CDH	Notes
≥ 50 % reduction in headache days at 24 weeks	PREEMPT 1&2 RR 1.3 (95% CI 1.2, 1.5) RD 12.0% (6.5%, 17.4%)	Mathew 2005 RR 1.6, (95% CI 1.2, 2.2) RD 15.2%,(5.5%,24.9%)	Pooled across types: RR 1.4, (95% CI 1.2, 1.6) RD 12.8%, (8.0%,17.5%)
Reduction of HA Days (24 Wks)	Pooled (3 trials) -1.77(-2.49, -1.06)	NR	Clinical significance unclear
Change in mean # HA –Free days (24 weeks)	NR	Pooled (2 trials) MD 0.74 (CI -1.51, 2.99)	NS

97

Washington State Health Care Authority

Final key questions and background

Treatment of chronic migraine and chronic tension-type headache

Background

Headaches are among the most common reasons for patient visits in primary care and neurology settings. 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 and accounts for 90% of all headaches; 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. CCTH and CM will be evaluated in this report. Both chronic tension-type headache and chronic migraine are associated with substantial impact on the physical, psychological and social well-being of patients as well as healthcare costs. They are a leading cause of disability and diminished quality of life.

Usual management of tension-type headache includes pharmacotherapy, psychological therapy and physical therapy. Migraine management generally focuses on pharmacological 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. Some of the treatments that are used in the acute setting are also employed for prevention/long term treatment. 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 headaches in adults with chronic migraine (≥ 15 days per months with headache lasting ≥4 hours a day). 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. Pain may not be confined to the affected muscle and may affect distant areas such as the head and neck, which is called referred pain. 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. FDA approval has been received for the Cerena Transcranial Magnetic Stimulator (TMS).

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, transcranial magnetic stimulations, acupuncture, manipulation, manual therapy and massage. The topic is 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.

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, 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, 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, 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, acupuncture, transcranial magnetic stimulation, manipulation/manual therapy and massage compared with standard alternative treatment options, placebo, sham, waitlist or no treatment?

Proposed scope:

Population: Adults with chronic migraine (with or without aura) or chronic tension-type headache. Chronic headache is defined as 15 or more days each month for at least 3 months or more than 180 days a year.

Interventions: Botulinum toxin injection, trigger point injection, acupuncture, transcranial magnetic stimulation (TMS), manipulation/manual therapy, massage

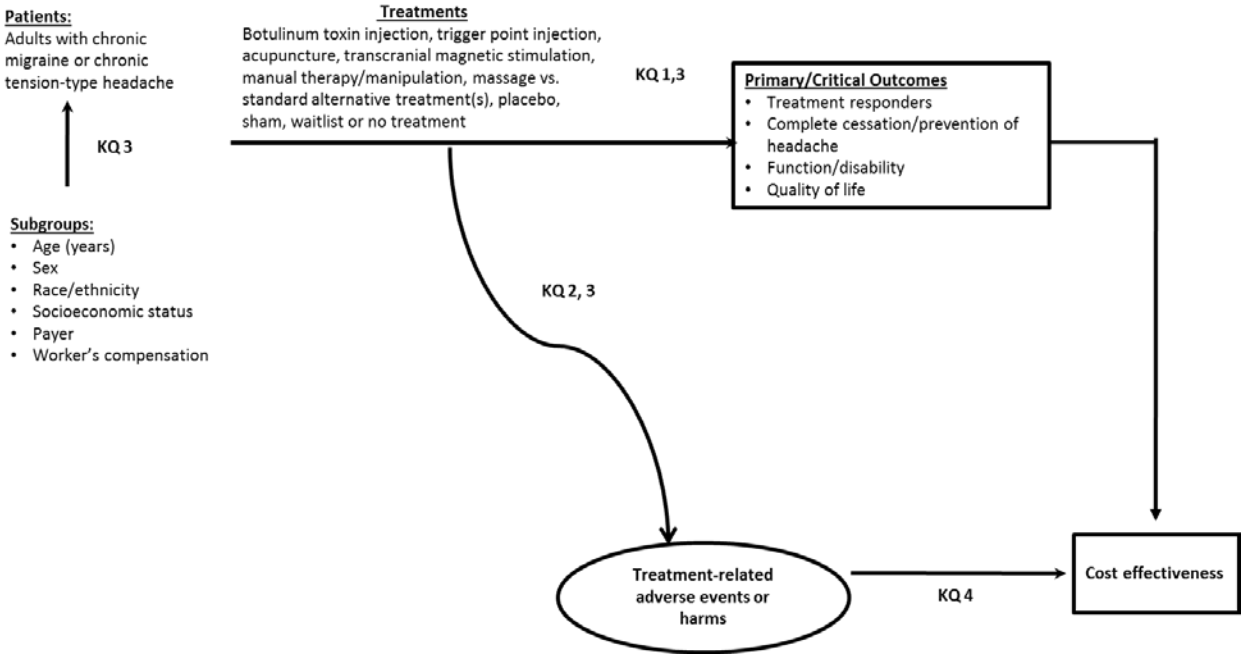
Comparators: Standard alternative treatment(s), sham, placebo, waitlist or no treatment

Outcomes: Primary/critical outcomes are 1) the proportion of treatment responders, 2) complete cessation/prevention of headache, 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.

Analytic Framework



Public comment and response

See **Draft key questions: Comment and response** published separately.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety Outcomes	Importance of Outcome	Safety Evidence / Confidence in Evidence
Adverse events		

Efficacy – Effectiveness Outcomes	Importance of Outcome	Efficacy / Effectiveness Evidence
Response to treatment (success)		
Reduction in episodes		
Reduction in headache days		
Function/disability measures (validated)		
Headache intensity/pain		

Cost Outcomes	Importance of Outcome	Cost Evidence
Cost-utility		
Cost-effectiveness		
Direct cost		

Special Population / Considerations Outcomes	Importance of Outcome	Special Populations/ Considerations Evidence
Headache type		
Age		
Gender		
Chronicity		
Baseline function		
Treatment expectations		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

For Safety: Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Efficacy/Effectiveness: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Cost Outcomes/Cost-Effectiveness: Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered _____ Covered Unconditionally _____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

Medicare and Coverage Guidelines

[From page 122 of the Final Evidence Report]
Centers for Medicare Medicaid Services (CMS)

National Coverage Decision (NCD) There is no NCD from CMS for the use of botulinum toxin A for headache or chronic migraine.

Guidelines

[From page 100 of Final Evidence Report]

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] *Neuromodulation of chronic headaches: position statement from the European Headache Federation* European Union	1 sham-controlled study, 1 RCT, 1 study type NR	For repetitive transcranial magnetic stimulation in patients with chronic primary headache‡: 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	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
		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 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†. 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†.	NR
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

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
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* Scotland	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
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	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
		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).	
Japanese Society for Neurology (2013)[125] *Clinical Practice Guidelines for Chronic Headache* Japan	12 studies, study type NR 8 studies, study type NR NR NR	Botox **may be considered** for chronic migraine where other treatments have failed. 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 A†† Grade C†† 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.