Washington State Health Care Authority

Treatment of chronic migraine and chronic tension-type headache

Final evidence report: Appendices

April 14, 2017

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Treatment of Chronic Migraine and Chronic Tension-Type Headache

Provided by:

Spectrum Research, Inc.

Final Report
APPENDICES

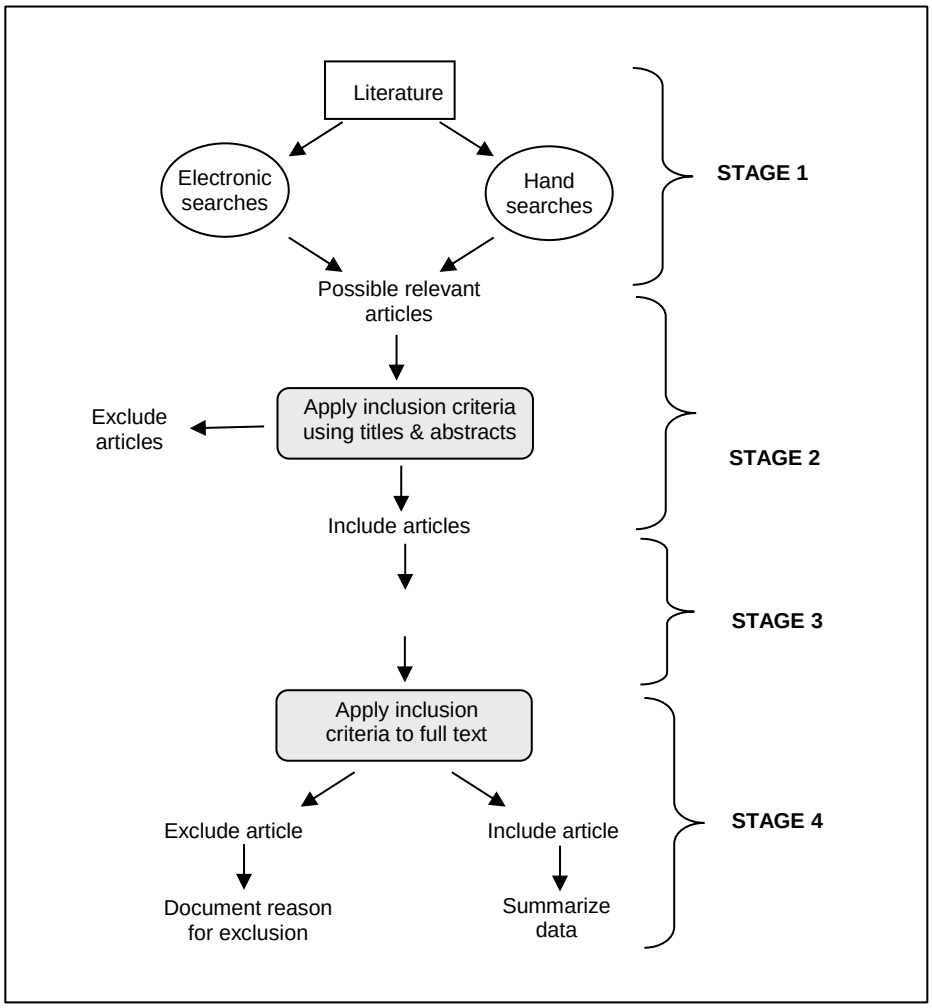
April 14, 2017

TABLE OF CONTENTS

APPENDICES

TABLES

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)
Search date: Inception through 10/23/2016
Filters: Abstract available, English, Human

	Search terms	Citations
	TRIGGER POINTS	
1.	Headache Disorders[MeSH] OR Headache Disorders, Primary[MeSH] OR Tension-Type Headache[MeSH] OR Migraine Disorders[MeSH] OR Headache/therapy [MeSH] OR "tension headache"[TIAB] OR "migraine"[TIAB] OR migrain*[TIAB] OR tension*[TIAB]	57,433
2.	Injections[MeSH] OR Injections, intramuscular[MeSH] OR inject*[TIAB] OR injection*[TIAB] OR "Injection"[TIAB]	227,743
3.	Trigger Points[MeSH] OR trigger*[TIAB] OR trigger point*[TIAB] OR "trigger"[TIAB] OR "trigger point"[TIAB] OR "trigger points"[TIAB] OR "dry needling"[TIAB] OR "dry needle"[TIAB] OR Anesthetics, local[MeSH] OR Steroids[MeSH]	395,049
4.	#1 AND #2 AND #3	**310**
	BOTULINUM TOXIN	
5.	Botulinum Toxins, Type A[MeSH] OR "botulinum toxin type a"[TIAB] OR onabotulinumtoxinA[All Fields] OR "botox"[TIAB] OR "botulinum"[TIAB] OR botox*[TIAB] OR botulinum*[TIAB]	8,174
6.	#1 AND #5	**394**
7.	**TRANSCRANIAL MAGNETIC STIMULATION**	
8.	Transcranial Magnetic Stimulation[MeSH] OR Magnetic Field Therapy[MeSH] OR Magnets[MeSH] OR "transcranial magnetic stimulation"[TIAB] OR "magnetic stimulation"[TIAB] OR "magnetic stimulation therapy"[TIAB] OR "magnetic therapy"[TIAB] OR "transcranial stimulation therapy"[TIAB] OR "transcranial stimulation"[TIAB] OR "transcranial therapy"[TIAB] OR magnetic stimulation*[TIAB] OR transcranial stimulation*[TIAB]	13,431
9.	#1 AND #7	**170**
	ACUPUNCTURE	
10.	Acupuncture[MeSH] OR Acupuncture Therapy[MeSH] OR "acupuncture"[TIAB] OR "acupuncture therapy"[TIAB] OR "manual acupuncture"[TIAB] OR "electroacupuncture"[TIAB] OR "auricular acupuncture"[TIAB] OR "eye acupuncture"[TIAB] or "scalp acupuncture"[TIAB] OR acupunct*[TIAB] OR acupuncture*[TIAB] OR electroacupunct*[TIAB] OR electro-acupunct*[TIAB]	7,712
11.	#1 AND #9	**350**

	Search terms	Citations
	CHIROPRACTIC/MANUAL THERAPY	
12.	Musculoskeletal Manipulations[MeSH] OR Manipulation, Spinal[MeSH] OR Manipulation, Chiropractic[MeSH] OR Manipulation, Osteopathic[MeSH] OR "chiropractic"[TIAB] OR "osteopathic manipulation"[TIAB] OR "chiropractic manipulation"[TIAB] OR "cervical manipulation"[TIAB] OR "spinal manipulation"[TIAB] OR "manual therapy"[TIAB] OR chiropract*[TIAB] OR osteopath*[TIAB]	10,118
13.	#1 AND #11	**358**
	MASSAGE	
14.	Massage[MeSH] OR "massage"[TIAB] OR "massage therapy"[TIAB] OR massage*[TIAB] OR massage therapy*[TIAB]	4832
15.	#1 AND #13	**174**

Search strategy (EMBASE)
Search date: Inception through 11/10/2016
Filters: age (young adult through elderly), study type (human, controlled study, clinical trial, randomized controlled trial, controlled clinical trial, systematic review), publication type (article)

	Search terms	Citations
	TRIGGER POINTS	
1.	"Headache Disorders"/exp OR "Headache Disorders, Primary"/exp OR "Tension-Type Headache"/exp OR "Migraine Disorders"/exp OR "Headache/therapy"/exp OR "tension headache":ab,ti OR "migraine":ab,ti OR migrain*:ab,ti OR tension*:ab,ti	355,493
2.	Injections/exp OR Injections, intramuscular/exp OR inject*:ab,ti OR injection*:ab,ti OR "Injection":ab,ti	807,364
3.	"Trigger Points"/exp OR trigger*:ab,ti OR "trigger point":ab,ti OR "trigger points":ab,ti OR "dry needling":ab,ti OR "dry needle":ab,ti OR "Anesthetics, local"/exp OR "local anesthetics"/exp OR Steroids/exp	1,770,890
4.	#1 AND #2 AND #3	**1,146**
	BOTULINUM TOXIN	
5.	"Botulinum Toxins, Type A"/exp OR "botulinum toxin type a":ab,ti OR onabotulinumtoxinA OR "botox":ab,ti OR botox*:ab,ti OR botulinum*:ab,ti	27,186
6.	#1 AND #5	**486**
	TRANSCRANIAL MAGNETIC STIMULATION	
7.	"Transcranial Magnetic Stimulation"/exp OR "Magnetic Field Therapy"/exp OR Magnets/exp OR "transcranial magnetic stimulation":ab,ti OR "magnetic stimulation":ab,ti OR "magnetic stimulation therapy":ab,ti OR "magnetic	27,005

	Search terms	Citations
	therapy":ab,ti OR "transcranial stimulation therapy":ab,ti OR "transcranial stimulation":ab,ti OR "transcranial therapy":ab,ti OR "magnetic stimulation*":ab,ti OR "transcranial stimulation*":ab,ti	
8.	#1 AND #7	**311**
	ACUPUNCTURE	
9.	Acupuncture/exp OR "Acupuncture Therapy"/exp OR "acupuncture":ab,ti OR "acupuncture therapy":ab,ti OR "manual acupuncture":ab,ti OR "electroacupuncture":ab,ti OR "auricular acupuncture":ab,ti OR "eye acupuncture":ab,ti or "scalp acupuncture":ab,ti OR acupunct*:ab,ti OR acupuncture*:ab,ti OR electroacupunct*:ab,ti OR electro-acupunct*:ab,ti	40,097
10.	#1 AND #9	**740**
	CHIROPRACTIC/MANUAL THERAPY	
11.	"Musculoskeletal Manipulations"/exp OR "Manipulation, Spinal"/exp OR "Manipulation, Chiropractic"/exp OR "Manipulation, Osteopathic"/exp OR "chiropractic":ab,ti OR "osteopathic manipulation":ab,ti OR "chiropractic manipulation":ab,ti OR "cervical manipulation":ab,ti OR "spinal manipulation":ab,ti OR "manual therapy":ab,ti OR chiropract*:ab,ti OR osteopath*:ab,ti	34,957
12.	#1 AND #11	**586**
	MASSAGE	
13.	Massage/exp OR "massage":ab,ti OR "massage therapy":ab,ti OR massage*:ab,ti OR massage therapy*:ab,ti	4,746
14.	#1 AND #13	**117**

Search strategy (Cochrane)
Search date: Inception through 11/10/2016

	Search terms	Citations
	TRIGGER POINTS	
1.	"Headache Disorders"(MeSH) OR "Headache Disorders, Primary"(MeSH) OR "Tension-Type Headache"(MeSH) OR "Migraine Disorders"(MeSH) OR "Headache/therapy"(MeSH) OR "tension headache":ab,ti OR "migraine":ab,ti OR migrain*[TIAB] OR tension*[TIAB]	8293
2.	Injections(MeSH) OR Injections, intramuscular(MeSH) OR inject*:ab,ti OR injection*:ab,ti OR "Injection":ab,ti	43422
3.	"Trigger Points"(MeSH) OR trigger*:ab,ti OR "trigger point":ab,ti OR "trigger points":ab,ti OR "dry needling":ab,ti OR "dry needle":ab,ti OR "Anesthetics, local"(MeSH) OR "local anesthetics"(MeSH) OR Steroids(MeSH)	5649
4.	#1 AND #2 AND #3	**24***

	Search terms	Citations
	BOTULINUM TOXIN	
5.	"Botulinum Toxins, Type A"(MeSH) OR "botulinum toxin type a":ab,ti OR onabotulinumtoxinA OR "botox":ab,ti OR botox*:ab,ti OR botulinum*:ab,ti	2126
6.	#1 AND #5	**132**
	TRANSCRANIAL MAGNETIC STIMULATION	
7.	"Transcranial Magnetic Stimulation"(MeSH) OR "Magnetic Field Therapy"(MeSH) OR Magnets(MeSH) OR "transcranial magnetic stimulation":ab,ti OR "magnetic stimulation":ab,ti OR "magnetic stimulation therapy":ab,ti OR "magnetic therapy":ab,ti OR "transcranial stimulation therapy":ab,ti OR "transcranial stimulation":ab,ti OR "transcranial therapy":ab,ti OR "magnetic stimulation"*:ab,ti OR "transcranial stimulation"*:ab,ti	2643
8.	#1 AND #7	**37**
	ACUPUNCTURE	
9.	Acupuncture(MeSH) OR "Acupuncture Therapy"(MeSH) OR "acupuncture":ab,ti OR "acupuncture therapy":ab,ti OR "manual acupuncture":ab,ti OR "electroacupuncture":ab,ti OR "auricular acupuncture":ab,ti OR "eye acupuncture":ab,ti or "scalp acupuncture":ab,ti OR acupunct*:ab,ti OR acupuncture*:ab,ti OR electroacupunct*:ab,ti OR electro-acupunct*:ab,ti	8618
10.	#1 AND #9	**319**
	CHIROPRACTIC/MANUAL THERAPY	
11.	"Musculoskeletal Manipulations"(MeSH) OR "Manipulation, Spinal"(MeSH) OR "Manipulation, Chiropractic"(MeSH) OR "Manipulation, Osteopathic"(MeSH) OR "chiropractic":ab,ti OR "osteopathic manipulation":ab,ti OR "chiropractic manipulation":ab,ti OR "cervical manipulation":ab,ti OR "spinal manipulation":ab,ti OR "manual therapy":ab,ti OR chiropract*:ab,ti OR osteopath*:ab,ti	1777
12.	#1 AND #11	**85**
	MASSAGE	
13.	Massage(MeSH) OR "massage":ab,ti OR "massage therapy":ab,ti OR massage*:ab,ti OR massage therapy*:ab,ti	2485
14.	#1 AND #13	**98**

*"Other review" identified from search was excluded
†Method study identified from search was excluded

Parallel strategies were used to search the Cochrane Library, EMBASE, and others listed below. Keyword searches were conducted in the other listed resources. In addition, handsearching of included studies was performed.

Electronic Database Searches

The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

	Citation	Reason for exclusion after full-text review
	RCTs considered and excluded	
1.	(2014). "Medical devices; neurological devices; classification of the transcranial magnetic stimulator for headache. Final order." Fed Regist **79**(130): 38457-38459.	Regulatory document
2.	Alecrim-Andrade, J., J. A. Maciel-Junior, et al. (2008). "Acupuncture in migraine prevention: a randomized sham controlled study with 6-months posttreatment follow-up." Clin J Pain **24**(2): 98-105.	Included episodic and chronic migraine, did not stratify; baseline characteristics suggest primarily episodic migraine
3.	Alecrim-Andrade, J., J. A. Maciel-Junior, et al. (2006). "Acupuncture in migraine prophylaxis: a randomized sham-controlled trial." Cephalalgia **26**(5): 520-529.	Included episodic and chronic migraine, did not stratify; baseline characteristics suggest primarily episodic migraine
4.	Almaraz, A. C., E. Dilli, et al. (2010). "The effect of prophylactic medications on TMS for migraine aura." Headache **50**(10): 1630-1633.	Subgroup analysis of Lipton 2010 study, which was excluded because study population did not meet inclusion criteria of interest
5.	Ambrosio, E. M., K. Bloor, et al. (2012). "Costs and consequences of acupuncture as a treatment for chronic pain: a systematic review of economic evaluations conducted alongside randomised controlled trials." Complement Ther Med **20**(5): 364-374.	Systematic review article of economic evaluations, includes conditions beyond chronic headache; 2 headache econ evaluations included episodic and chronic headache, did not stratify
6.	Anand, K. S., A. Prasad, et al. (2006). "Botulinum toxin type A in prophylactic treatment of migraine." Am J Ther **13**(3): 183-187.	Included episodic and chronic migraine, did not stratify
7.	Anderson, R. E. and C. Seniscal (2006). "A comparison of selected osteopathic treatment and relaxation for tension-type headaches." Headache **46**(8): 1273-1280.	< 15 subjects per group
8.	Astin, J. A. and E. Ernst (2002). "The effectiveness of spinal manipulation for the treatment of headache disorders: a systematic review of randomized clinical trials." Cephalalgia **22**(8): 617-623.	Review article, not a formal systematic review
9.	Bendtsen, L., S. Evers, et al. (2010). "EFNS guideline on the treatment of tension-type headache - report of an EFNS task force." Eur J Neurol **17**(11): 1318-1325.	Guideline with minimal detail about studies and evidence base

	Citation	Reason for exclusion after full-text review
10.	Bhola, R., E. Kinsella, et al. (2015). "Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program." J Headache Pain **16**: 535.	Case series, not designed to primarily assess safety; 69% chronic migraine, not stratified
11.	Biondi, D. M. (2005). "Noninvasive treatments for headache." Expert Rev Neurother **5**(3): 355-362.	Older systematic review, not a formal analysis; the 1 included acupuncture study does not meet inclusion criteria for HTA
12.	Blumenfeld, A. M., J. D. Schim, et al. (2008). "Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine." Headache **48**(2): 210-220.	< 15 subjects per group
13.	Boline, P. D., K. Kassak, et al. (1995). "Spinal manipulation vs. amitriptyline for the treatment of chronic tension-type headaches: a randomized clinical trial." J Manipulative Physiol Ther **18**(3): 148-154.	Included episodic and chronic migraine, did not stratify; did not assess outcome measures of interest
14.	Bronfort, G., N. Nilsson, et al. (2004). "Non-invasive physical treatments for chronic/recurrent headache." Cochrane Database Syst Rev(3): Cd001878.	Cochrane systematic review; included studies that did not meet inclusion criteria for HTA
15.	Bronfort, G., W. J. Assendelft, et al. (2001). "Efficacy of spinal manipulation for chronic headache: a systematic review." J Manipulative Physiol Ther **24**(7): 457-466.	More recent systematic review is Bronfort 2014
16.	Bryans, R., M. Descarreaux, et al. (2011). "Evidence-based guidelines for the chiropractic treatment of adults with headache." J Manipulative Physiol Ther **34**(5): 274-289.	Guideline; some included studies did not meet inclusion criteria for HTA
17.	Cady, R. and C. Schreiber (2008). "Botulinum toxin type A as migraine preventive treatment in patients previously failing oral prophylactic treatment due to compliance issues." Headache **48**(6): 900-913.	Included episodic and chronic migraine, did not stratify
18.	Carlsson, J. and U. Rosenhall (1990). "Oculomotor disturbances in patients with tension headache treated with acupuncture or physiotherapy." Cephalalgia **10**(3): 123-129.	Did not meet inclusion criteria for outcomes of interest
19.	Castien, R., A. Blankenstein, et al. (2013). "The working mechanism of manual therapy in participants with chronic tension-type headache." J Orthop Sports Phys Ther **43**(10): 693-699.	Nonrandomized, comparative study
20.	Cernuda-Morollon, E., C. Ramon, et al. (2015). "Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year?" Cephalalgia **35**(10): 864-868.	Case series, not designed to primarily assess safety
21.	Chaibi, A. and M. B. Russell (2014). "Manual therapies for primary chronic headaches: a systematic review of randomized controlled trials." J Headache Pain **15**: 67.	Systematic review; included studies that did not meet inclusion criteria for HTA

Citation	Reason for exclusion after full-text review
22. Chaibi, A., P. J. Tuchin, et al. (2011). "Manual therapies for migraine: a systematic review." J Headache Pain **12**(2): 127-133.	More recent systematic review is Chaibi 2014
23. Conforto, A. B., E. Amaro, Jr., et al. (2014). "Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine." Cephalalgia **34**(6): 464-472.	< 15 subjects per group
24. Cummings, M. (2009). "Modellvorhaben Akupunktur--a summary of the ART, ARC and GERAC trials." Acupunct Med **27**(1): 26-30.	Review of 4 large trials, all of which included episodic and chronic migraine and tension type headache, not stratified
25. Davis, M. A., R. W. Kononowech, et al. (2008). "Acupuncture for tension-type headache: a meta-analysis of randomized, controlled trials." J Pain **9**(8): 667-677.	Systematic review; included studies did not meet inclusion criteria for HTA
26. De Hertogh, W., P. Vaes, et al. (2009). "Preliminary results, methodological considerations and recruitment difficulties of a randomised clinical trial comparing two treatment regimens for patients with headache and neck pain." BMC Musculoskelet Disord **10**: 115.	Did not assess population of interest
27. Deng, Z. Q., H. Zheng, et al. (2012). "Health economic evaluation of acupuncture along meridians for treating migraine in China: results from a randomized controlled trial." BMC Complement Altern Med **12**: 75.	Cost-effectiveness analysis of RCTs that included episodic and chronic migraine, did not stratify
28. Diener, H. C., D. W. Dodick, et al. (2014). "Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine." Eur J Neurol **21**(6): 851-859.	Pooled analysis of multiple trials for safety outcomes
29. Diener, H. C., K. Kronfeld, et al. (2006). "Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial." Lancet Neurol **5**(4): 310-316.	Included episodic and chronic migraine, did not stratify; baseline characteristics suggest primarily episodic migraine
30. Dodick, D. W., C. T. Schembri, et al. (2010). "Transcranial magnetic stimulation for migraine: a safety review." Headache **50**(7): 1153-1163.	Review article with focus on safety, includes conditions beyond chronic headache
31. Dodick, D. W., A. Mauskop, et al. (2005). "Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study." Headache **45**(4): 315-324.	Subgroup analysis of subjects who were not taking prophylactic headache medication, from Mathew 2005
32. Dowson, D. I., G. T. Lewith, et al. (1985). "The effects of acupuncture versus placebo in the treatment of headache." Pain **21**(1): 35-42.	Included episodic and chronic migraine, did not stratify; comparator is “mock transcutaneous nerve stimulation”

	Citation	Reason for exclusion after full-text review
33.	Endres, H. G., G. Bowing, et al. (2007). "Acupuncture for tension-type headache: a multicentre, sham-controlled, patient-and observer-blinded, randomised trial." J Headache Pain **8**(5): 306-314.	>50% episodic tension type headache, did not stratify
34.	Erdemoglu, A. K. and A. Varlibas (2007). "The long-term efficacy and safety of botulinum toxin in refractory chronic tension-type headache." J Headache Pain **8**(5): 294-300.	Case series, not designed to primarily assess safety
35.	Ernst, E. (2004). "Manual therapies for pain control: chiropractic and massage." Clin J Pain **20**(1): 8-12.	Review article, not a formal systematic review
36.	Espi-Lopez, G. V., A. Gomez-Conesa, et al. (2014). "Treatment of tension-type headache with articulatory and suboccipital soft tissue therapy: A double-blind, randomized, placebo-controlled clinical trial." J Bodyw Mov Ther **18**(4): 576-585.	>50% episodic tension type headache, did not stratify
37.	Espi-Lopez, G. V., C. Rodriguez-Blanco, et al. (2014). "Effect of manual therapy techniques on headache disability in patients with tension-type headache. Randomized controlled trial." Eur J Phys Rehabil Med **50**(6): 641-647.	>50% episodic tension type headache, did not stratify
38.	Evers, S., J. Vollmer-Haase, et al. (2004). "Botulinum toxin A in the prophylactic treatment of migraine--a randomized, double-blind, placebo-controlled study." Cephalalgia **24**(10): 838-843.	Included episodic and chronic migraine, did not stratify
39.	Facco, E., A. Liguori, et al. (2013). "Acupuncture versus valproic acid in the prophylaxis of migraine without aura: a prospective controlled study." Minerva Anestesiol **79**(6): 634-642.	Included episodic and chronic migraine, did not stratify
40.	Farinelli, I., G. Coloprisco, et al. (2006). "Long-term benefits of botulinum toxin type A (BOTOX) in chronic daily headache: a five-year long experience." J Headache Pain **7**(6): 407-412.	Case series, not designed to primarily assess safety
41.	Fernandez-de-Las-Penas, C., C. Alonso-Blanco, et al. (2006). "Are manual therapies effective in reducing pain from tension-type headache?: a systematic review." Clin J Pain **22**(3): 278-285.	Systematic review, included articles did not assess the interventions of interest for HTA
42.	Fernandez-de-las-Penas, C., C. Alonso-Blanco, et al. (2006). "Methodological quality of randomized controlled trials of spinal manipulation and mobilization in tension-type headache, migraine, and cervicogenic headache." J Orthop Sports Phys Ther **36**(3): 160-169.	Review, does not provide enough detail of included literature
43.	France, S., J. Bown, et al. (2014). "Evidence for the use of dry needling and physiotherapy in the management of cervicogenic or tension-type headache: a systematic review." Cephalalgia **34**(12): 994-1003.	Many articles included in systematic review did not meet criteria for population of interest
44.	Garcia-Leiva, J. M., J. Hidalgo, et al. (2007). "Effectiveness of ropivacaine trigger points inactivation in the prophylactic	Case series; < 80% with chronic migraine diagnosis

	Citation	Reason for exclusion after full-text review
	management of patients with severe migraine." Pain Med **8**(1): 65-70.	
45.	Gil-Gouveia, R. and P. J. Goadsby (2009). "Neuropsychiatric side-effects of lidocaine: examples from the treatment of headache and a review." Cephalalgia **29**(5): 496-508.	Review and case series; did not assess population of interest
46.	Goldberg, L. D. (2005). "The cost of migraine and its treatment." Am J Manag Care **11**(2 Suppl): S62-67.	Not a formal economic study
47.	Griggs, C. and J. Jensen (2006). "Effectiveness of acupuncture for migraine: critical literature review." J Adv Nurs **54**(4): 491-501.	Systematic review that assessed quality elements only of publications, did not meet inclusion criteria for HTA
48.	Hansen, P. E. and J. H. Hansen (1985). "Acupuncture treatment of chronic tension headache--a controlled cross-over trial." Cephalalgia **5**(3): 137-142.	Unclear if episodic or chronic tension type headache; did not report outcomes of interest
49.	Hao, X. A., C. C. Xue, et al. (2013). "Factors associated with conflicting findings on acupuncture for tension-type headache: qualitative and quantitative analyses." J Altern Complement Med **19**(4): 285-297.	Systematic review; included studies did that not meet inclusion criteria for HTA
50.	Harden, R. N., J. Cottrill, et al. (2009). "Botulinum toxin a in the treatment of chronic tension-type headache with cervical myofascial trigger points: a randomized, double-blind, placebo-controlled pilot study." Headache **49**(5): 732-743.	CTTH with cervicogenic pain
51.	He, W., X. Zhao, et al. (2012). "Adverse events following acupuncture: a systematic review of the Chinese literature for the years 1956-2010." J Altern Complement Med **18**(10): 892-901.	Review of adverse events from acupuncture in Chinese studies; population not specified
52.	Hedborg, K. and C. Muhr (2011). "Multimodal behavioral treatment of migraine: an Internet-administered, randomized, controlled trial." Ups J Med Sci **116**(3): 169-186.	Combination therapy
53.	Hesse, J., B. Mogelvang, et al. (1994). "Acupuncture versus metoprolol in migraine prophylaxis: a randomized trial of trigger point inactivation." J Intern Med **235**(5): 451-456.	Included episodic and chronic migraine, did not stratify
54.	Hopton, A. and H. MacPherson (2010). "Acupuncture for chronic pain: is acupuncture more than an effective placebo? A systematic review of pooled data from meta-analyses." Pain Pract **10**(2): 94-102.	Systematic review of pooled data from meta-analysis; included studies did not meet inclusion criteria for HTA
55.	Jackson, J. L., A. Kuriyama, et al. (2012). "Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis." Jama **307**(16): 1736-1745.	Systematic review; included studies that did not meet inclusion criteria for HTA

Citation	Reason for exclusion after full-text review
56. Jena, S., C. M. Witt, et al. (2008). "Acupuncture in patients with headache." Cephalalgia **28**(9): 969-979.	>90% episodic migraine and tension type headache, did not stratify
57. Karakurum, B., O. Karaalin, et al. (2001). "The 'dry-needle technique': intramuscular stimulation in tension-type headache." Cephalalgia **21**(8): 813-817.	< 80% with chronic tension-type headache
58. Karst, M., M. Reinhard, et al. (2001). "Needle acupuncture in tension-type headache: a randomized, placebo-controlled study." Cephalalgia **21**(6): 637-642.	>30% episodic tension type headache, did not stratify
59. Keeratitanont, K., M. P. Jensen, et al. (2015). "The efficacy of traditional Thai massage for the treatment of chronic pain: A systematic review." Complement Ther Clin Pract **21**(1): 26-32.	Systematic review did not include any studies with population of interest
60. Kim M, Danielsson A, Ekelund A-C, Kemppainen E, Sjogren P, Svanberg T, Szalo G, Samuelsson O. Botulinum toxin type A for prophylactic treatment of chronic migraine. Health Technology Assessment, HTA-centrum; May 2014.	Health technology assessment; excluded studies that met inclusion criteria for this HTA
61. Krishnan, A. and N. Silver (2009). "Headache (chronic tension-type)." BMJ Clin Evid **2009**.	Review article
62. Lattes, K., P. Venegas, et al. (2009). "Local infiltration of gonyautoxin is safe and effective in treatment of chronic tension-type headache." Neurol Res **31**(3): 228-233.	Case series; gonyautoxin not FDA-approved for use in the United States
63. Lee, M. S. and E. Ernst (2011). "Acupuncture for pain: an overview of Cochrane reviews." Chin J Integr Med **17**(3): 187-189.	Overview of Cochrane reviews; does not comprehensively assess quality of Cochrane systematic reviews
64. Lenhard, L. and P. M. Waite (1983). "Acupuncture in the prophylactic treatment of migraine headaches: pilot study." N Z Med J **96**(738): 663-666.	Included episodic and chronic migraine, did not stratify; combination treatment with naloxone
65. Lenssinck, M. L., L. Damen, et al. (2004). "The effectiveness of physiotherapy and manipulation in patients with tension-type headache: a systematic review." Pain **112**(3): 381-388.	Systematic review, some included studies did not meet inclusion criteria for HTA
66. Li, Y., H. Zheng, et al. (2012). "Acupuncture for migraine prophylaxis: a randomized controlled trial." Cmaj **184**(4): 401-410.	Included episodic and chronic migraine, did not stratify
67. Liguori, A., F. Petti, et al. (2000). "Comparison of pharmacological treatment versus acupuncture treatment for migraine without aura--analysis of socio-medical parameters." J Tradit Chin Med **20**(3): 231-240.	Population unclear; comparator was different/unclear in 2 of 4 centers

Citation	Reason for exclusion after full-text review
68. Linde, K., G. Allais, et al. (2016). "Acupuncture for the prevention of tension-type headache." Cochrane Database Syst Rev **4**: Cd007587.	Cochrane systematic review; included studies that did not meet inclusion criteria for HTA
69. Linde, K., G. Allais, et al. (2009). "Acupuncture for migraine prophylaxis." Cochrane Database Syst Rev(1): Cd001218. *	Cochrane systematic review; included studies that did not meet inclusion criteria for HTA
70. Linde, K., G. Allais, et al. (2009). "Acupuncture for tension-type headache." Cochrane Database Syst Rev(1): Cd007587.	More recent Cochrane review on this topic is Linde 2016
71. Linde, K., A. Streng, et al. (2007). "Randomized trial vs. observational study of acupuncture for migraine found that patient characteristics differed but outcomes were similar." J Clin Epidemiol **60**(3): 280-287.	Included episodic and chronic migraine, did not stratify
72. Linde, K., C. M. Witt, et al. (2007). "The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain." Pain **128**(3): 264-271.	Pooled analysis of studies that included episodic and chronic migraine and tension type headache, did not stratify
73. Linde, K., A. Streng, et al. (2005). "Acupuncture for patients with migraine: a randomized controlled trial." Jama **293**(17): 2118-2125.	Included episodic and chronic migraine, did not stratify
74. Lipton, R. B., D. W. Dodick, et al. (2010). "Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial." Lancet Neurol **9**(4): 373-380.	Included episodic and chronic migraine, did not stratify
75. MacPherson, H., E. Vertosick, et al. (2014). "Influence of control group on effect size in trials of acupuncture for chronic pain: a secondary analysis of an individual patient data meta-analysis." PLoS One **9**(4): e93739.	Systematic review/meta-analysis of effect of control group selection, includes conditions beyond headache
76. Martelletti, P., R. H. Jensen, et al. (2013). "Neuromodulation of chronic headaches: position statement from the European Headache Federation." J Headache Pain **14**: 86.	Review article, includes conditions beyond chronic headache
77. Meissner, K., M. Fassler, et al. (2013). "Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis." JAMA Intern Med **173**(21): 1941-1951.	Systematic review/meta-analysis to assess different types of placebo treatments for migraine prophylaxis
78. Melchart, D., K. Linde, et al. (2001). "Acupuncture for idiopathic headache." Cochrane Database Syst Rev(1): Cd001218.	More recent Cochrane reviews on this topic are Linde 2009 and Linde 2016
79. Melchart, D., K. Linde, et al. (1999). "Acupuncture for recurrent headaches: a systematic review of randomized controlled trials." Cephalalgia **19**(9): 779-786; discussion 765.	More recent Cochrane reviews on this topic are Linde 2009 and Linde 2016

	Citation	Reason for exclusion after full-text review
80.	Melchart, D., A. Streng, et al. (2005). "Acupuncture in patients with tension-type headache: randomised controlled trial." Bmj **331**(7513): 376-382.	>50% episodic tension type headache, did not stratify
81.	Mesa-Jimenez, J. A., C. Lozano-Lopez, et al. (2015). "Multimodal manual therapy vs. pharmacological care for management of tension type headache: A meta-analysis of randomized trials." Cephalalgia **35**(14): 1323-1332.	Systematic review, some included studies did not meet inclusion criteria for HTA
82.	Millan-Guerrero, R. O., S. Isais-Millan, et al. (2009). "Subcutaneous histamine versus botulinum toxin type A in migraine prophylaxis: a randomized, double-blind study." Eur J Neurol **16**(1): 88-94.	Included episodic and chronic migraine, did not stratify
83.	Misra, U. K., J. Kalita, et al. (2012). "High frequency repetitive transcranial magnetic stimulation (rTMS) is effective in migraine prophylaxis: an open labeled study." Neurol Res **34**(6): 547-551.	Case series, not designed to primarily assess safety; did not meet criteria for population of interest
84.	Mitchell, M. P., K. Schaecher, et al. (2008). "Humanistic, utilization, and cost outcomes associated with the use of botulinum toxin for treatment of refractory migraine headaches in a managed care organization." J Manag Care Pharm **14**(5): 442-450.	Not a formal economic study
85.	Moraska, A. F., L. Stenerson, et al. (2015). "Myofascial trigger point-focused head and neck massage for recurrent tension-type headache: a randomized, placebo-controlled clinical trial." Clin J Pain **31**(2): 159-168.	>30% episodic tension type headache, did not stratify
86.	Park, J. M., S. U. Park, et al. (2011). "Carthami-Semen acupuncture point injection for chronic daily headache: a pilot, randomised, double-blind, controlled trial." Complement Ther Med **19 Suppl 1**: S19-25.	Injection into acupoints, not trigger points; intervention was Carthami-Semen (Safflower Seed)
87.	Porta, M. (2000). "A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of tension-type headache." Curr Rev Pain **4**(1): 31-35.	< 15 subjects per group
88.	Posadzki, P. and E. Ernst (2011). "Spinal manipulation: an update of a systematic review of systematic reviews." N Z Med J **124**(1340): 55-71.	Systematic review of systematic reviews, many populations from included studies did not meet inclusion criteria for HTA
89.	Posadzki, P. and E. Ernst (2011). "Spinal manipulations for the treatment of migraine: a systematic review of randomized clinical trials." Cephalalgia **31**(8): 964-970.	Systematic review, some included studies did not meet inclusion criteria for HTA
90.	Posadzki, P. and E. Ernst (2011). "Systematic reviews of spinal manipulations for headaches: an attempt to clear up the confusion." Headache **51**(9): 1419-1425.	Systematic review, some populations from included studies did not meet inclusion criteria for HTA

	Citation	Reason for exclusion after full-text review
91.	Posadzki, P. and E. Ernst (2012). "Spinal manipulations for tension-type headaches: a systematic review of randomized controlled trials." Complement Ther Med **20**(4): 232-239.	Systematic review, some included studies did not meet inclusion criteria for HTA
92.	Quinn, C., C. Chandler, et al. (2002). "Massage therapy and frequency of chronic tension headaches." Am J Public Health **92**(10): 1657-1661.	Case series, not designed to primarily assess safety
93.	Richards, K. C., R. Gibson, et al. (2000). "Effects of massage in acute and critical care." AACN Clin Issues **11**(1): 77-96.	Review; did not include any studies with population of interest
94.	Robbins, M. S., D. Kuruvilla, et al. (2014). "Trigger point injections for headache disorders: expert consensus methodology and narrative review." Headache **54**(9): 1441-1459.	Narrative review article
95.	Rollnik, J. D., O. Tanneberger, et al. (2000). "Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study." Headache **40**(4): 300-305.	Intervention was Dysport
96.	Rothrock, J. F., L. M. Bloudek, et al. (2014). "Real-world economic impact of onabotulinumtoxinA in patients with chronic migraine." Headache **54**(10): 1565-1573.	Not a formal economic study
97.	Sabatke, S., R. H. Scola, et al. (2015). "Injecction of trigger points in the temporal muscles of patients with miofascial syndrome." Arq Neuropsiquiatr **73**(10): 861-866.	Did not meet criteria for population of interest (fibromyalgia population)
98.	Shamliyan TA, Kane RL, Taylor FR. AHRQ Comparative Effectiveness Reviews. Migraine in Adults: Preventive Pharmacologic Treatments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.	Health technology assessment; included studies that did not meet inclusion criteria for HTA
99.	Silberstein, S., N. Mathew, et al. (2000). "Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group." Headache **40**(6): 445-450.	Included subjects with episodic migraine only
100	Silberstein, S. D., A. M. Blumenfeld, et al. (2013). "OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline." J Neurol Sci **331**(1-2): 48-56.	Pooled subgroup analysis of subjects with acute headache medication overuse at baseline, from PREEMPT 1 and 2
101	Silberstein, S. D., D. W. Dodick, et al. (2015). "Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT." J Neurol Neurosurg Psychiatry **86**(9): 996-1001.	Pooled subgroup analysis of responders to botox only, from PREEMPT 1 and 2
102	Streng, A., K. Linde, et al. (2006). "Effectiveness and tolerability of acupuncture compared with metoprolol in migraine prophylaxis." Headache **46**(10): 1492-1502.	Included episodic and chronic migraine, did not stratify; baseline characteristics suggest primarily episodic migraine

	Citation	Reason for exclusion after full-text review
103	Sun, Y. and T. J. Gan (2008). "Acupuncture for the management of chronic headache: a systematic review." Anesth Analg **107**(6): 2038-2047.	Systematic review and meta-analysis; most included studies reported episodic and chronic headache, did not stratify
104	Venancio Rde, A., F. G. Alencar, Jr., et al. (2009). "Botulinum toxin, lidocaine, and dry-needling injections in patients with myofascial pain and headaches." Cranio **27**(1): 46-53.	Unclear if episodic or chronic migraine and tension-type headache, did not stratify
105	Venancio Rde, A., F. G. Alencar, et al. (2008). "Different substances and dry-needling injections in patients with myofascial pain and headaches." Cranio **26**(2): 96-103.	Unclear if episodic or chronic migraine and tension-type headache, did not stratify
106	Vernon, H., G. Jansz, et al. (2009). "A randomized, placebo-controlled clinical trial of chiropractic and medical prophylactic treatment of adults with tension-type headache: results from a stopped trial." J Manipulative Physiol Ther **32**(5): 344-351.	< 15 subjects per group
107	Vickers, A. J., A. M. Cronin, et al. (2012). "Acupuncture for chronic pain." Arch Intern Med **172**(19): 1444-1453.	Systematic review, includes conditions beyond headache
108	Vincent, C. A. (1989). "A controlled trial of the treatment of migraine by acupuncture." Clin J Pain **5**(4): 305-312.	Included episodic and chronic migraine, did not stratify
109	Voigt, K., J. Liebnitzky, et al. (2011). "Efficacy of osteopathic manipulative treatment of female patients with migraine: results of a randomized controlled trial." J Altern Complement Med **17**(3): 225-230.	Included episodic and chronic migraine, did not stratify
110	Wang, K., P. Svensson, et al. (2007). "Effect of acupuncture-like electrical stimulation on chronic tension-type headache: a randomized, double-blinded, placebo-controlled trial." Clin J Pain **23**(4): 316-322.	Needleless electroacupuncture, not true acupuncture; not widely used or available
111	Wang, Y., C. C. Xue, et al. (2015). “Acupuncture for frequent migraine: A randomized, patient/assessor blinded, controlled trial with one-year follow-up.” Evidence-Based Complementary and Alternative Medicine 2015, article ID 920353: 14 pgs; doi:10.1155/2015/920353	Included episodic and chronic migraine, did not stratify; baseline characteristics suggest primarily episodic migraine
112	Witt, C. M., T. Reinhold, et al. (2008). "Cost-effectiveness of acupuncture treatment in patients with headache." Cephalalgia **28**(4): 334-345.	>90% episodic migraine and tension type headache, did not stratify
113	Wonderling, D., A. J. Vickers, et al. (2004). "Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care." Bmj **328**(7442): 747.	Cost utility study; included episodic and chronic migraine, did not stratify
114	Xue, C. C., L. Dong, et al. (2004). "Electroacupuncture for tension-type headache on distal acupoints only: a randomized, controlled, crossover trial." Headache **44**(4): 333-341.	>45% episodic tension type headache, did not stratify

	Citation	Reason for exclusion after full-text review
115	Zhang, C. S., H. Y. Tan, et al. (2015). "Placebo Devices as Effective Control Methods in Acupuncture Clinical Trials: A Systematic Review." PLoS One **10**(11): e0140825.	Systematic review and meta-analysis of placebo as a control, did not meet inclusion criteria for HTA
116	Zhao, H. J., J. Y. Tan, et al. (2015). "Auricular therapy for chronic pain management in adults: A synthesis of evidence." Complement Ther Clin Pract **21**(2): 68-78.	Systematic review and meta-analysis of auricular therapy for a variety of pain conditions, most included studies did not meet inclusion criteria for HTA
117	Zhao, L., Y. Guo, et al. (2011). "Systematic review on randomized controlled clinical trials of acupuncture therapy for neurovascular headache." Chin J Integr Med **17**(8): 580-586.	Systematic review and meta-analysis of “neurovascular headache” RCTs, most included studies did not meet inclusion criteria for HTA
118	Zhao, L., F. W. Zhang, et al. (2011). "Adverse events associated with acupuncture: three multicentre randomized controlled trials of 1968 cases in China." Trials **12**: 87.	Pooled analysis of acupuncture tirals to assess adverse events, most included studies did not meet inclusion criteria for HTA
119	Zheng, H., W. Huang, et al. (2015). "Association of pre- and post-treatment expectations with improvements after acupuncture in patients with migraine." Acupunct Med **33**(2): 121-128.	Subanalysis of Li 2012 study, Included episodic and chronic migraine, did not stratify

APPENDIX D. Risk of Bias and Strength of Evidence

Each study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. The criteria are listed in the Tables below.

Definition of the class of evidence and risk of bias for studies on therapy*

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Low risk: Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	Random sequence generation Statement of allocation concealment Intent-to-treat analysis Blind or independent assessment for primary outcome(s) Co-interventions applied equally F/U rate of 80%+ and <10% difference in F/U between groups Controlling for possible confounding‡
Moderately low risk: Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	Violation of one or two of the criteria for good quality RCT
	Good quality cohort	Blind or independent assessment for primary outcome(s) Co-interventions applied equally F/U rate of 80%+ and <10% difference in F/U between groups Controlling for possible confounding‡
Moderately High risk: Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	Violation of three or more of the criteria for good quality RCT
	Moderate or poor quality cohort	Violation of any of the criteria for good quality cohort
	Case-control	Any case-control design
High risk: Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt[3]:
† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.
‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)

Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
Was the subgroup hypothesis one of a smaller number tested?

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (CoE), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

High – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
Insufficient – Evidence either is unavailable or does not permit a conclusion.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, publication bias) are assessed Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. HIGH = majority of articles RCTs. LOW = majority of articles cohort studies.

DOWNGRADE: Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown"

APPENDIX E. Study Quality: RoB evaluation

Appendix Table E1. Risk of Bias for RCTs Evaluating BoNTA in Chronic Migraine

	BONTA vs. Placebo									BONTA vs. Active Comparator	
Methodological Principle	**Aurora 2010**	**Aurora 2011: DBS‡**	**Dodick 2010‡**	**Lipton 2011‡**	**Aurora 2014: DBS§**	**Aurora 2011, 2014: OL§**	**Denier 2010**	**Freitag 2008**	**Vo 2007**	**Magalhaes 2010**	**Mathew 2009‡‡**
Study design											
Randomized controlled trial	■	■			■		■	■	■	■	■
Prospective cohort study											
Retrospective cohort study											
Case-control											
Case-series						■					
Random sequence generation*	Yes	Yes			Yes	N/A	Yes	Unclear	Yes	Yes	No
Statement of concealed allocation*	Yes	Yes			Yes	N/A	Yes	No	No	No††	No
Intention to treat*	Yes	Yes			Yes	N/A	Yes	Yes	No	No††	No
Independent or blind assessment	Yes	Yes			Yes	Yes	Yes	Yes	Yes	Yes	Yes‡‡
Co-interventions applied equally	Yes	Yes			Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes			Yes	Yes	Yes	No**	No	Unclear	No‡‡
<10% difference in follow-up between groups	Yes	Yes			Yes	N/A	Yes	Yes	Yes	Unclear	No
Controlling for possible confounding†	Yes	Yes			Yes	Yes	Yes	Yes	Yes	No††	Yes
Risk of Bias	Low	Low			Low	High	Low	Moderately High	Moderately High	Moderately High	Moderately High

DBS, double-blind study phase; OL, open-label phase

*Applies to randomized controlled trials only. If authors did not describe a methodologic principle, the study did not receive credit for the criterion.

†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡Aurora 2011 (DBS), Dodick 2010, Lipton 2011 report on PREEMPT 1 & 2 studies, pooled analyses of the same population through 24-week follow-up (N=1384).

§Aurora 2011, 2014: PREEMPT 1 & 2 studies, participants underwent a double-blind study through 24 weeks, and then participants were invited to participate in an open-label phase beginning at 24 weeks through 56 weeks. All participants in open-label phase received botulinum toxin at 24, 36, 48 weeks and were followed through 56 weeks after baseline. Authors imputed for missing data for some outcomes.
**Freitag 2008: 60 patients were randomized, but only 41 received treatment; 19 were excluded after randomization due to medication overuse; an additional 5 patients were lost to follow-up and 18 patients per group were available for analysis.
††Megalhaes: No statement of concealed allocation; no statement of ITT analysis and follow-up information not well described; limited patient demographic information provided, making it difficult to evaluate comparability of treatment groups at baseline.
‡‡Matthew 2009: Unclear if Physician Global Assessment, the primary outcome measure, occurred via blind or independent assessment; At 12 weeks, 80% of BoNTA and 70% of topiramate recipients had data available; by study completion, only 60% of the BoNTA and 50% of the topiramate groups were available. Authors report using last observation carried forward to account for missing data from patients who discontinued but do not present data for sensitivity analysis or evaluation of the impact for missing data.

Appendix Table E2. Risk of Bias for RCTs Evaluating BoNTA in Chronic Tension-Type Headache

Methodological Principle	Hamdy 2009	Kokoska 2004	Padberg 2004	Schmitt 2001	Silberstein 2006
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■	■
Random sequence generation*	Yes	No†	No	Yes	No
Statement of concealed allocation*	No	Yes	Unclear‡	No	No
Intention to treat*	No	No	No	No	Yes
Independent or blind assessment	Unclear	Yes	Yes	Yes	Yes
Co-interventions applied equally	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80%	Unclear	Unclear§	Yes	Yes	Yes
<10% difference in follow-up between groups	Unclear	Unclear§	Yes	Yes	Yes
Controlling for possible confounding**	Yes	Yes	Yes	Yes	Yes
Risk of Bias	Moderately High	Moderately High	Moderately High	Moderately Low	Moderately Low

All trials compared BoNTA to placebo. No trials were identified that met the inclusion criteria for the comparison of BoNTA to an active treatment.
*Applies to randomized controlled trials only.

†Authors state that allocation occurred by a physician blinded to other allocation procedures, by randomly choosing a slip of paper with the patient's name and treatment arm from a bag; the study did not receive credit for this criterion.
‡Authors state that a pharmacist prepared the drug, coded the syringes, and kept treatment codes. However, it is unclear how the pharmacist received the information.
§Article stated that all patients completed the trial, but that 24 of 40 patients had a full 6 months of follow-up.
**Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table E3. Risk of Bias for RCTs Evaluating BoNTA in Chronic Daily Headache

	BoNTA vs. Placebo				BoNTA vs. Topiramate	
Methodological Principle	**Mathew 2005**	**Ondo 2004: DPS**	**Ondo 2004: OL**	**Silberstein 2005**	**Cady 2011: DBS***	**Cady 2011: OL***
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■	■	■
Random sequence generation†	Yes	No	N/A	Yes	Unclear	N/A
Statement of concealed allocation†	No	No	N/A	No	Yes	N/A
Intention to treat†	Yes	Yes	N/A	Yes	No	N/A
Independent or blind assessment	Yes	Yes	Yes	Yes	Yes	Yes
Co-interventions applied equally	Yes	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80%	No	Yes	Yes	No	No	No
<10% difference in follow-up between groups	Yes	Yes	Yes	Yes	Yes	No
Controlling for possible confounding‡	Yes	Unclear§	Yes	Yes	No	No
Risk of Bias	Moderately Low	Moderately High	High	Moderately Low	Moderately High	High

DBS, double-blind study phase; OL, open-label phase
*Cady 2011: Participants underwent a double-blind study through 12 weeks, followed by a 2-week taper. Then, participants who did not have ≥50% treatment response were invited to participate in a 12-week open-label phase, continuing with previously-administered intervention, through 26 weeks; Baseline differences noted – a higher proportion of BoNTA recipients were dissatisfied with their prescription meds, frequency of symptoms and severity of symptoms; credit for ITT not given as authors don't state this was done;
†Applies to randomized controlled trials only.
‡Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
§Ondo: Fewer HA days for BoNTA group (4.8 ± 0.8) compared with placebo (25.5 ± 0.9) are noted during the run-in phase; authors report performing step-wise regression apparently to evaluate predictive factors versus controlling for potential confounders. It is not clear that differences in baseline frequency of headache were controlled for. While authors state that there were no baseline differences between groups, it is possible that sample size may preclude detection of a statistical difference.

Appendix Table E4. Risk of Bias for RCTs Evaluating Acupuncture in Chronic Migraine

	Acupuncture vs. Usual Care	Acupuncture vs. Topiramate
Methodological Principle	**Vickers 2004**	**Yang 2011**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■
Random sequence generation*	Yes	Yes
Statement of concealed allocation*	Yes	Unclear
Intention to treat*	No†	Yes
Independent or blind assessment	No‡	No‡
Co-interventions applied equally	Yes	Yes
Complete follow-up of ≥80%	No	Yes
<10% difference in follow-up between groups	Yes	Yes
Controlling for possible confounding§	Yes	Yes
Risk of Bias	Moderately High	Moderately Low

*Applies to randomized controlled trials only.
†In the acupuncture and usual care group, respectively, 19 and 3 patients did not received treatment after randomization and are not accounted for in any analysis.
‡Outcomes were self-reported (patients kept a daily headache diary) and patients could not be blinded due the nature of the treatments: acupuncture vs. usual care (Vickers 2004) and vs. topiramate (Yang 2011)
§Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table E5. Risk of Bias for RCTs Evaluating Acupuncture in Chronic Tension-Type Headache

	Acupuncture vs. Sham		Acupuncture vs. Active Control*	
Methodological Principle	**Karst 2000**	**Tavola 1992**	**Carlsson 1990**	**Soderberg 2006, 2011**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■
Random sequence generation†	Unclear	Unclear	Unclear	Unclear
Statement of concealed allocation†	Unclear	Unclear	Unclear	Unclear
Intention to treat†	Unclear	Unclear	Unclear	Yes
Independent or blind assessment	Yes	Yes	No‡	No‡
Co-interventions applied equally	Yes	Yes	Yes	Unclear
Complete follow-up of ≥80%	Unclear	Yes	Yes	12 wks.: Yes 26 wks.: No
<10% difference in follow-up between groups	Unclear	Yes	No§	Yes
Controlling for possible confounding**	No††	Yes	No‡‡	No§§
Risk of Bias	Moderately High	Moderately High	Moderately High	Moderately High

*Acupuncture was compared with physiotherapy (Carlsson 1990) and with both physical training and relaxation (Soderberg 2006, 2011; this trial had three arms).
†Applies to randomized controlled trials only.
‡Outcomes were self-reported (self-assessments and/or daily headache diary) and patients could not be blinded due the nature of the treatments: acupuncture vs. physiotherapy (Carlsson 1990) and vs. physical training and vs. relaxation (Soderberg 2006, 2011)
§20% difference between acupuncture (74%) and physiotherapy (94%) in the number of patients completing follow-up.
**Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
††Authors say that the groups did not differ in any baseline factors, however, the proportion of females in each group was disproportionate 38% vs. 61%.
‡‡The authors say that the social, demographic, and disease characteristics were similar between the treatment groups; however, they do not provide any detailed information for confirmation (they only present demographic data for the study population vs. a reference sample of "normal" patients).
§§The following difference were noted at baseline between groups and were not controlled for:

- Acupuncture vs. Physical Training: headache duration (median 10 years [range, 2-35] vs. 5 years [range, 2-30], respectively).
- Acupuncture vs. Relaxation, respectively: sex (77% vs. 90% female; authors report p=NS), age (median 35 vs. 44 years, p=0.002), and education (higher level, 80% vs. 27%; authors report p=NS).

Appendix Table E6. Risk of Bias for RCTs Evaluating Manual Therapy in Chronic Migraine

	Manual Therapy vs. Amitriptyline
Methodological Principle	**Nelson 1998**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■
Random sequence generation*	Yes
Statement of concealed allocation*	Yes
Intention to treat*	Yes
Independent or blind assessment	No†
Co-interventions applied equally	Yes
Complete follow-up of ≥80%	No
<10% difference in follow-up between groups	Yes
Controlling for possible confounding‡	Yes
Risk of Bias	Moderately Low

*Applies to randomized controlled trials only.
†Outcomes were self-reported (patients kept a daily headache diary) and patients could not be blinded due the nature of the treatments: manipulation vs. amitriptyline.
‡Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table E7. Risk of Bias for RCTs Evaluating Manual Therapy in Chronic Tension-Type Headache

	Manual Therapy vs. Usual Care
Methodological Principle	**Castien 2011**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■
Random sequence generation*	Yes
Statement of concealed allocation*	Unclear
Intention to treat*	Yes
Independent or blind assessment	No†
Co-interventions applied equally	Yes
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Controlling for possible confounding‡	Yes
Risk of Bias	Moderately Low

*Applies to randomized controlled trials only.
†Outcomes were self-reported (patients kept a daily headache diary) and patients could not be blinded due the nature of the treatments: manipulation vs. amitriptyline.
‡Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table E8. Risk of Bias for RCTs Evaluating Massage in Chronic Daily Headache

	Massage vs. Sham Ultrasound
Methodological Principle	**Chatchawan 2014**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■
Random sequence generation*	Yes
Statement of concealed allocation*	Yes
Intention to treat*	Yes
Independent or blind assessment	Yes
Co-interventions applied equally	Yes
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Controlling for possible confounding†	Yes
Risk of Bias	Low

*Applies to randomized controlled trials only.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table E9. Risk of Bias for RCTs Evaluating Transcranial Magnetic Stimulation in Chronic Migraine

	TMS vs. Sham	
Methodological Principle	**Misra 2013**	**Teepker 2010Z**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■
Random sequence generation*	Yes	Unclear
Statement of concealed allocation*	Unclear	Unclear
Intention to treat*	Yes	Unclear
Independent or blind assessment	Yes	Yes
Co-interventions applied equally	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes
<10% difference in follow-up between groups	Yes	Unclear
Controlling for possible confounding†	No‡	No§
Risk of Bias	Moderately Low	Moderately High

TMS: Transcranial Magnetic Stimulation.
*Applies to randomized controlled trials only.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡Frequency of attacks per month (mean 20.8 vs. 17.0) and migraine index scores (mean 62.5 vs. 51.1) were higher at baseline in the TMS vs. sham group, respectively (though the authors did not find a statistical difference between groups in these characteristic, p=0.06 for both, the p-value approach significance).
§Authors did not provide a robust description of patient characteristics at baseline.

Appendix Table E10. Risk of Bias for RCTs Evaluating Trigger Point Injection in Chronic Tension-Type Headache

	TPI vs. Sham
Methodological Principle	**Karadas 2013**
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■
Random sequence generation*	Unclear
Statement of concealed allocation*	Unclear
Intention to treat*	Unclear
Independent or blind assessment	Yes
Co-interventions applied equally	Unclear
Complete follow-up of ≥80%	Unclear
<10% difference in follow-up between groups	Unclear
Controlling for possible confounding†	No‡
Risk of Bias	Moderately High

TPI: trigger point injection.
*Applies to randomized controlled trials only.

†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡Authors did not provide a robust description of patient characteristics at baseline (only age and sex were given).

APPENDIX F. Study Characteristics and Patient Demographics

Appendix Table F1. Study Characteristics and Patient Demographics for BoNTA in Chronic Migraine

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
OnabotulinumtoxinA vs. Placebo							
Aurora 2010 Canada, United States (multi-center) RCT Study period: Jan 2006—July 2008	679	**OnabotulinumtoxinA (n=341)** Units: 155-195 No. of muscle areas: 7 in head/neck area No. of injection sites: 31-39 No. of treatments: 2 Injection strategy: Combination of fixed injection sites and 'follow-the-pain' strategy **Placebo (n=338)** Same set-up but placebo injection was administered **Cointerventions** None	**Inclusion criteria**: History of migraine meeting diagnostic criteria listed in ICHD-II section 1 migraine,* ≥ 15 headache days out of 28 days with each day consisting of ≥ 4 hours of continuous headache, ≥ 50% of days being migraine or probably migraine, ≥ 4 distinct headache episodes each lasting ≥ 4 hours, 18 to 65 years old **Exclusion criteria:** Any medical condition that might put patients at increased risk if exposed to BoNTA, diagnosis of other primary or secondary headache disorders, use of any headache prophylactic medication within 28 days of baseline measurements, Beck Depression Inventory (BDI) score > 24 at baseline, fibromyalgia, psychiatric disorders, previous exposure	Age (SD): 41.6 years Female: 87.5% Mean duration of chronicity (SD): 20.5 years Mean frequency of migraine, days (SD): 19.1 (4.0) days per 28 days Mean frequency of headache, days (SD): 19.9 (3.7) days per 28 days Patients having migraine with aura (for migraine only): NR Patients who had prior preventative treatments: 61.8 % Patients who overused medications: 68.0 % Mean number of analgesic medications used at baseline: NR	F/U (% BoNTA, % Placebo): 6 mos (86.8%, 87.3%) Cross-over: At 6 month f/u, patients were entered into open-label BoNTA injections†	• Mean change from baseline in: ○ frequency of *headache days* in 28 day period ○ frequency of *migraine days* in 28 day period ○ frequency of *headache episodes* in 28 day period ○ frequency of *migraine episodes* in 28 day period • Overall acute headache pain medication use • Headache Impact Test-6 (HIT-6) • Proportion of patients with severe (≥60) HIT-6 score • Migraine Specific Quality of Life Questionnaire (MSQ v.2)	Allergan, Inc. COI: Several authors have received grants, funding, or other financial support from the manufacturer. Three authors are employees and stockholders for the manufacturer. Two authors are on the advisory board of Allergan.

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
			to any botulinum neurotoxin serotype, pregnancy			• Headache Impact Score (HIS) • Adverse events (any; treatment-related; serious; treatment-related serious; discontinuation due to adverse events; death)	
Aurora 2011, Lipton 2011, Dodick 2010 Canada, US, Croatia, Germany, Switzerland, UK (multicenter) RCT Study period: Jan 2006—July 2008	1384	**OnabotulinumtoxinA (n=688)** Units: 155-195 No. of muscle areas: 7 in head/neck area No. of injection sites: 31-39 No. of treatments: 2 Injection strategy: Combination of fixed injection site and 'follow-the-pain' strategy **Placebo (n=696)** Same set-up but placebo injection was administered **Cointerventions** None	**Inclusion criteria**: History of migraine meeting diagnostic criteria listed in ICHD-II section 1 migraine,* ≥ 15 headache days out of 28 days with each day consisting of ≥ 4 hours of continuous headache, ≥ 50% of days being migraine or probably migraine, ≥ 4 distinct headache episodes each lasting ≥ 4 hours, 18 to 65 years old **Exclusion criteria:** Any medical condition that might put patients at increased risk if exposed to BoNTA, diagnosis of other primary or secondary headache disorders, use of any headache prophylactic medication within 28 days of baseline measurements, Beck Depression Inventory score > 24 at baseline, fibromyalgia, psychiatric disorders, previous exposure to any botulinum	Age (SD): 41.3 (10.6) years Female: 86.4% Mean duration of chronicity (SD): 19.2 years Mean frequency of migraine (SD): 19.0 (4.1) days per 28 days Mean frequency of headache (SD): 19.9 (3.7) days per 28 days Patients who had prior preventative treatments: NR Patients who overused medications: 65.5% Mean number of analgesic medications used at baseline (SD): 27.35 (19.9)	F/U: Aurora 2011 (% BoNTA, % Placebo): 6 mos (88.2%, 90.4%) Lipton (2011): 6 mos.‡ Dodick (2010): 6 mos. (> 93%) ▪ Crossover: At 6 month f/u, all patients were entered into open-label BoNTA injections§	• Proportion with ≥50% reduction from baseline AND mean change from baseline in: ○ frequency of *headache days* in 28 day period ○ frequency of *headache episodes* in 28 day period ○ frequency of *migraine days* in 28 day period ○ frequency of *migraine episodes* in 28 day period • Overall acute headache pain medication use • Headache Impact Test-6 (HIT-6) • Proportion of patients with	Allergan, Inc COI: Several authors have received grants, funding, or other financial support from the manufacturer. Three authors are employees and stockholders for the manufacturer. Two authors are on the advisory board of Allergan.

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
			neurotoxin serotype, pregnancy			severe (≥60) HIT-6 score • Migraine Specific Quality of Life Questionnaire (MSQ v.2) • Headache Impact Score (HIS) • Adverse events (any; treatment-related; serious; treatment-related serious; discontinuation due to adverse events; death)	
Aurora 2014 66 sites across North America and Europe Study period: Jan 2006—July 2008 RCT	1384	**OnabotulinumtoxinA (n=513)** Units: 195 U (max dose) No. of muscle areas: 7 in head/neck area No. of injection sites: 31-39 No. of treatments: 1 every 12 weeks for 24 weeks (2 cycles) Injection strategy: fixed-site, fixed-dose, intramuscular injections. If needed, 40 U more of BoNTA or placebo was administered among three muscle groups using follow-the-pain strategy. **Placebo (n= 492)**	**Inclusion criteria**: Persons aged 18-65 years with a history of migraine (ICHD definition) with headache occurring 15 or above days/4 weeks, with each day having 4 or more hours of continuous headache and 50% or over of headache days being migraine or possible migraine days; 4 or more distinct headache episodes each last 4 or more hours; no prior use of BoNTA. **Exclusion criteria**: No use of any headache prophylactic medication with 4 weeks prior to baseline, (but overuse of acute medications was not an exclusion criterion during baseline)	Age (SD): 41.8 (10.4) years Female: 87% Mean duration of chronicity (SD): 19.5 (12.5) years** Mean frequency of migraine (SD): 19.05 (4.0) days/month Mean frequency of headache (SD): 19.9 (3.7) days/month Patients who had prior preventative treatments: NR Patients who overused medications: 66.7%	F/U (% BoNTA only, %Placebo and BoNTA): 24wks. (88.2%, 90.4%) Crossover: At 6 month f/u, all patients were entered into open-label BoNTA injections††	• Proportion with ≥50% reduction from baseline AND mean change from baseline in: ○ frequency of *headache days* in 28 day period ○ frequency of *headache episodes* in 28 day period ○ frequency of *migraine days* in 28 day period ○ frequency of *migraine episodes* in 28 day period	Allergan, Inc. COI: Of the 7 authors, 1 is an employee of the sponsor, Allergan, 6 have received or receive research support, funding, and/or honoraria from and have consulted for and/or served on an advisory board for the sponsor as well as other pharmaceutical companies.

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Same procedure but placebo injections were administered **Cointerventions** None		Mean number of analgesic medications used at baseline: 27.4 (19.5) units		• Overall acute headache pain medication use • Headache Impact Test-6 (HIT-6) • Proportion of patients with severe (≥60) HIT-6 score • Proportion of patients with ≥5-point reduction HIT-6 score • Migraine Specific Quality of Life Questionnaire (MSQ v.2) • Headache Impact Score (HIS) • Adverse events (any; treatment-related; serious; treatment-related serious; discontinuation due to adverse events; death)	
Deiner 2010 50 North American sites, 16 European sites (multicenter)	705	**OnabotulinumtoxinA (n=347)** Units: 155-195 No. of muscle areas: 7 in head/neck area No. of injection sites: 31-39 No. of treatments: 2 Injection strategy: Combination of fixed	**Inclusion criteria**: History of migraine meeting diagnostic criteria listed in ICHD-II section 1 migraine*, ≥ 15 headache days out of 28 days with each day consisting of ≥ 4 hours of continuous headache, ≥ 50% of days being migraine or probably migraine, ≥ 4 distinct headache episodes each	Age (SD): 40.9 years Female: 85.4% Mean duration of chronicity: 18.0 years Mean frequency of migraine (SD): 18.9 (4.0) days per 28 days	F/U (% BoNTA, % Placebo): 6 mos (89.6%, 93.3%) Crossover: At 3 month f/u, patients were offered open-label BoNTA injections‡‡	• Mean change from baseline in: ○ frequency of *headache days* in 28 day period ○ frequency of *migraine days* in 28 day period ○ frequency of *headache*	Allergan, Inc. COI: Several authors have received funding or grants from Allergan and several are consultants for pharmaceutical

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Study period: Feb 2008—Aug 2008 RCT		injection sites and 'follow-the-pain' strategy **Placebo (n=358)** Same set-up but placebo injection was administered **Cointerventions** None	lasting ≥ 4 hours, 18 to 65 years old **Exclusion criteria:** Any medical condition that might put patients at increased risk if exposed to BoNTA, diagnosis of other primary or secondary headache disorders, use of any headache prophylactic medication within 28 days of baseline measurements, BDI score > 24 at baseline, fibromyalgia, psychiatric disorders, previous exposure to any botulinum neurotoxin serotype, pregnancy	Mean, frequency of headache (SD): 19.8 (3.7) days per 28 days Patients having migraine with aura (for migraine only): NR Patients who had prior preventative treatments: 65.1% Patients who overused medications: 63% Mean number of analgesic medications used at baseline: NR		*episodes* in 28 day period ○ frequency of *migraine episodes* in 28 day period • Overall acute headache pain medication use • Headache Impact Test-6 (HIT-6) • Proportion of patients with severe (≥60) HIT-6 score • Migraine Specific Quality of Life Questionnaire (MSQ v.2) • Headache Impact Score (HIS) • Adverse events (any; treatment-related; serious; treatment-related serious; discontinuation due to adverse events; death)	companies. Two authors are on the advisory board of Allergan
Freitag 2008 United States Study period: NR RCT	60 rand, 41 treated	**OnabotulinumtoxinA (n=30)** Units: 100 U total No. of muscle areas: 5 No. of injection sites: 22 No. of treatments: 1 Injection strategy: Fixed injection sites	**Inclusion criteria**: Head pain ≥ 15 days per month and headache duration ≥ 4 hours, associated symptoms decreasing in severity but headache frequency increasing, 18-65 years old, stable doses of preventative	Age (range): 42.3 (19-64) years Female: 73.2% Mean duration of chronicity (SD): NR	F/U (% BoNTA, % Placebo): 4 wks, 2 mos, 3 mos, 4 mos (60%, 60%) Crossover: None	• Proportion with ≥50% reduction from baseline AND mean change from baseline in *migraine episode* frequency in 28-day period	Allergan, Inc. COI: Analysis was supported by Allergan, Inc. Dr. Freitag has received research grant support and

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Placebo (n=30) Same procedure but placebo injection was administered **Cointerventions** None	medications for 60 days prior to study entry **Exclusion criteria:** Use of botulinum toxin of any serotype, myasthenia gravis, Eaton-Lambert syndrome, any disorder of neuromuscular function, use of agents that might interfere with neuromuscular function, first migraine diagnosis after 50 years old, cluster headaches, basilar or ophthalmoplegic or hemiplegic migraine, migraine aura without headache, painful condition more painful than migraine pain, progressive neurological disorders, structural disorder of the brain from birth or trauma or past infection, injections or oral corticosteroids within 30 days of study, psychiatric disorder, antipsychotic medication, BDI Scores > 24, use of investigational drug or device within 30 days of study, triptans used > 3 days per week, ergotamine or dihydroergotamine > 2 days per week, caffeine consumption > 500 mg per day for > 28 days, opioids taken > 2 days per week, simple analgesics > 2 tablets per day ≥ 5 days per week	Mean frequency of migraine (SD): NR Mean frequency of headache (SD): 23 days per 28 days		• Mean change from baseline in total *days with headache* in 28 day period • Headache Index (HAI) score • Acute mediation usage • Migraine Disability Assessment Scores (MIDAS) • Headache Pain Specific Quality of Life questionnaire • Adverse events	consulting fees from Allergan, Inc.

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Vo 2007*** United States Study period: NR RCT	32 treated (No. rand NR)	**OnabotulinumtoxinA (n=15)** Units: 135 or 205††† No. of muscle areas: 6 No. of injection sites: 22 No. of treatments: NR Injection strategy: NR **Placebo (n=17)** Same procedure but placebo saline injections were administered **Cointervention** None	**Inclusion criteria**: 18-65 years old, > 5 headache days per month, migraine headache with or without aura according to IHS classification **Exclusion criteria:** NR	Age (SD): 42.4 (7.5) years Female: 84.4% Mean duration of chronicity (SD): 19.5 (10.6) years Mean frequency of migraine (SD): 19.4 (7.1) days per month Mean frequency of headache (SD): NR % of patients having migraine with aura (for migraine only): NR % of patients who had prior preventative treatments: NR % of patients who overused medications: NR Mean number of analgesic medications used at baseline: NR	F/U (% Total): 4 wks, 3 mos (65.3%) Crossover: None	• Mean frequency of headache days in 30 day period • Mean severity of headache attacks (VAS 0-10) • Migraine Specific Quality of Life questionnaire (MSQ v.2.1) • Adverse events	Comprehensive Neuroscience Program and The Uniformed Services University of the Health Science Award COI: NR
OnabotulinumtoxinA vs. Active Comparator							
Magalhaes 2010 Brazil Study period: June 2006—Feb 2008	72	**OnabotulinumtoxinA (n=35)** Units: 250 No. of muscle areas: NR No. of injection sites: 15 No. of treatments: 1 Injection strategy: NR **Amitriptyline (n=37)**	**Inclusion criteria**: 18 to 60 years old, chronic daily migraines according to ICHD-II **Exclusion criteria:** History of more than one primary headache according to ICHD-II, neurological or systemic diseases that cause headache,	Age (range): 34.1 (18-56) years Female: 97.2% Mean duration of chronicity (SD): NR Mean frequency of migraine (SD): NR	F/U: 4 wks, 2 mos, 3 mos‡ Crossover: none	• Reduction of ≥50% in number of pain episodes • Reduction in intensity of pain of ≥3 on VAS • Reduction of ≥50% in number of pain drug doses	Brazilian government grant by CAPES and a CNPq research grant COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		25-50 mg per day **Cointerventions** None	contraindications for any medications used in the study, use of any antidepressant or other drug with potential preventative effects on headache with 3 mos prior to enrollment	Mean frequency of headache (SD): 24.0 (6.5) days per 90 days % of patients who had prior preventative treatments: NR % of patients who overused medications: NR Mean number of analgesic medications used at baseline: NR		• Self- and physician-assessed improvement • Adverse events	
Mathew 2009 United States Study period: 10.5 mos (dates NR) RCT	60	**OnabotulinumtoxinA (n=30)** Units: max 200 at baseline and month 3 (100 U fixed-site and 100 U follow-the-pain) No. of muscle areas: NR No. of injection sites: NR No. of treatments: 1 Injection strategy: Mixed fixed injection and follow-the-pain approach **Placebo/Topiramate (n=30)** Placebo saline injections along with topiramate. **Cointervention**	**Inclusion Criteria:** Outpatient male or female patients of any race between 18 and 65 years old diagnosed with CM, not previously treated with BoNTA or topiramate. **Exclusion Criteria:** Pregnant or planning pregnancy during study period, breastfeeding or were of childbearing potential and not using reliable contraceptive; patients with CTTH; underlying conditions judged to preclude treatment with either test medication; patients who previously used study medications for any reason; patients unable to discontinue any prohibited meds or agents that might	Age (SD): 36.8 (10.3) years Female: 90% Mean duration of chronicity (SD): NR Mean frequency of headache/migraine (SD): 15.5 (7.1) days per month % of patients who had prior preventative treatments: NR % of patients who overused medications: NR Mean number of analgesic medications used at baseline: NR	F/U (% BoNTA, % Topiramate): 9 mos (60.0%, 50.0%) Crossover: None	• Improvement of ≥50% Physician Global Assessment • Mean change from baseline in: ○ number of HA/migraine days per month, ○ HA/migraine-free days per months ○ days on HA medication, and average ○ severity of HA/migraine episodes per month • Headache Impact Test (HIT)-6 • Migraine Disability Assessment	Comprehensive Neuroscience Program and The Uniformed Services University of the Health Science Award COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Either an oral placebo (BoNTA) or topiramate (placebo) with 4-week titration to 100 mg/day with option for extra 4 week titration to 200 mg/day. Continued through the end of the study.	interfere with neuromuscular function; patients with evidence of recent alcohol/drug abuse or acute medication overuse.			(MIDAS) questionnaire, • Migraine Impact Questionnaire (MIQ). • Adverse events (any; drug-related; probable/ possible drug-related; discontinuation due to adverse events)	

BDI, Beck Depression Inventory; BoNTA, onabotulinumtoxinA; CM, chronic migraine; COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; ICHD-II, International Classification of Headache Disorders 2nd Edition; mg, milligrams; mos., months; NA, not applicable; No, number; NR, not reported; U, units; wks., weeks.
* With the exception of "complicated migraine", i.e. hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction.
† Data for open-label phase was not reported.
‡ Percent follow-up not reported.
§ From Aurora 2011, 513 subjects in the BoNTA group and 492 subjects in the control group completed the open-label phase. From Lipton 2011 and Dodick 2010, data for open-label phase was not reported.
** Data is only reported for participants who completed all 5 cycles of treatment.
††513 subjects in the BoNTA group and 492 subjects in the control group completed the open-label phase.
‡‡ Number of patients that entered open-label phase was not reported.
§§ Patients overusing medication were excluded from the study.
*** Study drew participants from an Army Medical Center Neurology clinic.
†††Patients less than 65 kg received 135 U while patients 65 kg or greater received 205 U.

Appendix Table F2. Study Characteristics and Patient Demographics for Acupuncture in Chronic Migraine

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Acupuncture vs. Active Comparator							
Vickers 2004 UK Study period: Nov 1999-Nov 2001 RCT	401 rand, 379 treated	**Acupuncture (n=161)** No. of treatments: Up to 12 treatments over 3 months Type of needle: NR Acupoints: Individualized to each patient No. of needles: NR No. of insertions per needle: NR Insertion depth: NR Time length of treatment: NR **Control (n=140)** Patients randomized to the control group received usual care from their practitioner and were not referred to acupuncture.	**Inclusion criteria**: patients 18-65 with migraine or tension-type headache (following IHS criteria) who reported avg. of at least 2 headaches per month **Exclusion criteria:** onset of headache disorder less than one year before or at age 50 or older, pregnancy, malignancy, cluster headache, suspicion that headache disorder had a specific etiology, cranial neuralgias, acupuncture treatment in the previous 12 months	Age (SD): 46.3 (10.3) years Female: 84% Mean duration of chronicity (SD): 21.5 (13.9) years Mean frequency of migraine (SD): NR Mean frequency of headache (SD): 15.8 (6.64) days in 28 days Patients having migraine with aura: NR Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic medications used at baseline: NR	F/U (% Acupuncture, % Control): 3 mos. (75%, 75%), 12 mos. (75%, 75%) Crossover: None	• Proportion of patients with ≥ 35% improvement Headache score • Proportion of patients with ≥ 50% improvement in Headache Frequency (reduction in days with headache) • Proportion of patients who used any prophylactic medication in past month • Mean headache days/month • Mean headache severity (0-10 VAS) • SF-36 health status questionnaire • Adverse events (serious and nonserious, discontinuation due to adverse events)	Sponsor: NHS R&D National Coordinating Centre for Health Technology Assessment (NCCHTA) grant: 96/40/15 COI: One author (Nadia Ellis) provides acupuncture as part of her private physiotherapy practice

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Yang 2011, 2013* Taiwan Study period: NR RCT	66	**Acupuncture (n=33)** No. of treatments: twice per week for 12 wks. Type of needle: Carbo and Viva; 32 (Chinese) gauge, 0.25 x 40mm, sterile disposable steel needles Acupoints: fixed and classic (BL-2, GB-20 (Ex-HN-5) No. of needles: 7 No. of insertions per needle: NR Insertion depth: standard to each point according to classic acupuncture point Time length of treatment: 30 mins **Topiramate (n=33)** 4 week titration, beginning with 25mg/day increased by 25mg/day weekly to maximum 100mg/day followed by 8 week maintenance period. **Cointerventions** None	**Inclusion criteria**: Age 18-65, a diagnosis based on the published guidelines of the Task Force of the International Headache Society Clinical Trials Subcommittee for controlled trials of prophylactic treatment of CM in adults criteria A–C during the 3 months before trial entry, and an established migraine history for at least 1 year **Exclusion criteria:** HA experience for 15 or more days per month or no response to triptans or ergots on at least 8 days during baseline period, headaches other than CM, migraine prophylaxis agents used in past 3 months, migraine onset after age 50 or over 60 years of age at onset of CM, history of hepatic disorder, nephrolithiasis or other severe illness, cognitive impairment interfering with instructionability and symptom description; previous fear of acupuncture or acupuncture treatment in previous 3 months, bleeding diathesis or anticoagulation usage, pregnancy or nursing; severe depression	Age (SD): 47.85 (6.9) years Female: 89.3% Mean duration of chronicity: 13.35 (4) years Mean frequency of migraine (SD): NR Mean frequency of headache, days (SD): 21.15 (1.5) per month Patients having migraine with aura: NR Patients who had prior preventative treatments: NR Patients who overused medications: 74.2% Mean number of days with analgesic medication intake at baseline (SD): 14.8 (2.45) units per month	F/U: NR† Crossover: None	• Proportion of patients with ≥ 50% improvement in Headache Frequency (reduction in days with headache) • Mean headache days per month • Migraine disability assessment (MIDAS) • Short Form 36 • Beck Depression Inventory-II • Hospital Anxiety and Depression Scale • Adverse events (serious and nonserious, death, discontinuation due to adverse events)	Sponsor: Taiwan Department of Health Clinical Trial and Research Center for Excellence, grant from Kuang Tien General Hospital COI: None stated

CM, chronic migraine; COI, conflict of interest; F/U, follow-up; HA, headache; mg, milligrams; min, minutes; mos, months; No, number; NR, not reported; SD, standard deviation; wks, weeks
* Yang 2013 is a secondary analysis of the Yang 2011; it was included for KQ3 only addressing differential efficacy in subpopulations.
† Percent follow-up not reported.

Appendix Table F3. Study Characteristics and Patient Demographics for Manual Therapy in Chronic Migraine

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Manual Therapy/Manipulation vs. Amitriptyline vs. Combined Therapy							
Nelson 1998 United States Study period: NR RCT	218	**Spinal Manipulation (n=77)** No. sessions: 14 sessions over 8 weeks (no more than 2 sessions per week) Length of sessions: NR Segments targeted: Cervical and thoracic spinal segments Description of technique: High-velocity, low-amplitude, short-lever arm **Amitriptyline (n=70)** 3 visits with clinician. 25 mg once daily for first week, 50 mg daily during second week, 75 mg in third week, and max of 100 mg for remaining 5 weeks **Combine Treatment (n=71)*** Patients received both SMT and amitriptyline therapy. **Cointerventions** None	**Inclusion criteria**: 18 to 65 years old, migraine headaches for ≥ 1 year, ≥ 4 headache days per month **Exclusion criteria:** Migraine headache according to IHS classification, women that are pregnant or nursing, patients underactive chiropractic or medical care within previous month, contraindications to SMT or amitriptyline therapy	Age (SD): 37.9 (10.8) years Female: 78.9% Mean duration of chronicity: ▪ 1-5 years: 12.8% ▪ 5-10 years: 22.9% ▪ > 10 years: 64.2% Frequency of migraine (SD): 52.9% of days per month Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic medications used at baseline (SD): 2.1 (1.8) pills per day	F/U (% Manual Therapy, % Amitriptyline, % Combined Care): 4 wks (75.3%, 71.4%, 76.1%) Crossover: None	• Change in headache index (HI) score (derived from daily headache pain over a 4 week period) • Proportion of patients with >20%, >40%, and >60% reduction in HI scores • Headache frequency (% of days with headache) • Headache severity on VAS • SF-36 global score • Medication intake (OTC pills/day) • Adverse events (discontinuation due to complications)	Sponsor: NR COI: NR

COI, conflict of interest; F/U, follow-up; IHS, International Headache Society; max, maximum; mg, milligrams; mos, months; NR, not reported; SD, standard deviation; SMT, spinal manipulation therapy; wks, weeks.

*This group did not meet our inclusion criteria and was not included in the results of this report.

Appendix Table F4. Study Characteristics and Patient Demographics for Transcranial Magnetic Stimulation in Chronic Migraine

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
rTMS vs Sham							
Misra 2013 India Study period: NR RCT	100	**High rate rTMS (n=50)** Device: Magstim Rapid-2 Coil diameter: 7 cm Location of coil: anterioposteriorly parallel to midline on left frontal cortex No. pulses: 600 Length of session: 412.4 seconds Hz used per pulse: 10Hz No. sessions: 3 sessions on alternate days **Sham (n=50)** Same procedure but sham coil was used	**Inclusion criteria**: > 15 years old, > 4 headache attacks per month for ≥ 3 months **Exclusion criteria:** Pregnancy, liver or kidney diseases, malignancy, severe hypertension, pacemaker or metallic implants, history of seizure or structural brain lesions, focal neurological deficit	Age (SD): 35.3 (10.2) years Female: 88% Mean duration of chronicity (SD): 10.5 (7.)3 years Frequency of migraine (SD): 18.9 (9.9) days per month Duration of attacks (SD): 0.96 (0.58) days % Patients with migraine with aura patients: 7% % Patients with prior preventative treatments: 98% % Patients overusing medications: 28%* Mean no. analgesics used (SD): 19.1 (17.4) units per month†	F/U (% rTMS, % Sham): 4 wks (94%, 96%) Crossover: None	• Proportion with >50% reduction in headache frequency • Proportion with >50% improvement in pain severity (0-100 VAS) • Proportion of patients with headache severity rated: normal, mild, moderate, severe • Proportion of patients with functional disability rated: normal, mild, moderate, severe • Mean headache frequency (attacks/mo.) • Mean headache severity (0-3, worst) • Mean functional disability (0-3, worse) • Analgesic use per month • Patient satisfaction • Adverse events (various,	Sponsor: None; authors state the trial was "an investigator-initiated single-center trial without any external funding." COI: None

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
						discontinuation due to adverse events)	
Teepker 2010 Germany Study period: NR RCT	32	**Low frequency rTMS (n=14)** Device: MagPro compact Coil diameter: 13 cm Location of coil: Right dorsolateral prefrontal cortex No. pulses: NR Length of session: NR Hz used per pulse: 1 Hz No. sessions: 5 **Sham (n=13)** Same procedure but sham 'figure-of-eight' (11 cm diameter) coil was used	**Inclusion criteria**: ≥ 4 migraine attacks per month **Exclusion criteria:** Any prophylactic treatment of migraine, cardiac or cerebral pacemaker, metal in the cranium, epilepsy, pregnancy, severe psychiatric or neurological diseases, complex migraine forms	Age (SD) : 35.5 (10.2) Female: 68.8% Mean duration of chronicity (SD): NR Frequency of migraine (SD): 15.9 (8.2) days per month Duration of attacks (SD): NR % Patients with migraine with aura patients: 40.6% % Patients with prior preventative treatments: NR % Patients overusing medications: NR Mean no. analgesics used (SD): 14.7 (10.7) pills per month	F/U (%Total): 2 mos (84.4%) Crossover: None	• Mean migraine frequency – attacks (attacks per 8 week period) • Mean migraine frequency – days (days per 8 week period) • Mean headache migraine severity (0-10 VAS over 8 week period) • Medication intake (mean pills per 8 weeks) • Adverse events (various, discontinuation due to adverse events)	Sponsor: NR COI: NR

cm, centimeters; COI, conflict of interest; F/U, follow-up; Hz, hertz; mos, months; No., number; NR, not reported; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; wks, weeks.

* All medication overuse patients were overusing analgesics.

† Refers to number of rescue analgesics used.

Appendix Table F5. Study Characteristics and Patient Demographics for BoNTA in Chronic Tension-Type Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
OnaboutlinumtoxinA vs. Placebo							
Hamdy 2009 Egypt Study period: Aug 2006—Aug 2007 RCT	28	**OnabotulinumtoxinA (n=14)** Units: Mean(SD) 50.14 (13.51) range 30-80 IU‡ No. of muscle areas: 6 No. of injection sites: 7 No. of treatments: 1 Injection strategy: Two methods; fixed-site and follow-the-pain approach. Potential tender points identified by history-taking and manual palpation **Placebo (n=14)** Same procedure but saline placebo injection was administered. **Cointerventions** None	**Inclusion Criteria:** A diagnosis of CTTH (according to IHS), had headache on equal or more than 15 days per month on avg. for at least 3 mos, headache duration of 1-10 years, history of failed treatment in the previous 3 mos with at least one prophylactic drug, ability to distinguish between the different headache types **Exclusion Criteria:** patients with migraine or other forms of primary or secondary headaches, planned or actual pregnancy, lactation, or women of childbearing age using inadequate contraceptive measures, any type of substance use disorder, drug induced headache, and patients with medication overuse in the last 2 years, previous exposure to BoNTA, any neuromuscular disease, or treatment with drugs affecting neuromuscular junction, prior injection of anesthetic or steroid into the muscles to be injected in the month prior to study entry,	Age (SD): 36.57 (7.61) years Female: 67.8% Mean duration of chronicity in Years (SD): 4.79 (2.57) years Mean frequency of headache (SD): 19.56 (3.46) days per month Mean headache duration (SD): 8.68 (1.06) hours/day Patients who had prior preventative treatments: 100% Patients who overused medications: 0% Mean number of analgesic medications used at baseline (SD): 10.92 (2.46) days per month	F/U : 3 mos§ Crossover: None	• Headache days per month • Headache severity (VAS) • Headache Disability Index (HDI) • Number of days with acute headache medication use per month • Adverse events (serious, non-serious)	Sponsor: NR COI: Authors state there were none

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
			serious physical or psychiatric disease.				
Kokoska 2004 United States Study period: July 1998—June 2000 RCT	40	**OnabotulinumtoxinA (n=20)** Units: 50 U No. of muscle areas: 3 No. of injection sites: 10 (5 U each) No. of treatments: 1 Injection strategy: Fixed-site **Placebo (n=20)** Same procedure but saline placebo injection was administered **Cointerventions** None	**Inclusion Criteria:** All persons over 18 with episodic or chronic frontal headache (IHS definition) with a frequency equal or greater than 1/month and a frontal pain distribution **Exclusion Criteria:** History of stroke, migraine alone, previous use of BoNTA, previous corrugator or frontalis muscle surgery, previous Bell's palsy, active lid ptosis or lagophthalmos, current aminoglycoside therapy, and known adverse reaction to BoNTA or human albumin, pregnant or nursing.	Age (range) : 46.45 (19-80) years Female: 77.5 % Mean duration of chronicity (SD): NR Mean frequency of headache: 23.3 episodes per month Patients who had prior preventative treatments: 92.5% Patients who overused medications: NR Patients who used analgesic medications at baseline: 95 %	F/U: 6 mos** Crossover: none	• Mean number of headache episodes per month • Mean change in headache intensity • Adverse events	Sponsor: Allergan, Inc. COI: NR
Padberg 2004 Netherlands Study period: Oct 1999—Aug 2001 RCT	40	**OnabotulinumtoxinA (n=19)** Units: 100 (maximum) 10-20 U per muscle No. of muscle areas: 7 No. of injection sites: NR No. of treatments: 1 Injection strategy: 'Follow the pain' strategy **Placebo (n=21)**	**Inclusion criteria**: Chronic tension type headache according to IHS criteria **Exclusion criteria:** Under 18 years old, pregnancy, neuromuscular disorders, use of other investigational drugs within 30 days of screening visit, previous use of botulinum toxin, migraine frequency > 1 attack per month, analgesics or caffeine abuse	Age (SD): 44.6 years Female: 70% Mean headache duration (SD): 12.8 hours per day Frequency of headache, percentage of days/month (SD): 92.5% (14.6) Patients who had prior preventative treatments: NR	F/U (% BoNTA, % Placebo): 3 mos (100%, 100%) Crossover: None	• Mean change in headache intensity (VAS) • Mean number of headache days • Mean number of days on which symptomatic treatment was taken • Mean number of symptomatic tablets per day • Self-assessed improvement	Sponsor: In part by Allergan, Inc. COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Same procedure but placebo injection was administered **Cointerventions** None		Patients who overused medications: NR Mean number of analgesic medications used at baseline: 0.65 (0.8) units per day		• Adverse events	
Schmitt 2001 Switzerland Study period: NR RCT	60 rand, 59 treated	**OnabotulinumtoxinA (n=30)** Units: 20 per injection, 80 total No. of muscle areas: 2 No. of injection sites: NR No. of treatments: 1 Injection strategy: Fixed injection sites **Placebo (n=29)** Same procedure but saline placebo injection was administered **Cointerventions** None	**Inclusion criteria**: Chronic tension-type headache according to IHS criteria **Exclusion criteria:** Head trauma or whiplash injury, episodic tension-type headache, severe medical, neurologic, or psychiatric disorder, recent introduction of new headache therapy, previous treatment with botulinum injections, pregnancy, lactation, alcohol or drug abuse	Age (SD): 45.8 (15.6) years Female: 60% Mean duration of chronicity (SD): 22.3 (17.2) years Mean frequency of headache, days (SD): NR Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic medications used at baseline: 24.5 (25.08) units per month	F/U (% BoNTA, % Placebo): 4 wks, (100%, 83%) 8 wks (93%, 80%) Crossover: None	• Proportion of patients with ≥25% decrease in daily pain scores • West Haven-Yale Multidimensional Pain Inventory • Mean number of pain-free days • Mean pain severity on VAS • Mean analgesic intake per month	Sponsor: NR COI: NR
Silberstein 2006 United States, Canada, UK, Germany, Belgium, and Denmark	300	**OnabotulinumtoxinA (n=250)** Units: ▪ 150 U (n=49) ▪ 100 U (n=51) ▪ 100 Usub (n=52) ‡‡ ▪ 86 Usub (n=51) ▪ 50 U (n=47)	**Inclusion criteria**: 18 to 65 years old, chronic tension-type headache according to IHS criteria, stable headache frequency and severity for ≥ 6 mos. prior to screening period, ≥ 15 headaches per month for ≥ 6 moss prior to screening period, ability to	Age (range): 42.6 (18-65) years Female: 62.3% Mean duration of chronicity (range): 14.7 (0-54) years	F/U (% Total): 4 wks, 2 mos, 3 mos, 4 mos (93%) Crossover: None	• Proportion of patients with ≥50% decrease in headache days • Mean change from baseline in number of headache free days per month	Sponsor: NR COI: NR; however 3 of the 7 authors listed are cited as being affiliated with Allergan, Inc.

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Study period: Jan 2000— Feb 2001 RCT		No. of muscle areas: 3 or 5§§ No. of injection sites: 10 No. of treatments: 1 Injection strategy: NR **Placebo (n=50)** Same procedure but placebo injection was administered into 5 muscle areas **Cointerventions** None	distinguish tension-type headaches from non-tension-type headaches **Exclusion criteria:** Medical condition or use of agent that increased risk when using BoNTA, symptomatic medication overuse, > 1 migraine headache per month for ≥ 6 mos. prior to screening period, cluster headache, cranial neuralgias, consistently refractory to multiple acute therapies for treatment of CTTH, use of prophylactic headache medications for < 3 mos. prior to day-30 visit, injection of anesthetics or steroids injected in study targeted muscles in 1 month prior to day-30 visit, previous therapy with botulinum toxin of any serotype, women that were pregnant or nursing	Mean frequency of headache: 24.0 days per 30 days Patients who had prior preventative treatments: 87.9% Patients who overused medications: NA†† Mean number of analgesic medications used at baseline: NR		• Percentage of the day with headache • Mean headache severity • Concurrent headache medication usage • Beck Depression Inventory • Headache Pain Specific Quality of Life Questionnaire • Tension-Type Headache Impact Questionnaire • SF-36 • Patient-assessment • Global Assessment Scale • Adverse events	

Avg, average; BoNTA, onabotulinumtoxinA; COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; HA, headache; IHS, International Headache Society; max, maximum; mL, milliliters; mos., months; NA, not applicable; No, number; NR, not reported; SD, standard deviation; U, units; wks., weeks;
‡ Dosage varied between patients, but each patient received equal dose for each injection site
§ Percent follow-up not reported
** Twenty-four patients had a full 6 month follow up and all patients turned in HA diaries
†† Patients the overused medication were excluded from the study
‡‡ 'Sub' was used as an identifier in the study for the groups in which only 3 muscle groups received treatment. Other groups received treatment in 5 muscle groups
§§ Three groups received injections at 5 muscle areas (50U, 100U, 150U) while two groups received injections at 3 muscle areas (86Usub, 100Usub)

Appendix Table F6. Study Characteristics and Patient Demographics for Acupuncture in Chronic Tension-Type Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Acupuncture vs. Placebo or Sham							
Karst 2000 Germany Study period: NR Study period NR	39	**Acupuncture (n=21)** No. of treatments: Twice per week for 5 weeks Type of needle: Seirine B-type needle no. 8 (0.3 x 0.3 mm) and no. 3 (0.2 x 0.15 mm) Acupoints: GB 20, L 14, LR 3, GB 8, GB 14, GB 21, GB 41, UB 2, UB 10, UB 60 No. of needles: Max of 15 No. of insertions per needle: NR Insertion depth: NR Time length of treatment: 30 min **Placebo (n=18)** Blunt placebo needle simulated puncturing sensation without being inserted. Elastic foam was used to shield needle type **Cointervention** None	**Inclusion criteria**: CTTH according to IHS classification **Exclusion criteria:** Anticoagulation, predominantly operating factors, rebound analgesic headache syndrome, symptomatic or other concomitant headaches, history of or current migraines	Age (SD): 49.0 (14.8) years Female: 48.7% Mean duration of chronicity: NR Mean frequency of headache (SD): 27.0 (6.5) days/month Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic medications used at baseline: 9.2 (11.9) units per month	F/U: last day of tx (NR), 6wks. (NR) Crossover: None	• Frequency of headache attackes (per month) • Headache severity (VAS 0-10) • Clinical global impression • Mean analgesic intake/month • Pressure pain threshold	Sponsor: NR COI: NR
Tavola 1992 Italy Study period: NR RCT	30	**Acupuncture (n=15)** No. of treatments: 1 treatment per week for 8 weeks Type of needle: stainless steel, 0.3 mm diameter Acupoints: placements made according to traditional Chinese	**Inclusion Criteria:** Diagnosis of muscle-tensive and tension-type headache, exclusion of organic pathology, frequency of headache episodes greater than once a week having a mean	Age (SD): 32.9 (11.6) years Female: 86.6% Mean duration of chronicity (SD): 7.8 (7.9) years	F/U: 6 mos., 12 mos.* Crossover: None	• Proportion of patients with >33% and >50% improvement over baseline on Headache Index	Sponsor: NR COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		medicine criteria on an individual basis No. of needles: 6-10 No. of insertions per needle: NR Insertion depth: 10-20mm Time length of treatment: 20 minutes **Sham (n=15)** No. of treatments: 1 treatment per week for 8 weeks No. of needles: 6-10 Acupoints: same regions, but not in specific acupoints Insertion depth: 2-4mm Time length of treatment: 20 minutes **Cointervention** None	intensity not less than 'moderate,' abstainment from other therapies previously undertaken (except for non-narcotic analgesics). **Exclusion Criteria:** NR	Mean frequency of headache (SD): 17.5 (9.2) days/month Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic medications used at baseline (SD): 11.5 (11.3) units/month		• Headache frequency (no./month) • Headache intensity • Headache index (HI) • Frequency of analgesic use	
Acupuncture vs. Active Comparator							
Carlsson 1990 Sweden Study period: 1987—1988 RCT	60 rand, 58 treated	**Acupuncture (n=23)** No. of treatments: 4-5 Type of needle: NR Acupoints: classical Chinese acupuncture points (GB20, GB21, LI4) No. of needles: 3 No. of insertions per needle: NR Insertion depth: 10-30mm Time length of treatment: 20 min **Physiotherapy (n=29)**	**Inclusion Criteria:** Females between 18-60 with duration of headache of more than 6 months, those who could speak and read Swedish **Exclusion Criteria:** patients with malignant or other serious diseases, headaches with close temporal relation to	Age (SD): 34 (12) years % Female: 100% Mean duration of chronicity (SD): 9 (8) years Mean frequency of headache (SD): NR Patients who had prior preventative treatments: 96%	F/U (% Acupuncture, % Physiotherapy): 12 mos. (74%, 93%) Crossover: None	• Sickness Impact Profile • Mood Adjective Check List • Intensity of headache (VAS 0-100), frequency • Analgesic consumption • Adverse events	Sponsor: Swedish Fund for Scientific Research without Animal Experiments COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Specific for each patient including: relaxation techniques, auto-massage, cryotherapy and transcutaneous electrical nerve stimulation. No. of treatments: 1-2 sessions per week, 10-12 sessions over 2-3 months Time length of treatment: 30-45 minutes **Crossover** None	an organic disorder or generalized myalgia, headaches as part of fibromyalgic syndrome	Patients who overused medications: NR Mean number of analgesic medications used at baseline: NR			
Soderberg 2011 Sweden (multicenter) Study period: March 1997—Sept 1999 RCT	90	**Acupuncture (n=30)** No. of treatments: 10-12 sessions in 10-12 weeks Type of needle: 15 x 0.25mm and 30 or 40 x 0.30mm Acupoints: GB 20, GB 14, LI 14, and ST 44 (PC 6, PC 7, SP 6, GB 34, ST 8, EX 2, AMD EX 1 were optional) No. of needles: 10-12 No. of insertions per needle: 3 per session Insertion depth: 2-5 mm or 10-30 mm based on location Time length of treatment: 30 min **Physical Training (n=30)** 10 sessions done over 2.5-3 months. Sessions were a combination of in-clinic and home-training but all	**Inclusion criteria**: 18 to 65 years old, CTTH according to IHS classification **Exclusion criteria:** Headache that began after age 50, > 1 migraine per month in the past year, inability to speak or read Swedish, serious somatic or psychiatric disease, drug abuse of use of analgesics and triptans > 10 days per month	Age (range): 37.5 (18-59) years Female: 81.1% Mean duration of chronicity (range): 7.5 (2-37) years Mean frequency of headache (SD): NR Patients who had prior preventative treatments: NR Patients who overused medications: NR Mean number of analgesic used at baseline: 9.2 (11.9) units per month	F/U (% Acupuncture, % Physical Training, % Relaxation Training): 3 mos (90%, 86.7%, 86.7%), 6 mos (56.7%, 63.3%, 63.3%) Crossover: None	• Headache-free periods • Headache-free days • Headache intensity (VAS 0-100) • Minor Symptom Evaluation Profile	Sponsor: Vardalsstiftelsen Kommunala Landstingsforbundet for Landstinsangelagenheter, te Renee Eanders Fond, and GlaxoSmith Kline COI: NR

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		focused on neck and shoulder muscles **Relaxation Training (n=30)** 8-10 sessions performed individually with a physiotherapist. Combination of neuromuscular and self-hypnotic techniques, as well as breathing techniques, stress coping mechanisms, and how to relax during the day and during activity. **Cointervention** None					

COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; IHS, International Headache Society; max, maximum; min, minutes; mm, millimeters; mos, months; NA, not applicable; No, number; NR, not reported; SD, standard deviation; Tx, treatment; wks, weeks
* Percent follow-up not reported

Appendix Table F7. Study Characteristics and Patient Demographics for Manual Therapy in Chronic Tension-Type Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Manual Therapy/Manipulation vs. Active Comparator							
Castien 2011 The Netherlands (multicenter) Study period: June 2007—Dec 2008 RCT	82 rand, 80 treated	**Spinal manipulation (n=41)** No. sessions: Max of 9 Length of sessions: 30 min Segments targeted: Cervical, thoracic, and lumbar spinal segments Description of technique: NR **Usual Care (n=41)** General practitioner provided information and advice, first prescribing life-style changes. Analgesics or NSAIDs were prescribed and pain medication was changed as needed. Treatment spanned on average 2-3 visits **Cointervention** None	**Inclusion criteria**: 18 to 65 years old, diagnosed with CTTH according to IHS classification **Exclusion criteria:** Rheumatoid arthritis, suspected malignancy, pregnancy, intake of triptans, ergotamines, or opioids ≥ 10 days per month, simple analgesics ≥ 15 days per month for ≥ 3 months, manual therapy treatment within 2 months of enrollment	Age (SD): 40.4 (10.8) years Female: 78% Mean duration of chronicity: 12.8 (11.5) years Mean frequency of headache, days (SD): 23.9 (6.9) days per month Patients who had prior preventative treatments: NR Patients who overused medications: NA* Mean number of analgesic medications used at baseline (SD): ▪ 1.3 (2.8) pills per week NSAIDs ▪ 3.2 (4.5) pills per week analgesics	F/U (% Manual Therapy, % Usual Care): 2 mos (97.6%, 97.6%), 26 wks (92.7%, 90.2%) Crossover: None	• Proportion of patients with 50% reduction in headache frequency • Mean headache frequency (days with headache in 2 week time period) • Mean headache intensity (0-10 NRS) • Headache Impact Test-6 • Headache Disability Inventory • Analgesic/NSAID use • Patient-reported improvement • Resource use • Adverse events	Sponsor: NR COI: NR

AM, Amitriptyline; COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; IHS, International Headache Society; max, maximum; mg, milligrams; min, minutes; mos, months; NA, not applicable; No, number; NR, not reported; NSAIDs, non-steroidal ant inflammatory drugs; SD, standard deviation; TTH, tension-type headache; wks, weeks
*Patients that overused medication were excluded from the study.

Appendix Table F8. Study Characteristics and Patient Demographics for Trigger Point Injections in Chronic Tension-Type Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Trigger Point Injections vs. Placebo							
Karadas 2013 Turkey Study period: NR	49 rand, 48 treated	**Trigger Point Injections (n=24)** Injection: 0.5% lidocaine Muscle areas: muscles innervated by trigeminal nerve and cervical nerves originating from C1-C3 No. injections: 2 per muscle area No. sessions: 3 sessions, 1 every 3 days **Placebo (n=24)** Same procedure but saline injections were administered **Cointerventions** None	**Inclusion criteria**: Headache for ≥ 15 days per month, 18 to 65 years old, CTTH for ≥ 6 months, no response to optimal doses of antidepressants for ≥ 3 months **Exclusion criteria:** Use of prophylactic headache treatment in last 20 days, medication-overuse headache according to ICHD-II, BoNTA therapy, pregnancy, allergy to local anesthetics, malignancy, cervical and cranial surgery, primary headaches other than TTH, nonpharmacological therapy in previous 6 months, > 500 mg/day of caffeine in past month, anemia and bleeding diathesis, major psychiatric disorders, use of antipsychotic, antidepressant or antiepileptic drugs within previous 3 months, neuromuscular dysfunction, agents that affect neuromuscular functions, uncontrolled hypertensions, hypothyroidism, hyperthyroidism	Age (SD): 40.5 (12.6) years Female: 83.0% Mean duration of chronicity: NR Mean frequency of headache (SD): 19.7 (8.5) days per 30 days Mean duration of attacks (SD): NR % Patients with prior preventative treatments: NR % Patients overusing medications: NR Mean no. analgesics used (SD): 9.9 (2.3) pills per month	F/U (% Trigger Point Injections, % Placebo): 6 mos (100%, 95.8%) Crossover: None	• Number of painful days in a month • Severity of pain • Number of analgesics used in a month • Hamilton depression scores • Hamilton anxiety scores • Adverse events (serious and nonserious)	Sponsor: NR COI: Authors declare no conflicts of interest

BoNTA, botulinum toxin type A; COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; ICHD-II, International Classification of Headache Disorders 2nd Edition; mg, milligrams; mos, months; NA, not applicable; No., number; NR, not reported; SD, standard deviation; TTH, tension-type headache; wks, weeks.

Appendix Table F9. Study Characteristics and Patient Demographics for BoNTA in Chronic Daily Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
OnabotulinumtoxinA vs. Placebo or Sham							
Mathew 2005* United States (multicenter) Study period: NR RCT	355	**OnabotulinumtoxinA (n=173)** Units: 105-260 No. of muscle areas: NR No. of injection sites: 23-58 No. of treatments: 3 Injection strategy: 'Follow the pain' strategy **Placebo (n=182)** Same procedure but saline placebo injection was administered **Cointerventions** None	**Inclusion criteria**: 18 to 65 years old, > 15 headaches in 30 days, stable medical condition, stable chronic medication regiments for ≥3 mos. prior to baseline period, compliance with study instructions, willingness to stay on current medications for the course of the study **Exclusion criteria:** Medical condition or use of agent that increased risk when using BoNTA, infection or skin problem at injection site, allergy to study medication, history of complicated migraine, a Beck Depression Inventory (BDI) score > 24, previous therapy with botulinum toxin of any serotype, injection of anesthetics or steroids in study-targeted muscles with 30 days of baseline period, overuse or abuse of symptomatic medication, alcohol, or drugs, chronic use within 3 mos. of baseline	Age (SD): 43.5 years Female: 84.5% Mean duration of chronicity (SD): 14.5 (12.4) years Mean frequency of migraine (SD): 11.0 (7.3) days per month Mean frequency of headache, days (SD): 13.1 (8.0) days per month Patients who had prior preventative treatments: 35.8% Patients who overused medications: 47.3% Mean number of analgesic medications used at baseline: NR	F/U (% Total): 9 mos (77.2%) Crossover: None	• Proportion of patients with ≥50% decrease in the frequency of headache *days* and headache *episodes* per 30-day period • Mean change from baseline in frequency of headache-free days in a 30 day period • Number of days that acute headache medication was used • Number of uses (intakes) of acute headache medication • Migraine Disability Assessment Scale (MIDAS) • Headache Pain-Specific Quality	Sponsor: Allergan, Inc. COI: Three authors are employed by Allergan, Inc., and own stock in the company

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
			period of muscle relaxants, pregnancy			of Life Questionnaire • Adverse events	
Ondo 2004 United States Study period: NR RCT	60	**OnabotulinumtoxinA (n=30)** Units: 200 No. of muscle areas: NR No. of injection sites: NR No. of treatments: 1 Injection strategy: 'Follow the pain' strategy **Placebo (n=30)** Same procedure but placebo injection was administered **Cointerventions:** None	**Inclusion criteria**: 18 to 80 years old, headaches > 15 days per month **Exclusion criteria:** NR	Age (SD): 47 (11.1) years Female: 81.7% Mean duration of chronicity (SD): NR Mean frequency of headache (SD): 23 (7) days per month Patients having migraine with aura (for migraine only): NR Patients who had prior preventative treatments: 66.6% Patients who overused medications: 56.6 % Mean number of analgesic medications used at baseline (SD): 45.35 doses (26.3) per month	F/U (% BoNTA, % Placebo): 3 mos (96.7%, 96.7%) Crossover: At 3 month f/u, patients were offered open-label BoNTA injections†	• Mean number of headache free days • Global impressions • Mean use of abortive headache medications • Beck Depression Inventory (BDI) • Psychosocial Adjustement to Illness Scale (PAIS) • Adverse events	Sponsor: NR COI: NR
Silberstein 2005* United States (multicenter) Study period: July 2001—Nov 2003 RCT	702	**OnabotulinumtoxinA (n=524)** Units: ▪ 225 U (n=182) ▪ 150 U (n=168) ▪ 75 U (n=174) No. of muscle areas: 7 No. of injection sites: 20 No. of treatments: 3 Injection strategy: Fixed injection sites	**Inclusion criteria**: 18 to 65 years old, < 15 headache days in 30 day screening period, medically stable, no changes in long term medication within 3 mos. of enrollment, willingness to stay on current medications for the course of the study	Age (range): 43.4 (18-65) years Female: 82.9% Mean duration of chronicity (SD): 13.7 (12.2) years Mean frequency of migraine, days (SD): 10.5 (7.5) days per 30 days	F/U (% Placebo-nonresponders, % Placebo-responders): 6 mos (71.9%, 75.6%) Crossover: None	• Proportion of patients with ≥50% decrease in headache days per 30-days • Proportion of patients with ≥50% decrease in *migraine*	Sponsor: Allergan, Inc. COI: One author is on the advisory panel for Allergan, Inc., two authors have received research fees or support from the sponsor, one author

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
		Placebo (n=178) Same procedure but placebo injection was administered **Cointerventions** None	**Exclusion criteria:** Medical condition or use of agent that increased risk when using BoNTA, infection or skin problem at any of the injection sites, allergy to study medication, cluster headaches, chronic paroxysmal hemicranias, analgesic rebound headache, headache secondary to head trauma or whiplash, "complicated" migraine,‡ BDI score > 24, previous therapy with botulinum toxin of any serotype, injection of anesthetics or corticosteroids in study-targeted muscles with 30 days of baseline period, abuse of symptomatic medication, alcohol, or drugs, concurrent or long term use of muscle relaxants within 3 mos. of screening period, women that were pregnant or nursing	Mean frequency of headache, days (SD): 13.8 (8.6) days per 30 days Patients who had prior preventative treatments: 49.6 % Patients who overused medications: 42.1% Mean number of analgesic medications used at baseline: NR		*headaches* per 30-days • Proportion of patients with ≥50% decrease in 2 or more *migraine headaches* per 30-days • Mean change from baseline in number of headache free days per 30-days • Mean frequency of *any type of headache* and of *migraine* headache • Number of days with acute medication usage • Migraine Disability Assessment (MIDAS) • Headache Pain Specific Quality of Life Questionnaire • Adverse events	has worked as a principal investigator within Allergan Inc., one author has worked as a consultant for Allergan, Inc., and two authors are stockholders and employees of the sponsor
OnabotulinumtoxinA vs. Topiramate							
Cady 2011 Country NR	59	**OnabotulinumtoxinA (n=29)** Units: 100-200	**Inclusion criteria**: Outpatient, Subject met criteria for CM	Age (range): 39.6 (19.6-64.0) years Female: 91.5%	F/U (% BoNTA, % Topiramate): 4 wks (96.5%,	• Treatment Responder Rate based on the	Funding: Industry

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Study period: Sept 2004— Aug 2006 RCT (3 centers)		No. of muscle areas: NR No. of injection sites: NR No. of treatments: 1 Injection strategy: Combination of fixed injection sites and 'follow-the-pain' strategy **Topiramate (n=30)** 25 mg given daily increased to 100 mg in weekly incremental changes of 25 mg. Treatment spanned 12 weeks **Cointerventions** None	defined by ICHD-II, 18 to 65 years old **Exclusion criteria:** Pregnancy, headache disorders other than CM, medical disorders that would increase risk with exposure to BoNTA, liver or renal impairment, ketogenic diets, previous used of botulinum toxin of any type or topiramate, alcohol/drug abuse or overuse of acute medication	Mean duration of chronicity: 16 years Mean frequency of migraine (SD): 11.1 days per 28 days Mean frequency of headache (SD): 21.1 days per 28 days Patients who had prior preventative treatments: 98.3 % Patients who overused medications: NR** Mean analgesic usage: 14.5 days per month	90.0%), 3 mos (85.7%, 80.0%) Crossover: At 3 month f/u, patients who had not reduced no. of headache days per month by ≥ 50% were offered open-label BoNTA injections§	Global Physician Assessment • Mean change from baseline in number of headache days per month • Mean change from baseline in headache free days per month • Migraine Impact and Disability Assessment (MIDAS) • Headache Impact Test-6 (HIT-6) • Money spent on migraine medication • Adverse events	COI: One author is a consultant for GlaxoSmithKline, Merck and received grants. Several authors received research grants from companies within the industry

BDI, Beck Depression Inventory; BoNTA, onabotulinumtoxinA; COI, conflict of interest; F/U, follow-up; mos., months; No, number; NR, not reported; SD, standard deviation; wks., weeks;

* After baseline, patients went through placebo injections to test for "placebo responders" and "placebo nonresponders"
† Only one patients decided to not to receive open-label injections, however 7 patients total did not complete the phase
‡ Including migrainous infarction, hemiplegic migraine, opthalmoplegic migraine, or basilar migraine
§Of the 27 subjects that did not have at least a 50% reduction in headache days per month, 9 from the topiramate group and 11 from the BoNTA group started the open-label phase
**Assumed to be 0% since medication overuse was an exclusion criteria.

Appendix Table F10. Study Characteristics and Patient Demographics for Massage vs. Sham in Chronic Daily Headache

Study	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U %	Outcomes	Funding
Massage vs. Sham US							
Chatchawan 2014 Thailand Study period: NR RCT	72	**Thai Traditional Massage (n=36)** TTM massage for 25 minutes, stretching for 5 minutes. Technique was consistent with pattern of royal Thai massage, pressing along meridian lines at massage points for 5-10 second, repeated 3-5 times. Targeted 5 different muscle areas **Sham US (n=36)** US given using detuned US device. Nine 30 minute sessions over 3 weeks	**Inclusion criteria**: 20 to 50 years old, CTTH or migraine according to IHS classification, headache diagnosis for ≥ 3 months prior to study, headaches for ≥ 15 days per month and ≥ 2 times per week, VAS score for headache intensity ≥ 4 **Exclusion criteria:** Headache cause by cervical disorders, skin disease, hemiplegia/paresis, hypertension, antiplatelet drugs, massage therapy within the past month	Mean age (SD): 27.4 (8.1) years Female:76.4 % Mean duration of chronicity: NR Mean frequency of headache* (SD): 16.3 (4.4) days per month % Migraine patients: 42% Mean duration of attacks (SD): 6.5 ± 9.24 hours % Patients with migraine with aura patients: NR % Patients with prior preventative treatments: NR % Patients overusing medications: NR Mean no. analgesics used (SD): NR	F/U (% TTM, % Sham US): 4 wks (97.2%, 100%) Crossover: None	• Headache Intensity on VAS • Frequency of pain (times/wk.) • Headache Disability Index (HDI) • Pressure Point Threshold • Cervical range of motion • Adverse events	Sponsor: Under Incubation Researcher Project, Neuroscience Research and Development Group, Kohn Kaen University, and the Back, Neck, and Other Joint Pain Research Group COI: Authors declare no conflicts of interest

COI, conflict of interest; CTTH, chronic tension-type headache; F/U, follow-up; IHS, International Headache Society; mos, months; No, number; NR, not reported; SD, standard deviation; Sx, symptom; TTM, Thai traditional massage; VAS, visual analog score; US, ultrasound; wks, weeks
*Reported migraine and tension-type headache frequency together; value reported here includes migraine population.

APPENDIX G. Data Abstraction Tables: Efficacy Outcomes

Appendix Table G1. Efficacy Outcomes from RCTs Evaluating BoNTA for Chronic Migraine

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
BoNTA vs. Placebo						
Aurora 2010 (PREEMPT 1) 24 week study period	Frequency of headache episodes/month, Δ from baseline	24	-5.2	-5.3	NR	0.344
	Frequency headache days/month, Δ from baseline	24	-7.8	-6.4	NR	0.006
	Δ from baseline, frequency of migraine episodes/month	24	-4.8	-4.9	NR	0.206
	Δ from baseline, frequency migraine days/month	24	-7.6	-6.1	NR	0.002
	Δ from baseline, frequency of acute HA medication intake/month	24	-10.3	-10.4	NR	0.795
	Δ from baseline, HIT-6 score	24	-4.7	-2.4	NR	<.001
	% patients with severe (≥60) HIT-6 score from baseline	24	68.9%	79.9%	NR	0.001
	Δ from baseline, HRQoL: restrictive (MSQ)	24	NR	NR	NR	<.001
	Δ from baseline, HRQoL: preventive (MSQ)	24	NR	NR	NR	0.005
	Δ from baseline, HRQoL: emotional (MSQ)	24	NR	NR	NR	0.029
Diener 2010 (PREEMPT 2) 24 week study period	Δ from baseline, frequency of headache episodes/month	24	-5.3	-4.6	NR	p=.003
	Δ from baseline, frequency headache days/month	24	-9.0	-6.7	NR	p<.001
	Δ from baseline, frequency migraine days/month	24	-8.7	-6.3	NR	p<.001
	Δ from baseline, frequency of acute HA medication intake/month	24	-9.9	-8.4	NR	NS
	Δ from baseline, HIT-6 score	24	-4.9	-2.4	NR	<.001
	% patients with severe (≥60) HIT-6 score from baseline	24	66.3	76.5	NR	p=.003

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Δ from baseline, HRQoL: restrictive (MSQ)	24	NR	NR	NR	<.001
	Δ from baseline, HRQoL: preventive (MSQ)	24	NR	NR	NR	<.001
	Δ from baseline, HRQoL: emotional (MSQ)	24	NR	NR	NR	<.001
Aurora 2011, **Dodick 2010, Lipton 2011 (PREEMPT 1&2)** 24 week study period	Δ from baseline, frequency headache days/month	24	-8.4 (-8.9, -7.9)	-6.6 (-7.1, -6.1)	NR	<.001
	Δ from baseline, ≥50% reduction in frequency headache days/month	24	47.1%	35.1%	NR	<.001
	Δ from baseline, frequency headache episodes/month	24	-5.2 (-5.6, -4.8)	-4.9 (-5.3, -4.5)	NR	p=.009
	Δ from baseline, ≥50% reduction in frequency headache episodes/month	24	48.6%	43.1%	NR	NS
	Δ from baseline, frequency migraine days/month	24	-8.2 (-8.7, -7.7)	-6.2 (-6.7, -5.7)	NR	<.001
	Δ from baseline, ≥50% reduction in frequency migraine days/month	24	48.2%	36.4%	NR	<.001
	Δ from baseline, frequency of migraine episodes/month	24	-4.9 (-5.3, -4.5)	-4.5 (-4.9, -4.1)	NR	p=.004
	Δ from baseline, ≥50% reduction in frequency migraine episodes/month	24	48.1%	43.4%	NR	NS
	Δ from baseline, frequency of acute HA medication intake/month	24	-10.1 (-11.4, -8.8)	-9.4 (-10.6, -8.1)	NR	NS
	Δ from baseline, frequency of acute HA medication days/month	24	-6.1 (-6.6, -5.5)	-5.3 (-5.8, -4.8)	NR	p=.016
	Δ from baseline, HIT-6 score	12	-4.7	-2.6	NR	<.001
		24	-4.8 (-5.3, -4.3)	-2.4 (-2.9, -2.0)	NR	<.001
	% patients with severe (≥60) HIT-6 score from baseline	24	67.6% (64.1%, 71.1%)	78.2% (75.1%, 81.2%)	NR	<.001
	Δ from baseline, HRQoL: restrictive (MSQ)	12	16.2	9.9	NR	<.001
		24	17.0 (18.7, 15.2)	8.6 (10.2, 7.0)	NR	<.001
	Δ from baseline, HRQoL: preventive (MSQ)	12	13	8	NR	<.001
		24	13.1 (14.8, 11.4)	6.4 (8.0, 4.9)	NR	<.001

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Δ from baseline, HRQoL: emotional (MSQ)	12	18.3	11	NR	<.001
		24	17.9 (20.1, 15.8)	9.5 (11.4, 7.5)	NR	<.001
Aurora 2014 (PREEMPT 1&2) 24 week study period	Δ from baseline, frequency headache days/month	24	-8.8 (-9.4, -8.2)	-6.5 (-7.1, -5.9)	NR	<.001
	Δ from baseline, frequency headache episodes/month	24	-5.9 (-6.1, -5.2)	-4.8 (-5.4, -4.4)	NR	<.001
	Δ from baseline, frequency migraine days/month	24	-8.6 (-9.2, -8.0)	-6.2 (-6.7, -5.5)	NR	<.001
	Δ from baseline, frequency of migraine episodes/month	24	-5.5 (-5.8, -4.9)	-4.4 (-5.0, -4.1)	NR	<.001
	Δ from baseline, frequency of acute HA medication intake/month	24	-10.4 (-11.8, -8.7)	-9.3 (-11.0, -8.0)	NR	NS
	Δ from baseline, HIT-6 score	24	-5.5 (-6.1, -4.8)	-2.3 (-2.8, -1.8)	NR	<.001
	% patients with severe (≥60) HIT-6 score from baseline	24	62.6% (58.4%, 66.8%)	78.5% (74.8%, 82.1%)	NR	<.001
	Δ from baseline, HRQoL: restrictive (MSQ)	24	18.3 (16.4, 20.3)	8.5 (6.8, 10.3)	NR	<.001
	Δ from baseline, HRQoL: preventive (MSQ)	24	14.4 (12.5, 16.3	6.7 (-5.0, 8.4)	NR	<.001
	Δ from baseline, HRQoL: emotional (MSQ)	24	19.6 (17.2, 22.0)	9.7 (7.5, 11.8)	NR	<.001
Freitag 2007 16 week study treatment period	Δ from baseline, frequency of migraine episodes/month	16	-4.2 (-31%)	-1.3 (-8.9%)	NR	<.001
	Δ from baseline, ≥50% reduction in migraine episodes	16	6/18 (33%)	3/18 (16.7%)	NR	NR
	Δ from baseline, HAI (headache index)	16	-6.1 (30.5%)	-3.8 (-21%)	NR	p=.003
	Δ from baseline, frequency headache days/month	16	-4.0	-2.0	NR	p=.018
	Δ from baseline, frequency of acute HA medication intake/month	16	-1.0	0.0	NR	NS
	Δ from baseline, MIDAS	16	-11	+2	NR	NS
	Δ from baseline, Headache Pain Specific QoL	16	14	22	NR	NS
Magalhaes 2010 12 week study period	Δ from baseline, ≥50% reduction in # pain days/90 days	12	67.8%	72.0%	NR	NS
	Δ from baseline, ≥3 point VAS reduction in pain intensity/90 days	12	50.0%	55.6%	NR	NS

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Δ from baseline, ≥50% reduction in migraine drug doses/90 days	12	77.0%	71.0%	NR	NS
	Self-reported improvement/90 days	12	84.0%	88.0%	NR	NS
	Physician-reported improvement/90 days	12	88.0%	87.0%	NR	NS
	# pain days at 90 days	12	11.8 ± 7.6	9.7 ± 6.8	NR	NS
Vo 2007 16 week study period	Δ from baseline, frequency of headache episodes/month	12	NR	NR	NR	NS
	Δ from baseline, severity of headache episodes/month	12	NR	NR	NR	NS
	Δ from baseline, HRQoL: restrictive (MSQ)	12	NR	NR	NR	NS
	Δ from baseline, HRQoL: preventive (MSQ)	12	NR	NR	NR	NS
	Δ from baseline, HRQoL: emotional (MSQ)	12	NR	NR	NR	NS
BoNTA vs. Active Comparator						
Magalhaes 2010 BoNTA vs. Amitriptyline 12 week study period	Δ from baseline, ≥50% reduction in # pain days/90 days	12	67.8%	72.0%	NR	NS
	Δ from baseline, ≥3 point VAS reduction in pain intensity/90 days	12	50.0%	55.6%	NR	NS
	Δ from baseline, ≥50% reduction in migraine drug doses/90 days	12	77.0%	71.0%	NR	NS
	Self-reported improvement/90 days	12	84.0%	88.0%	NR	NS
	Physician-reported improvement/90 days	12	88.0%	87.0%	NR	NS
	# pain days at 90 days	12	11.8 ± 7.6	9.7 ± 6.8	NR	NS
Mathew 2009 BoNTA vs. Topiramate 42 week study period (12 week treatment period)	Δ from baseline, ≥50% physician-reported treatment improvement	4	NR	NR	NR	NS
		12	NR	NR	NR	NS
		24	NR	NR	NR	NS
		36	NR	NR	NR	NS
	Δ from baseline, ≥50% reduction in frequency headache days/month	12	10/26 (38.5%)	5/22 (22.7%)	NR	NS
		24	14/24 (58.3%)	7/22 (31.8%)	NR	NS

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
		36	9/22 (40.9%)	9/21 (42.9%)	NR	NS
	Δ from baseline, severity of headache episodes/month	12	-0.2 ± 0.5	-0.4 ± 0.8	NR	NS
		24	-0.1 ± 0.5	-0.5 ± 0.8	NR	NS
		36	-0.2 ± 0.5	-0.4 ± 0.8	NR	NS
	Δ from baseline, days taking HA medication/month	12	-4.3 ± 4.3	-2.5 ± 4.6	NR	NS
		24	-6.1 ± 5.2	-4.1 ± 5.4	NR	NS
		36	-4.5 ± 5.9	-4.0 ± 6.7	NR	NS
	Δ from baseline, HIT-6 score	12	-3.5 ± 6.2	-6.7 ± 5.9	NR	NS
		24	-5.6 ± 6.4	-10.4 ± 7.1	NR	NS
		36	-3.5 ± 5.2	-8.8 ± 7.4	NR	NS
	Δ from baseline, MIDAS	12	-10.5 ± 24.1	-33.3 ± 53.1	NR	NS
		24	-11.3 ± 22.4	-46.3 ± 75.7	NR	NS
	Δ from baseline, MIQ score	4	-1.2 ± 2.1	-1.0 ± 2.1	NR	NS
		24	-0.5 ± 1.1	-1.3 ± 2.7	NR	NS

BDI, Beck Depression Index; BoNTA, OnabotulinumtoxinA; CI, confidence interval; F/U, follow-up; HA, headache; HDI, Henry Ford Hospital Headache Disability Inventory; HIT-6, Headache Impact Test-6; HRQoL, health related quality of life; MIDAS, Migraine Disability Assessment Scale; MIQ, Migraine Impact Questionnaire; NR, not reported; NS, not significant; PAIS, Psychosocial Adjustment to Illness Scale; PN, placebo non-responder; PR, placebo responder; QoL, quality of life; SD, standard deviation; SF-36, Short Form-36; TTHA, tension-type headache; Tx ,treatment; VAS, visual analog scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory

* Results are reported as either a mean or a percent. Confidence intervals or standard deviations are reported in parenthesis

† As reported by the authors.

Appendix Table G2. Efficacy Outcomes from RCTs Evaluating BoNTA for Chronic Tension-Type Headache

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
BoNTA vs. Placebo						
Hamdy 2009 16 week study period	Frequency headache days/month	Base-line	19.93 ± 3.75	19.21 ± 3.17	NR	NR
		4	15.00 ± 2.25	4 17.50 ± 2.03	NR	p=.005
		12	12.07 ± 1.94	15.92 ± 2.16	NR	p=.000
	Δ from baseline, % reduction in frequency headache days/month	12	37.8%	17.1%	NR	NR
	Headache severity (VAS)	Base-line	6.21 ± 1.05	6.36 ± 1.08	NR	NR
		4	4.79 ± 1.05	5.86 ± 0.86	NR	p=.007
		12	3.50 ± 1.22	5.21 ± 1.19	NR	p=.001
	Δ from baseline, % reduction in headache severity	12	43.7%	18.0%	NR	NR
	HDI score	Base-line	64.43 ± 8.74	60.57 ± 10.27	NR	NR
		4	44.29 ± 14.84	56.14 ± 11.70	NR	p=.027
		12	38.29 ± 19.84	56.57 ± 12.31	NR	p=.007
	Δ from baseline, % reduction in HDI score	12	40.6%	6.6%	NR	NR
	# days with acute HA medications/month	Base-line	11.14 ± 2.59	10.71 ± 2.33	NR	NR
		4	7.43 ± 1.09	9.64 ± 2.02	NR	p=.001
		12	6.43 ± 1.16	8.36 ± 1.65	NR	p=.001
	Δ from baseline, % decrease in # days with acute HA medications	12	42.3%	21.9%	NR	NR
Kokoska 2004	Δ from baseline, average headache intensity score (Likert 0-10 scale)	24	-0.54	-0.11	NR	NR

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
24 week study period	Δ from baseline, frequency headache days/month	24	-6.3	-4.8	NR	NS
Padberg 2004 12 week study period	Δ from baseline, headache intensity (100mm VAS)	12	-10.6	-7.1	NR	NS
	Δ from baseline, ≥45% VAS reduction in pain intensity	12	6/19 (31.6%)	3/21 (14.3%)	NR	NS
	Self-reported improvement from baseline	4	8/19 (42.1%)	11/21 (52.4%)	NR	NS
		8	10/19 (52.6%)	10/21 (47.6%)	NR	NS
		12	9/19 (47.4%)	6/21 (28.6%)	NR	NS
	Δ from baseline, % headache days	12	12 ± 20%	5 ± 14%	NR	NS
	Δ from baseline, % days on which analgesics were taken	12	0.12 ± 0.29%	0.10 ± 0.40%	NR	NS
Schmitt 2001 8 week study period	WHYMPI instrument‡	4	NR	NR	NR	NS
		8	NR	NR	NR	NS
	Pain severity (VAS)	Base-line	2.62 ± 1.62	2.81 ± 1.86	NR	NR
		4	2.46 ± 1.91	2.49 ± 2.29	NR	NS
		8	2.31 ± 2.09	2.26 ± 2.19	NR	NS
	Self-reported improvement from baseline	4	7/30 (23.3%)	6/29 (20.7%)	NR	NS
		8	7/30 (23.3%)	7/29 (24.1%)	NR	NS
	Δ from baseline, ≥25% VAS reduction in pain intensity	4	11/30 (36.7%)	8/29 (27.6%)	NR	NS
		8	15/30 (50.0%)	9/29 (31.0%)	NR	NS
	Monthly amount intake of analgesics	Base-line	23.87 ± 27.53	25.14 ± 22.80	NR	NR
		4	23.30 ± 26.68	25.18 ± 22.55	NR	NS
		8	20.32 ± 26.30	26.52 ± 27.12	NR	NS

			Results (mean or %)*		Effect Estimate (95% CI) †	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	# pain-free days	Base-line	3.63 ± 5.12	3.79 ± 5.60	NR	NR
		4	4.87 ± 6.85	6.14 ± 7.84	NR	NS
		8	6.00 ± 8.38	5.59 ± 7.71	NR	NS
Silberstein 2006 30 week study period	Δ from baseline, frequency headache-free days/60 days	8	2.8 (150U group; N=48)	4.5	NR	p=.007
	Δ from baseline, ≥50% reduction in TTHA days	12	150U: NR 100U: 15/47 (31.9%) 100U 3s: 15/49 (30.6%) 86U 3s: 15/47 (31.9%) 50U: NR	6/50 (12.0%)	NR	p=NS p=.017 p=.024 p=.017 p=NS
	Δ from baseline, headache severity/60 days	8	150U; N=48: -0.1 100U; N=NR: -0.1 100U 3s; N=NR: -0.2 86U 3s; N=47: -0.2 50U; N=NR: -0.2	-0.1	NR	NS for all groups
	Headache Pain Specific QoL score	8	NR	NR	NR	NS for all groups
	Tension-Type HA Impact score	8	NR	NR	NR	NS for all groups
	SF-36	8	NR	NR	NR	NS for all groups

BDI, Beck Depression Index; BoNTA, OnabotulinumtoxinA; CI, confidence interval; F/U, follow-up; HA, headache; HDI, Henry Ford Hospital Headache Disability Inventory; HIT-6, Headache Impact Test-6; HRQoL, health related quality of life; MIDAS, Migraine Disability Assessment Scale; MIQ, Migraine Impact Questionnaire; NR, not reported; NS, not significant; PAIS, Psychosocial Adjustment to Illness Scale; PN, placebo non-responder; PR, placebo responder; QoL, quality of life; SD, standard deviation; SF-36, Short Form-36; TTHA, tension-type headache; Tx ,treatment; VAS, visual analog scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory

* Results are reported as either a mean or a percent. Confidence intervals or standard deviations are reported in parenthesis

† As reported by the authors

‡ Study reported means and standard deviations for 11 domains of WHYMPI separately

Appendix Table G3. Efficacy Outcomes from RCTs Evaluating BoNTA for Chronic Daily Headache

			Results (mean or %)*		Effect Estimate (95% CI)†	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
BoNTA vs. Placebo						
Mathew 2005 BoNTA vs. Placebo 36 week study period (16 week treatment period)	Δ from baseline, frequency headache-free days/month	4	PN (n=134): 3.2±5.8 PR (n=39): 8.8±7.1	PN (n=145): 2.6±5.4 PR (n=37): 8.9±6.0	NR	p=NS p=NS
	Δ from baseline, frequency headache-free days/month	8	PN (n=134): 4.5±7.1 PR (n=39): 10.3±5.7	PN (n=145): 3.6±6.4 PR (n=37): 9.9±5.7	NR	p=NS p=NS
	Δ from baseline, frequency headache-free days/month	12	PN (n=134): 4.2±6.5 PR (n=39): 10.4±7.1	PN (n=145): 4.0±6.5 PR (n=37): 10.0±6.0	NR	p=NS p=NS
	Δ from baseline, frequency headache-free days/month	24	PN (n=134): 6.7±7.8 PR (n=39): 12.1±6.4	PN (n=145): 5.2±6.9 PR (n=37): 10.5±4.1	NR	p=NS p=NS
	Δ from baseline, frequency headache-free days/month	32	PN (n=134): 7.8±8.4 PR (n=39): 13.0±6.3	PN (n=145): 6.8±7.2 PR (n=37): 12.8±6.6	NR	p=NS p=NS
	Δ from baseline, ≥50% reduction in frequency headache days/month	24	PN: 32.7% PR: NR	PN: 15.0% PR: NR	NR	p=.027 p=NS
	Δ from baseline, ≥50% reduction in frequency headache days/month	24	40.3% (pooled)	25.3% (pooled)	NR	p=.05
	Δ from baseline, frequency headache days/month	24	PN: -6.1 PR: -9.9	PN: -3.1 PR: -5.6	NR	p=.013 p=.004
	Δ from baseline, frequency headache days/month	24	-7.1 (pooled)	-3.7 (pooled)	NR	p=.001
	Δ from baseline, frequency of acute HA medication intake days	24	PN: -6.0±7.9 PR: -10.2±6.3	PN: -5.0±6.5 PR: -7.8±3.7	NR	p=NS p=NS
Ondo 2004 BoNTA vs. Placebo 8 week study period	Self-reported improvement from baseline	12	17/29 (58.6%)	3/29 (10.3%)	NR	p<.05
	Physician-reported improvement from baseline	12	16/29 (55.2%)	2/29 (6.9%)	NR	p<.001
	Δ from baseline, frequency of abortive HA medication intake	12	106 ± 76	135 ± 81	NR	NS
	Beck Depression Inventory (BDI) score	12	NR	NR	NR	NS
	Psychosocial Adjustment to Illness Scale (PAIS) score	12	NR	NR	NR	NS

			Results (mean or %)*		Effect Estimate (95% CI)†	p-value†
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Silberstein 2005 BoNTA vs. Placebo 36 week study period (16 week treatment period)	Δ from baseline, frequency headache-free days/month	24	PN 225U: 6.1±7.1 PN 150U: 7.9±8.4 PN 75U: 7.9±7.8	PN: 8.0 ± 8.8	NR	NS
	Δ from baseline, frequency headache-free days/month	24	PR, 225U: 13.1±7.8 PR 150U: 11.4±7.5 PR 75U: 14.0±6.1	PR: 10.8 ± 7.2	NR	NS
	Δ from baseline, ≥50% reduction in frequency headache days/month	24	PN 225U: 25.4% PN, 150U: 35.1% PN 75U: 30.9%	PN: 31.7%	NR	NS
BoNTA vs. Active Comparator						
Cady 2011 BoNTA + placebo Tablets vs. Topiramate + Placebo Tablets 12 week study period	Improvement, Physician Global Assessment	4	17/28 (60.7%)	20/27 (74.0%)	NR	NS
		12	19/24 (79.2%)	17/24 (70.8%)	NR	NS
	Δ from baseline, frequency headache days/month	4	-3.0 (n=28)	-4.4 (n=28)	NR	NS
		12	-8.0 (n=24)	-8.1 (n=25)	NR	NS
		14	-3.2 (n=11)	-6.5 (n=9)	NR	NS
		26	-6.0 (n=8)	-8.5 (n=4)	NR	NS
	Δ from baseline, MIDAS	12	-38.5 (n=21)	-26.7 (n=21)	NR	NS
	Δ from baseline, HIT-6 score	4	-4.8 (n=25)	-5.9 (n=23)	NR	NS
		12	-6.3 (n=21)	-6.0 (n=19)	NR	NS

BDI, Beck Depression Index; BoNTA, OnabotulinumtoxinA; CI, confidence interval; F/U, follow-up; HA, headache; HDI, Henry Ford Hospital Headache Disability Inventory; HIT-6, Headache Impact Test-6; HRQoL, health related quality of life; MIDAS, Migraine Disability Assessment Scale; MIQ, Migraine Impact Questionnaire; NR, not reported; NS, not significant; PAIS, Psychosocial Adjustment to Illness Scale; PN, placebo non-responder; PR, placebo responder; QoL, quality of life; SD, standard deviation; SF-36, Short Form-36; TTHA, tension-type headache; Tx ,treatment; VAS, visual analog scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory

* Results are reported as either a mean or a percent. Confidence intervals or standard deviations are reported in parenthesis

† As reported by the authors

Appendix Table G4. Efficacy Outcomes from RCTs Evaluating Acupuncture for Chronic Migraine

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Acupuncture vs. Usual Care						
Vickers 2004 12 week treatment period	≥35% improvement in headache score† (protocol definition)	Immediate	41% (65/159)	27% (37/136)	NA	0.014
		9 months	54% (87/161)	32% (45/140)	NA	0.0001
	≥50% improvement in headache days‡ (IHS definition) – any	Immediate	23% (36/159)	13% (17/136)	NA	0.024
		9 months	30% (49/161)	15% (21/140)	NA	0.002
	≥50% improvement in headache days‡ (IHS definition) – at least mild headache	9 months	35% (56/161)	18% (25/140)	NA	0.001
	≥50% improvement in headache days‡ (IHS definition) – moderate or severe headache	9 months	39% (63/161)	26% (37/140)	NA	0.02
	Any prophylactic medication in past month	Baseline	25% (40/161)	32% (45/140)	NA	NR
		Immediate	21% (34/159)	29% (39/136)	Adjusted MD 7% (-3%, 17%)	0.15
		9 months	14% (22/161)	26% (37/140)	Adjusted MD 13% (4%, 22%)	0.005
	Headache score† (weekly)	Baseline	24.6 ± 14.1 (n=161)	26.7 ± 16.8 (n= 140)	NA	NR
		Immediate	18.0 ± 14.8 (n=159)	23.7 ± 16.8 (n=136)	Adjusted MD 3.9 (1.6, 6.3)	0.001
		9 months	16.2 ± 13.7 (n=161)	22.3 ± 17.0 (n=140)	Adjusted MD 4.6 (2.2, 7.0)	0.0002
	Headache days/month‡ – any	Baseline	15.6 ± 6.6 (n=161)	16.2 ± 6.7 (n= 140)	NA	NR
		Immediate	12.1 ± 7.2 (n=159)	14.3 ± 7.3 (n=136)	Adjusted MD 1.8 (0.7, 2.9)	0.002
		9 months	11.4 ± 7.5 (n=161)	13.6 ± 7.5 (n=140)	Adjusted MD 1.8 (0.6, 2.9)	0.003
	Headache days/month‡ – at least mild	Baseline	13.5 ± 6.3 (n=161)	13.8 ± 6.5 (n= 140)	NA	NR
		9 months	9.1 ± 6.5 (n=161)	10.9 ± 6.6 (n=140)	Adjusted MD 1.6 (0.5, 2.6)	0.004

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Headache days/month‡ – moderate or severe	Baseline	8.5 ± 65.0 (n=161)	8.9 ± 5.7 (n= 140)	NA	NR
		9 months	5.4 ± 4.8 (n=161)	6.9 ± 5.6 (n=140)	Adjusted MD 1.2 (0.4, 2.1)	0.006
	Scaled pain medication (weekly)	Baseline	16.5 ± 18.1 (n=161)	14.3 ± 17.6 (n= 140)	NA	NR
		Immediate	11.0 ± 13.6 (n=159)	11.4 ± 14.1 (n=136)	Adjusted MD 1.6 (-0.7, 3.9)	0.16
		9 months	8.5 ± 12.2 (n=161)	18.7 ± 12.6 (n=140)	Adjusted MD 1.2 (-0.6, 3.1)	0.19
	Scaled prophylactic medication (weekly)	Baseline	9.0 ± 17.8 (n=161)	13.3 ± 22.2 (n= 140)	NA	NR
		Immediate	7.9 ± 17.6 (n=159)	11.5 ± 21.3 (n=136)	Adjusted MD 0.7 (-2.4, 3.8)	0.7
		9 months	5.0 ± 14.4 (n=161)	11.1 ± 21.3 (n=140)	Adjusted MD 3.9 (0.5, 7.4)	0.026
	Total scaled medication (weekly)	Baseline	25.4 ± 25.1 (n=161)	27.6 ± 28.8 (n= 140)	NA	NR
		Immediate	18.9 ± 21.7 (n=159)	22.9 ± 24.8 (n=136)	Adjusted MD 2.9 (-1, 6.7)	0.14
		9 months	13.4 ± 18.2 (n=161)	19.8 ± 24.4 (n=140)	Adjusted MD 5.2 (5.3, 9.2)	0.009
	SF-36 physical function subscale	Baseline	81.9 ± 21.1 (n=161)	85.3 ± 18.4 (n= 139)	NA	NR
		Immediate	82.6± 20.7 (n=156)	81.7 ± 21.3 (n=134)	Adjusted MD 3.0 (-2.0, 6.2)	0.07
		9 months	82.6 ± 23.3 (n=157)	82.3 ± 20.2 (n=138)	Adjusted MD 2.7 (-0.7, 6.0)	0.12
	SF-36 role functioning physical subscale	Baseline	60.4 ± 40.2 (n=161)	59.4 ± 38.6 (n= 139)	NA	NR
		Immediate	63.5 ± 14.4 (n=154)	56.7 ± 40.8 (n=134)	Adjusted MD 5.0 (-3.6, 3.5)	0.3
		9 months	70.0 ± 39.2 (n=157)	60.3 ± 41.3 (n=138)	Adjusted MD 8.8 (0.6, 17.0)	0.036
	SF-36 role functioning emotional subscale	Baseline	73.2 ± 36.6 (n=160)	69.6 ± 39.4 (n= 140)	NA	NR
		Immediate	72.4 ± 39.7 (n=155)	74.7 ± 36.3 (n=130)	Adjusted MD -5.1 (-13, 2.9)	0.2

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
		9 months	76.0 ± 37.0 (n=154)	70.1 ± 39.2 (n=136)	Adjusted MD 4.9 (-3.5, 13.4)	0.3
	SF-36 energy/fatigue subscale	Baseline	47.9 ± 19.9 (n=161)	52.2 ± 20.2 (n= 140)	NA	NR
		Immediate	51.3 ± 21.6 (n=154)	51.8 ± 20.8 (n=134)	Adjusted MD 1.9 (-1.8, 5.7)	0.3
		9 months	55.4± 20.7 (n=158)	54.2 ± 20.7 (n=139)	Adjusted MD 4.2 (0.6, 7.7)	0.02
	SF-36 emotional well-being subscale	Baseline	66.0 ± 15.0 (n=161)	67.0 ± 14.1 (n= 140)	NA	NR
		Immediate	66.6 ± 15.3 (n=156)	67.8 ± 14.0 (n=134)	Adjusted MD -0.9 (-3.8, 2.0)	0.5
		9 months	68.3 ± 15.4 (n=158)	68.9 ± 14.7 (n=139)	Adjusted MD 0.0 (-2.9, 2.9)	1.0
	SF-36 social functioning subscale	Baseline	71.0 ± 24.9 (n=161)	73.6 ± 21.6 (n= 140)	NA	NR
		Immediate	73.6 ± 24.8 (n=156)	75.4 ± 22.6 (n=134)	Adjusted MD -0.8 (-5.6, 4.1)	0.8
		9 months	77.9 ± 25.2 (n=158)	74.8 ± 23.2 (n=138)	Adjusted MD 4.2 (-0.8, 9.2)	0.1
	SF-36 pain subscale	Baseline	59.8 ± 23.3 (n=160)	66.3 ± 21.3 (n= 140)	NA	NR
		Immediate	64.3 ± 23.6 (n=156)	64.6 ± 23.5 (n=134)	Adjusted MD 2.4 (-2.5, 7.3)	0.3
		9 months	65.0 ± 24.5 (n=158)	63.7 ± 22.2 (n=139)	Adjusted MD 4.4 (-0.2, 9.0)	0.063
	SF-36 general health subscale	Baseline	60.2 ± 21.1 (n=161)	64.0 ± 21.8 (n= 140)	NA	NR
		Immediate	61.1 ± 21.1 (n=156)	61.8 ± 22.1 (n=134)	Adjusted MD 2.1 (95% CI -1.0, 5.3)	0.2
		9 months	61.9 ± 22.5 (n=158)	62.5 ± 22.9 (n=139)	Adjusted MD 3.0 (-0.4, 6.5)	0.09
	SF-36 health change subscale	Baseline	52.5 ± 15.4 (n=161)	53.4 ± 17.0 (n= 140)	NA	NR
		Immediate	58.0 ± 18.9 (n=154)	50.6 ± 18.3 (n=133)	Adjusted MD 7.7 (3.5, 12.0)	0.0004
		9 months	62.8 ± 20.1 (n=158)	55.5 ± 18.4 (n=139)	Adjusted MD 7.9 (3.5, 12.3)	0.0004

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Number of visits to GP	9 months	1.7 ± 2.5 (n=161)	2.3 ± 3.6 (n=140)	Adjusted MD 0.77 (0.56, 1.06)	0.1
	Number of visits to Specialist	9 months	0.22 ± 0.9 (n=161)	0.14 ± 0.6 (n=140)	Adjusted MD 1.13 (0.34, 3.73)	0.8
	Number of visits to Complementary therapist	9 months	2.0 ± 7.1 (n=161)	2.3 ± 6.8 (n=140)	Adjusted MD 0.56 (0.18, 1.72)	0.3
Acupuncture vs. Topiramate						
Yang 2011 12 week treatment period	Responders (proportion of patients with ≥50% ↓ from baseline in number of moderate/severe headache days)	3 months post-tx	75.8% (25/33)	30.3% (10/33)	NR	<0.01
	Responders (proportion of patients with ≥50% ↓ from baseline in number of headache days)	3 months post-tx	63.6% (21/33)	15.2% (5/33)	NR	<0.01
	Δ from baseline, mean headache days/month	3 months post-tx	–10.7 ± 2.8 (n=33)	–7.9 ± 3.6 (n=33)	NR	<0.01
	Δ from baseline, mean moderate/severe headache days/month	3 months post-tx	–10.5 ± 2.8 (n=33)	–7.8 ± 3.6 (n=33)	NR	<0.01
	Δ from baseline, MIDAS score	3 months post-tx	–38.5 ± 10.7 (n=33)	–25.9 ± 9.3 (n=33)	NR	<0.01
	Δ from baseline, BDI-II score	3 months post-tx	–7.7 ± 4.8 (n=33)	–5.6 ± 2.4 (n=33)	NR	0.025
	Δ from baseline, HADS score	3 months post-tx	–7.1 ± 2.2 (n=33)	–2.9 ± 1.7 (n=33)	NR	<0.01
	Δ from baseline, mean days with acute headache med intake/month	3 months post-tx	–9.6 ± 3.3 (n=33)	–5.4 ± 4.7 (n=33)	NR	<0.01
	Δ from baseline, SF-36 physical function domain	3 months post-tx	18.7 ± 9.2 (n=33)	9.2 ± 4.9 (n=33)	NR	<0.01
	Δ from baseline, SF-36 role physical domain	3 months post-tx	27.6 ± 8.9 (n=33)	18.2 ± 9.3 (n=33)	NR	<0.01

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Δ from baseline, SF-36 bodily pain domain	3 months post-tx	13.7 ± 8 (n=33)	8.1 ± 4 (n=33)	NR	0.01
	Δ from baseline, SF-36 general health domain	3 months post-tx	22.3 ± 6.9 (n=33)	14.8 ± 11.9 (n=33)	NR	0.002
	Δ from baseline, SF-36 vitality domain	3 months post tx	22.1 ± 6.6 (n=33)	16.8 ± 6.6 (n=33)	NR	0.002
	Δ from baseline, SF-36 social functioning domain	3 months post tx	16 ± 8.1 (n=33)	9.8 ± 4.7 (n=33)	NR	<0.01
	Δ from baseline, SF-36 role emotion domain	3 months post tx	27.8 ± 10.7 (n=33)	17.5 ± 6.2 (n=33)	NR	<0.01
	Δ from baseline, SF-36 mental health domain	3 months post tx	22.2 ± 6.4 (n=33)	11 ± 6.5 (n=33)	NR	<0.01

F/U: follow-up; GP: general practitioner; IHS: International Headache Society; MD: mean difference; NA: not applicable; NR: not reported; SD: standard deviation; SF-36: Short-Form-36 questionnaire.
*As reported by the authors. Adjusted difference: positive favors acupuncture.
†Severity of headaches were recorded 4x/day on a 6-point Likert scale and the total summed to give a headache score.
‡"Days with headache" was defined very liberally as days on which a patient recorded headache severity of at least 1 out of 5 for at least one timepoint. The mean number of days with headache reported by this trial is accordingly larger than that seen in other trials. Therefore, the authors performed the analyses using more conservative definitions of days with headache (i.e., day on which mild or moderate/severe headache was reported); results indicated that differences between groups were not sensitive to the definition of headache day.

Appendix Table G5. Efficacy Outcomes from RCTs Evaluating Acupuncture for Chronic Tension-Type Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Acupuncture vs. Sham						
Karst 2000 5 week treatment period	VAS pain (mean) (0-10)	Baseline	6.2 ± 2.2 (n=21)	6.3 ± 2.2 (n=18)	NR	NR
		Immediate	4.3 ± 2.6 (n=21)	4.7 ± 2.4 (n=18)	NR	NR
		6 wks post tx	4.0 ± 2.5 (n=21)	3.9 ± 2.7 (n=18)	NR	NR
	Clinical global impression (CGI) (-4 to 4)	Immediate	1.6 ± 1.5 (n=21)	0.8 ± 1.5 (n=18)	NR	NR
		6 wks post tx	1.3 ± 1.4 (n=21)	1.1 ± 1.7 (n=18)	NR	NR
	Frequency of headache attacks/month	Baseline	26.9 ±7.0 (n=21)	27.2 ± 5.9 (n=18)	NR	NR
		Immediate	17.5 ± 12.6 (n=21)	22.8 ± 10.0 (n=18)	NR	NR
		6 wks post tx	22.1 ± 10.6 (n=21)	22.0 ± 9.9 (n=18)	NR	NR
	PPT (Pressure Point Threshold) Left (kPa)	Baseline	329.1 ± 70.5 (n=21)	373.2 ± 28.6 (n=18)	NR	NR
		6 wks post tx	360.0 ± 41.3 (n=21)	366.6 ± 57.1 (n=18)	NR	NR
	PPT (Pressure Point Threshold) Right (kPa)	Baseline	312.9 ± 78.8 (n=21)	354.7 ± 56.8(n=18)	NR	NR
		6 wks post tx	368.2 ± 439.4 (n=21)	358.9 ± 76.6 (n=18)	NR	NR
	Analgesics/month	Baseline	8.3 ± 11.8 (n=21)	10.2 ± 12.0 (n=18)	NR	NR
		Immediate	6.4 ± 11.2 (n=21)	4.3 ± 5.7 (n=18)	NR	NR
		6 wks post tx	13.7 ± 117.2 (n=21)	21.2 ± 27.6 (n=18)	NR	NR
Tavola 1992	Headache intensity (sum of the intensity of the headaches in a month [1 to 4; 1 = slight; 2	Baseline	4.3 ± 3.9 (n=15)	4.5 ± 3.4 (n=15)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
8 week treatment period	= medium: 3 = strong: 4 = very strong]/number of headaches)					
	Headache frequency (no. of headaches/month)	Baseline	3.4 ± 2.4* (n=15) (estimated from graph)	3.2 ± 2.5* (n=15) (estimated from graph)	NR	NS
	Duration of headaches (sum of duration of headaches in hrs./no. of headaches)	Baseline	2.8 ± 1.8 * (n=15) (estimated from graph)	3.2 ± 2.6* (n=15) (estimated from graph)	NR	NS
	Headache index (intensity X duration X frequency/30)	Baseline	4.3 ± 3.9 (n=15)	4.5 ± 3.4 (n=15)	NR	NS
		half-way thru tx (tx = 8 wks.)	3.4 ± 2.4* (n=15) (estimated from graph)	3.2 ± 2.5* (n=15) (estimated from graph)	NR	NS
		end of tx (tx = 8 wks.)	2.8 ± 1.8 * (n=15) (estimated from graph)	3.2 ± 2.6* (n=15) (estimated from graph)	NR	NS
		4 wks (1 mo.) after the end end of tx	2.4 ± 1.4 * (n=15) (estimated from graph)	3.0 ± 2.3* (n=15) (estimated from graph)	NR	NS
		26 wks (6 mos.) after the end end of tx	2.2 ± 1.6* (n=15) (estimated from graph)	3.1 ± 2.6* (n=15) (estimated from graph)	NR	NS
		52 wks (12 mos.) after the end end of tx	3.2 ± 2.1* (n=15) (estimated from graph)	3.7 ± 2.2* (n=15) (estimated from graph)	NR	NS
	Analgesic consumption (sum of the drugs taken per month)	baseline (1 month prior to tx)	11.6 ± 10.2 (n=15)	11.5 ± 12.7 (n=15)	NR	NS
		half-way thru tx (tx = 8 wks.)	7.3 ± * (n=15) (estimated from graph)	9.8 ± * (n=15) (estimated from graph)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
		end of tx (tx = 8 wks.)	4.3 ± * (n=15) (estimated from graph)	9.3 ± * (n=15) (estimated from graph)	NR	NS
		4 wks (1 mo.) after the end end of tx	5.0 ± * (n=15) (estimated from graph)	9.0 ± * (n=15) (estimated from graph)	NR	NS
		26 wks (6 mos.) after the end end of tx	5.0 ± * (n=15) (estimated from graph)	8.5 ± * (n=15) (estimated from graph)	NR	NS
		52 wks (12 mos.) after the end end of tx	6.5 ± * (n=15) (estimated from graph)	9.5 ± * (n=15) (estimated from graph)	NR	NS
	Mean decrease of episode frequency from baseline to 9 wks.	4 wks (1 mo.) after the end end of tx	44.3%	21.4%	NR	NR
	Mean decrease of headache index from baseline to 9 wks.	4 wks (1 mo.) after the end end of tx	58.3%	27.8%	NR	NR
	Mean decrease of analgesic consumption from baseline to 9 wks.	4 wks (1 mo.) after the end end of tx	57.7%	21.7%	NR	NR
	Responders 33% threshold (Proportion of patients with >33% improvement over baseline on Headache Index)	4 wks (1 mo.) after the end end of tx	86.7% (13/15)	60.0% (9/15)	NR	P=0.125
	Responders 50% threshold (Proportion of patients with >50% improvement over baseline on Headache Index)	4 wks (1 mo.) after the end end of tx	53.3% (8/15)	46.7% (7/15)	NR	P=1
	Responders 33% threshold (Proportion of patients with >33% improvement over baseline on Headache Index)	52 wks (12 mos.) after the end end of tx	53.3% (8/15)	46.7% (7/15)	NR	P=1

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Responders 50% threshold (Proportion of patients with >50% improvement over baseline on Headache Index)	52 wks (12 mos.) after the end end of tx	40.0% (6/15)	26.7% (4/15)	NR	P=0.7
Acupuncture vs. Active Comparator						
Soderberg 2006 Acupuncture vs. physical training vs. relaxation training 10-12 week treatment period	Headache intensity (VAS 0-100)	Baseline	26.75 (range, 0.72–69.6) (n=30)	22.03 (range, 4.66–48.2) (n=30)	NR	NS
		Immediate	21.21 (range, 0.93–72.45) (n=30)	15.5 (range, 0.30–51.53) (n=30)	NR	NS
		3 mos post tx	18.93 (range, 0.00–53.38) (n=30)	16.88 (range, 0.00–61.67) (n=30)	NR	NS
		6 mos post tx	17.72 (range, 0.00–50.27) (n=30)	14.66 (range, 0.00–56.75) (n=30)	NR	NS
	Headache-free periods (0-28 periods/wk.)	Baseline	4.13 (range, 0.00–18.25) (n=30)	5.74 (range, 0.00–23.25) (n=30)	NR	NS
		Immediate	3.85 (range, 0.00–26.25) (n=30)	8.33 (range, 0.00–27.50) (n=30)	NR	NS
		3 mos post tx	6.25 (range, 0.00–28.00) (n=30)	7.46 (range, 0.00–28.00) (n=30)	NR	NS
		6 mos post tx	7.58 (range, 0.00–28.00) (n=30)	9.37 (range, 0.00–28.00) (n=30)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Headache-free days (0-7 days/wk.)	Baseline	0.73 (range, 0.00–3.25) (n=30)	0.97 (range, 0.00–5.00) (n=30)	NR	NS
		Immediate	0.68 (range, 0.00–6.25) (n=30)	1.52 (range, 0.00–6.75) (n=30)	NR	P=0.01
		3 mos post tx	1.18 (range, 0.00–7.00) (n=30)	1.23 (range, 0.00–7.00) (n=30)	NR	NS
		6 mos post tx	1.56 (range, 0.00–7.00) (n=30)	1.66 (range, 0.00–7.00) (n=30)	NR	NS
	Headache intensity (VAS 0-100)	Baseline	26.75 (range, 0.72–69.6) (n=30)	26.14 (range, 3.77–61.71) (n=30)	NR	NS
		Immediate	21.21 (range, 0.93–72.45) (n=30)	16.77 (range, 0.00–56.24) (n=30)	NR	NS
		3 mos post tx	18.93 (range, 0.00–53.38) (n=30)	16.14 (range, 0.00–66.64) (n=30)	NR	NS
		6 mos post tx	17.72 (range, 0.00–50.27) (n=30)	15.08 (range, 0.00–70.48) (n=30)	NR	NS
	Headache-free periods (0-28 periods/wk.)	Baseline	4.13 (range, 0.00–18.25) (n=30)	3.32 (range, 0.00–19.50) (n=30)	NR	NS
		Immediate	3.85 (range, 0.00–26.25) (n=30)	6.98 (range, 0.00–28.00) (n=30)	NR	P=0.024
		3 mos post tx	6.25 (range, 0.00–28.00) (n=30)	7.67 (range, 0.00–29.00) (n=30)	NR	NS
		6 mos post tx	7.58 (range, 0.00–28.00) (n=30)	8.29 (range, 0.00–29.00) (n=30)	NR	NS
	Headache-free days (0-7 days/wk.)	Baseline	0.73 (range, 0.00–3.25) (n=30)	0.38 (range, 0.00–3.00) (n=30)	NR	NS
		Immediate	0.68 (range, 0.00–6.25) (n=30)	1.44 (range, 0.00–7.00) (n=30)	NR	P=0.01
		3 mos post tx	1.18 (range, 0.00–7.00) (n=30)	1.58 (range, 0.00–7.25) (n=30)	NR	NS
		6 mos post tx	1.56 (range, 0.00–7.00) (n=30)	1.73 (range, 0.00–7.25) (n=30)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Soderberg 2011 Acupuncture vs. physical training vs. relaxation training 10-12 week treatment period	Proportion of patients with Improved QoL (MSEP)	Immediate	56.7% (17/30)	63.3% (19/30)	NR	NS
		3 mos post tx	56.7% (17/30)	86.7% (26/30)	NR	P=0.036
		6 mos post tx	56.7% (17/30)	80.0% (24/30)	NR	NS
	Proportion of patients with Improved Vitality Dimension Score of ≥10 VAS units	Immediate	36.7% (11/30)	36.7% (11/30)	NR	NS
		3 mos post tx	26.7% (8/30)	43.3% (13/30)	NR	NS
		6 mos post tx	20.0% (6/30)	33.3% (10/30)	NR	NS
	Proportion of patients with Improved Vitality Dimension Score (MSEP) of ≥25 VAS units	Immediate	16.7% (15/30)	16.7% (15/30)	NR	NS
		3 mos post tx	16.7% (15/30)	16.7% (15/30)	NR	NS
		6 mos post tx	10.0% (3/30)	13.3% (14/30)	NR	NS
	Proportion of patients with Improved Sleep QoL Dimension (MSEP) of ≥10 VAS units	Immediate	26.7% (8/30)	26.7% (8/30)	NR	NS
		3 mos post tx	30.0% (9/30)	30.0% (9/30)	NR	NS
		6 mos post tx	40.0% (12/30)	33.3% (10/30)	NR	NS
	Proportion of patients with Improved Sleep QoL Dimension (MSEP) of ≥25 VAS units	Immediate	13.3% (4/30)	23.3% (7/30)	NR	NR
		3 mos post tx	10.0% (3/30)	13.3% (4/30)	NR	NR
		6 mos post tx	13.3% (4/30)	16.7% (5/30)	NR	NR
	Proportion of patients with Improved Contentment Dimension Score (MSEP) of ≥10 VAS units	Immediate	43.3% (13/30)	26.7% (8/30)	NR	NS
		3 mos post tx	30.0% (9/30)	30.0% (9/30)	NR	NS
		6 mos post tx	40.0% (12/30)	33.3% (10/30)	NR	NS
	Proportion of patients with Improved Contentment Dimension Score (MSEP) of ≥25 VAS units	Immediate	10.0% (3/30)	13.3% (4/30)	NR	NS
		3 mos post tx	10.0% (3/30)	13.3% (4/30)	NR	NS
		6 mos post tx	13.3% (4/30)	16.7% (5/30)	NR	NS
	Proportion of patients with Improved QoL (MSEP)	Immediate	56.7% (17/30)	76.7% (23/30)	NR	NS
		3 mos post tx	56.7% (17/30)	66.7% (20/30)	NR	NS
		6 mos post tx	56.7% (17/30)	73.3% (22/30)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Proportion of patients with Improved Vitality Dimension Score of ≥10 VAS units	Immediate	36.7% (11/30)	36.7% (11/30)	NR	NS
		3 mos post tx	26.7% (8/30)	30.0% (9/30)	NR	NS
		6 mos post tx	20.0% (6/30)	50.0% (15/30)	NR	P=0.04
	Proportion of patients with Improved Vitality Dimension Score (MSEP) of ≥25 VAS units	Immediate	16.7% (15/30)	10.0% (3/30)	NR	NS
		3 mos post tx	16.7% (15/30)	10.0% (3/30)	NR	NS
		6 mos post tx	10.0% (3/30)	33.3% (10/30)	NR	P=0.04
	Proportion of patients with Improved Sleep QoL Dimension (MSEP) of ≥10 VAS units	Immediate	26.7% (8/30)	30.0% (9/30)	NR	NS
		3 mos post tx	30.0% (9/30)	36.7% (11/30)	NR	NS
		6 mos post tx	40.0% (12/30)	53.3% (16/30)	NR	P=0.04
	Proportion of patients with Improved Sleep QoL Dimension (MSEP) of ≥25 VAS units	Immediate	13.3% (4/30)	16.7% (5/30)	NR	NS
		3 mos post tx	10.0% (3/30)	16.7% (5/30)	NR	NS
		6 mos post tx	13.3% (4/30)	26.7% (8/30)	NR	P=0.04
	Proportion of patients with Improved Contentment Dimension Score (MSEP) of ≥10 VAS units	Immediate	43.3% (13/30)	40.0% (12/30)	NR	NS
		3 mos post tx	30.0% (9/30)	36.7% (11/30)	NR	NS
		6 mos post tx	40.0% (12/30)	53.3% (16/30)	NR	NS
	Proportion of patients with Improved Contentment Dimension Score (MSEP) of ≥25 VAS units	Immediate	10.0% (3/30)	6.7% (2/30)	NR	NS
		3 mos. post tx	10.0% (3/30)	16.7% (5/30)	NR	NS
		6 mos. post tx	13.3% (4/30)	26.7% (8/30)	NR	NS
Carlsson 1990 (Health Status Acupuncture vs. physical training	Headache intensity (pain on VAS 0-100)	baseline (3-8 wks. before treatment)	41 (n=23) (estimated from graph)	52 (n=29) (estimated from graph)	NR	NR
		4-9 wks. after termination of tx	40 (n=23) (estimated from graph)	28 (n=29) (estimated from graph)	NR	NR

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
8-12 week treatment period		After 7-12 mos. (?after termination of tx?)	52 (n=23) (estimated from graph)	29 (n=29) (estimated from graph)	NR	NR
	Sickness Impact Profile (SIP) - Overall (0-100, poorer health)	before tx	12.5 (n=23) (estimated from graph)	9.5 (n=29) (estimated from graph)	NR	NR
		after tx	9 (n=23) (estimated from graph)	4.5 (n=29) (estimated from graph)	NR	NR
	Sickness Impact Profile (SIP) - Psychosocial index (0-100, poorer health)	before tx	15.5 (n=23) (estimated from graph)	14 (n=29) (estimated from graph)	NR	NR
		after tx	10 (n=23) (estimated from graph)	4.5 (n=29) (estimated from graph)	NR	NR
	Sickness Impact Profile (SIP) - Emotional Behavior (0-100, poorer health)	before tx	26 (n=23) (estimated from graph)	23 (n=29) (estimated from graph)	NR	NR
		after tx	19 (n=23) (estimated from graph)	7 (n=29) (estimated from graph)	NR	NR
	Sickness Impact Profile (SIP) - Sleep and rest (0-100, poorer health)	before tx	23.5 (n=23) (estimated from graph)	17 (n=29) (estimated from graph)	NR	NR
		after tx	12.5 (n=23) (estimated from graph)	10.5 (n=29) (estimated from graph)	NR	NR
	Mood Adjective Check List (MACL) - Overall scores (1-4, more positive emotional state)	before tx	2.79 ± 0.37 (n=23)	2.77 ± 0.43 (n=29)	NR	NR
		after tx	2.77 ± 0.48 (n=23)	2.97 ± 0.48 (n=29)	NR	NR
		before tx	2.78 ± 0.50 (n=23)	2.82 ± 0.66 (n=29)	NR	NR

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Mood Adjective Check List (MACL) - pleasantness/unpleasantness (1-4, more positive emotional state)	after tx	2.72 ± 0.62 (n=23)	3.01 ± 0.64 (n=29)	NR	NR
	Mood Adjective Check List (MACL) - activation/deactivation (1-4, more positive emotional state)	before tx	2.86 ± 0.51 (n=23)	2.80 ± 0.56 (n=29)	NR	NR
		after tx	2.77 ± 0.67 (n=23)	3.04 ± 0.58 (n=29)	NR	NR
	Mood Adjective Check List (MACL) - calmness/tension (1-4, more positive emotional state)	before tx	2.29 ± 0.63 (n=23)	2.28 ± 0.61 (n=29)	NR	NR
		after tx	2.39 ± 0.68 (n=23)	2.60 ± 0.69 (n=29)	NR	NR
	Mood Adjective Check List (MACL) - extraversion/introversion (1-4, more positive emotional state)	before tx	2.80 ± 0.44 (n=23)	2.89 ± 0.41 (n=29)	NR	NR
		after tx	2.79 ± 0.50 (n=23)	3.03 ± 0.49 (n=29)	NR	NR
	Mood Adjective Check List (MACL) - pos/neg social oreintation (1-4, more positive emotional state)	before tx	3.14 ± 0.46 (n=23)	3.10 ± 0.47 (n=29)	NR	NR
		after tx	3.07 ± 0.45 (n=23)	3.31 ± 0.47 (n=29)	NR	NR
	Mood Adjective Check List (MACL) - confidence/lack of confidence (1-4, more positive emotional state)	before tx	2.89 ± 0.52 (n=23)	2.74 ± 0.41 (n=29)	NR	NR
		after tx	2.87 ± 0.52 (n=23)	2.86 ± 0.49 (n=29)	NR	NR
	Headache frequency (1-to-5 scale: almost never, once or twice a month, once a week, several times a week and daily)	after tx			"reduced in both the groups p<0.001" (no data)	NR
		before tx	3.78 ± 0.96 (n=23)	3.72 ± 0.73 (n=29)	NR	NR

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Carlsson 1990 (Muscle Tenderness) Acupuncture vs. physical training 10-12 week treatment period	Headache intensity on a 5-point scale (1 none or negligible pain, 2 mild pain, 3 moderate pain, 4 severe pain and 5 incapacitating headache)	after tx	3.24 ± 1.04 (n=23)	2.52 ± 0.80 (n=29)	NR	NR
	Proportion of patients NOT TAKING analgesics	before tx	5% (n=23) (estimated from graph)	3% (n=29) (estimated from graph)	NR	NR
		after tx	7% (n=23) (estimated from graph)	18% (n=29) (estimated from graph)	NR	NR
	Proportion of patients with a LOW intake of analgesics	before tx	4% (n=23) (estimated from graph)	11% (n=29) (estimated from graph)	NR	NR
		after tx	3% (n=23) (estimated from graph)	7% (n=29) (estimated from graph)	NR	NR
	Proportion of patients with a MODERATE intake of analgesics	before tx	11% (n=23) (estimated from graph)	13% (n=29) (estimated from graph)	NR	NR
		after tx	11% (n=23) (estimated from graph)	4% (n=29) (estimated from graph)	NR	NR
	Proportion of patients with a HIGH intake of analgesics	before tx	3% (n=23) (estimated from graph)	2% (n=29) (estimated from graph)	NR	NR
		after tx	2% (n=23) (estimated from graph)	0% (n=29) (estimated from graph)	NR	NR

Appendix Table G6. Efficacy outcomes from RCTs Evaluating Manual Therapy for Chronic Migraine and Chronic Tension-Type Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Manipulation vs. Amitriptyline						
Nelson 1998 8 week treatment period	Adj. Headache index scores (mean of last 4 wks.) (0-70; weekly sum of pt's headache pain scores [VAS 0-10]) on days they had experienced a headache) (adj = baseline values)	last 4 wks. of the treatment period (8 wks. from randomization)	9.8 ± 6.3 (n=59)	9.1 ± 6.3 (n=49)	Adj. diff -0.7 (-4.2, 2.1)	NR
		4 wks. after the end of treatment (12 wks. after randomization)	9.8 ± 7.0 (n=58)	12.6 ± 7.0 (n=50)	Adj. 2.8 (-0.07, 6.3)	NS
	Adj. OTC pills/day (mean of last 28 days.) (adj = baseline values)	Last 4 wks. of the treatment period (8 wks. from randomization)	1.1 ± 1.1 (n=59)	0.9 ± 1.0 (n=49)	Adj. -0.2 (-0.7, 0.2)	NR
		4 wks. after the end of treatment (12 wks. after randomization)	1.1 ± 1.3 (n=58)	1.4 ± 1.3 (n=50)	Adj.0.4 (-0.2, 0.9)	NS
	SF-36 scores (global), %	4 wks. after the end of treatment (12 wks. after randomization)	73.6 ± 10.7 (n=58)	71.2 ± 10.5 (n=50)	Adj. -2.5 (-8.0, 3.1)	NS
	Headache frequency (% of days with headache)	baseline	53.1% ± 26.3% (n=58)	51.8% ± 24.4% (n=47)	NR	NR
		Last 4 wks. of the treatment period (8 wks. from randomization)	37.5% ± 25.9% (n=58)	26.8% ± 22.6% (n=47)	NR	NR
		4 wks. after the end of treatment (12 wks. after randomization)	36.9% ± 29.3% (n=58)	40.5% ± 23.3 (n=47)	NR	NS
	Headache severity on the days with reported headache (0-10)	baseline	5.0 ± 1.3 (n=56)	4.6 ± 1.1 (n=44)	NR	NR
		Last 4 wks. of the treatment period (8 wks. from randomization)	4.3 ± 1.5 (n=56)	4.3 ± 1.6 (n=44)	NR	NR
		4 wks. after the end of treatment (12 wks. after randomization)	4.4 ± 1.7 (n=56)	4.5 ± 1.3 (n=44)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Proportion of patients with >20% reduction in HI scores	Last 4 wks. of the treatment period (8 wks. from randomization)	85% (50/59)	80% (39/49)	NR	NR
		4 wks. after the end of treatment (12 wks. after randomization)	58% (34/59)	69% (34/49)	NR	NR
	Proportion of patients with >40% reduction in HI scores	Last 4 wks. of the treatment period (8 wks. from randomization)	22% (13/59)	49% (24/49)	NR	NR
		4 wks. after the end of treatment (12 wks. after randomization)	74% (43/58)	44% (22/50)	RR 1.68, NNT 3.3	NR
	Proportion of patients with >60% reduction in HI scores	last 4 wks. of the treatment period (8 wks. from randomization)	60% (35/58)	36% (18/50)	RR 1.67, NNT 4.1	NR
		4 wks. after the end of treatment (12 wks. after randomization)	22% (13/58)	16% (8/50)	RR 1.40, NNT 15.6	NR
Manipulation vs. Routine Care						
Castien 2011 8 week treatment period	Proportion of patients with 50% reduction in headache frequency	immediately after tx period	87.5% (35/40)	27.5% (11/40)	RR 3.2 (95% CI 1.9, 5.3) NNT 2 (95% CI 1.3, 2.2)	
		26 wks. after randomization (18 wks. after end of tx)	81.6% (31/38)	40.5% (15/37)	RR 2.0 (95% CI 1.3, 3.0) NNT 3 (95% CI 1.6, 4.8)	
	Δ from baseline, mean headache frequency (days/14 days (headache diary))	immediately after tx period	–9.1 ± 3.8 (n=40)	–2.7 ± 4.3 (n=40)	---	<0.001
	Mean difference in Δ scores from baseline, mean headache frequency (days/14 days (headache diary))	immediately after tx period	---	---	–6.4 ± 0.92 (95% CI –8.32, –4.56)	<0.001
	Δ from baseline, mean headache pain intensity (0-10 NRS)	immediately after tx period	–2.7 ± 0.9 (n=40)	–0.9 ± 2.4 (n=40)	--	0.003

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Mean difference in Δ scores from baseline, mean headache pain intensity (0-10 NRS)	immediately after tx period	---	---	–1.8 ± 0.6 (95% CI –3.07, –0.67)"	0.003
	Δ from baseline, mean headache duration (hrs./day)	immediately after tx period	–5.9 ± 8.7 (n=40)	–0.6 ± 10.0 (n=40)	---	0.013
	Mean difference in Δ scores from baseline, mean headache duration (hrs./day)	immediately after tx period	---	---	–5.3 ± 2.1 (95% CI –9.51, –1.15)	0.013
	Δ from baseline, Headache Impact Test-6 (36-78)	immediately after tx period	–8.9 ± 7.1 (n=40)	–2.4 ± 6.5 (n=40)	---	<0.001
	Mean difference in Δ scores from baseline, mean Headache Impact Test-6 (36-78)	immediately after tx period	---	---	–6.5 ± 1.5 (95% CI –9.62, –3.52)	<0.001
	Δ from baseline, mean Headache Disability Inventory (0-100)	immediately after tx period	–17.4 ± 16.1 (n=40)	–5.8 ± 12.8 (n=40)		0.001
	Mean difference in Δ scores from baseline, mean Headache Disability Inventory (0-100)	immediately after tx period	---	---	–11.6 ± 3.2 (95% CI –18.1, –5.1)	0.001
	Δ from baseline, mean headache frequency (days/14 days (headache diary))	26 wks. after randomization (18 wks. after end of tx)	–9.1 ± 4.2 (n=38)	–4.1 ± 4.4 (n=37)	---	<0.001
	Mean difference in Δ scores from baseline, mean headache frequency (days/14 days (headache diary))	26 wks. after randomization (18 wks. after end of tx)	---	---	–4.9 ± 0.99 (95% CI –6.95, –2.98)	<0.001
	Δ from baseline, mean headache pain intensity (0-10 NRS)	26 wks. after randomization (18 wks. after end of tx)	–3.1 ± 2.8 (n=38)	–1.7 ± 2.5 (n=37)	---	0.027
	Mean difference in Δ scores from baseline, mean headache pain intensity (0-10 NRS)	26 wks. after randomization (18 wks. after end of tx)	---	---	–1.4 ± 0.63 (95% CI –2.69, –0.16)	0.027
	Δ from baseline, mean headache duration (hrs./day)	26 wks. after randomization (18 wks. after end of tx)	–7.0 ± 10.4 (n=38)	–3.5 ± 7.3 (n=37)	---	0.095

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Mean difference in Δ scores from baseline, mean headache duration (hrs./day)	26 wks. after randomization (18 wks. after end of tx)	---	---	–3.5 ± 2.1 (95% CI –7.71, –0.63)	0.095
	Δ from baseline, Headache Impact Test-6 (36-78)	26 wks. after randomization (18 wks. after end of tx)	–10.6 ± 8.4 (n=38)	–5.5 ± 8.6 (n=37)	---	0.012
	Mean difference in Δ scores from baseline, mean Headache Impact Test-6 (36-78)	26 wks. after randomization (18 wks. after end of tx)	---	---	–5.0 ± 1.97 (95% CI –9.02, –1.16)	0.012
	Δ from baseline, Headache Disability Inventory (0-100)	26 wks. after randomization (18 wks. after end of tx)	–20.0 ± 22.6 (n=38)	–9.9 ± 18.0 (n=37)	---	0.037
	Mean difference in Δ scores from baseline, mean Headache Disability Inventory (0-100)	26 wks. after randomization (18 wks. after end of tx)	---	---	–10.1 ± 4.74 (95% CI –19.5, –0.64)	0.037
	Perceived recovery: proportion who considered themselves improved/much improved	immediately after tx period	87.5% (35/40)	25.0% (10/40)	Diff: 62.5% (95% CI 48.4%, 79.3%)	<0.05
	Proportion who used ≥1 sick leave day	26 wks. after randomization (18 wks. after end of tx)	7.9% (3/38)	32.4% (12/37)	Diff: 49% (95% CI 30.0%, 67.9%)	<0.05
	Proportion who used any additional health care (i.e., physical therapy, medical specialists, other)	26 wks. after randomization (18 wks. after end of tx)	13.2% (5/38)	59.4% (22/37)	Diff: 46.3% (95% CI 27.1%, 65.4%)	<0.05
	Proportion who used additional physical therapy	26 wks. after randomization (18 wks. after end of tx)	2.6% (1/38)	40.5% (15/37)	Diff: 37.9% (95% CI 21.2%, 54.3%)	<0.05
	Proportion who used additional medical specialist care	26 wks. after randomization (18 wks. after end of tx)	2.6% (1/38)	16.2% (6/37)	Diff: 13.5% (95% CI 0.7%, 26.5%)	<0.05
	Proportion who used additional "other" health care	26 wks. after randomization (18 wks. after end of tx)	7.8% (3/38)	2.7% (1/37)	Diff: 5.1% (95% CI -4.8%, -15.2%)	<0.05

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Use of analgesics/NSAIDs (decreased, no change, increased intake of tablets)	26 wks. after randomization (18 wks. after end of tx)	Data NR: "differences were not stat. diff. b/w groups"	---	---	NS
	Use of analgesics/NSAIDs (decreased, no change, increased intake of tablets)	26 wks. after randomization (18 wks. after end of tx)	Data NR: "differences were not stat. diff. b/w groups"	---	---	0.92

Appendix Table G7. Efficacy Outcomes from RCTS Evaluating Massage Therapy for Chronic Daily Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Massage vs. Sham						
Chatchawan 2014 3 week treatment period	Headache intensity (pain during past 24 hrs. on VAS 0-10)	baseline	5.54 ± 2.16 (n=36)	4.66 ± 2.40 (n=36)	NR	NR
		end of tx (after 3 wks. of tx)	1.66 (n=36)	2.60 (n=36)	Diff (95% CI): –0.94 (–1.95 to 0.07)	0.066
		3 wks. after last tx	2.32 (n=36)	2.93 (n=36)	Diff (95% CI): –0.61 (–1.77 to 0.56)	0.3
		9 wks. after last tx	2.63 (n=36)	2.70 (n=36)	Diff (95% CI): –0.07 (–1.18 to 1.04)	0.9
	Headache frequency (time/mo) (adjusted mean, for baseline)	baseline	16.26 ± 2.02 (n=36)	16.35 ± 6.68 (n=36)	NR	NR
		end of tx (after 3 wks. of tx)	3.16 (n=36)	3.86 (n=36)	Diff (95% CI): –0.70 (–1.84 to 0.43)	0.219
		3 wks. after last tx	2.46 (n=36)	5.02 (n=36)	Diff (95% CI): –2.56 (–5.17 to 0.04)	0.054
		9 wks. after last tx	3.07 (n=36)	2.91 (n=36)	Diff (95% CI): 0.16 (–1.10 to 0.78)	0.733
	Headache duration (hours by average/time) (adjusted mean, for baseline)	baseline	8.28 ± 13.81 (n=36)	4.65 ± 4.67 (n=36)	NR	NR
		end of tx (after 3 wks. of tx)	6.76 (n=36)	8.54 (n=36)	Diff (95% CI): –1.78 (–9.07 to 5.53)	0.629
		3 wks. after last tx	6.88 (n=36)	10.38 (n=36)	Diff (95% CI): –3.50 (–12.90 to 5.90)	0.459
		9 wks. after last tx	2.98 (n=36)	7.70 (n=36)	Diff (95% CI): –4.72 (–10.27 to 0.83)	0.094
	Headache Disability Index (HDI) score (0-100) (adjusted mean, for baseline)	baseline	37.47 ± 19.68 (n=36)	32.28 ± 17.96 (n=36)	NR	NR
		end of tx (after 3 wks. of tx)	29.95 (n=36)	29.83 (n=36)	Diff (95% CI): 0.12 (–6.62 to 6.85)	0.972
		3 wks. after last tx	26.40 (n=36)	28.25 (n=36)	Diff (95% CI): –1.85 (–9.97 to 6.25)	0.649

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
		9 wks. after last tx	28.12 (n=36)	27.77 (n=36)	Diff (95% CI): 0.35 (–7.32 to 8.01)	0.929
	PPT (pounds/cm2) (adjusted mean, for baseline)	baseline	2.71 ± 1.22 (n=36)	2.85 ± 1.20 (n=36)		
		end of tx (after 3 wks. of tx)	3.57 ± 1.41 (n=36)	2.62 ± 1.07 (n=36)	Diff (95% CI): 1.03 (0.54–1.53)	0.001
		3 wks. after last tx	3.72 ± 1.46 (n=36)	2.58 ± 1.05 (n=36)	Diff (95% CI): 1.22 (0.69–1.76)	0.001
		9 wks. after last tx	3.42 ± 1.46 (n=36)	2.63 ± 0.94 (n=36)	Diff (95% CI): 0.84 (0.28–1.40)	0.004
	Analgesic medication use	baseline	25 (69.4%)	25 (66.7%)	NR	NR
		Not reported	10 (27.8%)	9 (25.0%)	NR	NR

Appendix Table G8. Efficacy Outcomes from RCTS Evaluating Transcranial Magnetic Stimulation for Chronic Migraine

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
TMS vs. Sham						
Misra 2013 5 day treatment period	Proportion of patients with >50% improvement in headache frequency	4 wks. from end of tx	78.7% (37/47)	33.3% (16/48)	NR	P<0.0001
	Proportion of patients with >50% improvement in pain frequency and mean severity (VAS 0-100)	4 wks. from end of tx	76.6% (36/47)	27.1% (13/48)	NR	P<0.0001
	Proportion of patients - headache severity - Normal (0)	4 wks. from end of tx	6.4% (3/47)	0% (0/48)	NR	NR
	Proportion of patients - headache severity - Mild (1)	4 wks. from end of tx	38.3% (18/47)	14.6% (7/48)	NR	NR
	Proportion of patients - headache severity - Moderate (2)	4 wks. from end of tx	46.8% (22/47)	45.8% (22/48)	NR	NR
	Proportion of patients - headache severity - Severe (3)	4 wks. from end of tx	8.5% (4/47)	39.6% (19/48)	NR	NR
	Proportion of patients - functional disability - Normal (0)	4 wks. from end of tx	13.3% (6/45)	0% (0/48)	NR	NR
	Proportion of patients - functional disability - Mild (1)	4 wks. from end of tx	51.1% (23/45)	25.0% (12/48)	NR	NR
	Proportion of patients - functional disability - Moderate (2)	4 wks. from end of tx	33.3% (15/45)	43.8% (21/48)	NR	NR
	Proportion of patients - functional disability - Severe (3)	4 wks. from end of tx	2.2% (1/45)	31.3% (15/48)	NR	NR
	Analgesic use/mo.	baseline	20.58 ± 16.76 (n=50)	17.52 ± 18.10 (n=50)	NR	NS
		4 wks. from end of tx	5.09 ± 5.94 (n=47)	6.71 ± 5.75 (n=48)	NR	P=0.18
		baseline	20.8 ± 9.5 (n=50)	17.0 ± 10.3 (n=50)	NR	NS

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
	Headache frequency (attacks/mo.)	4 wks. from end of tx	5.2 ± 4.9 (n=47)	8.9 ± 6.6 (n=48)	NR	P<0.0001
	Headache severity (0-3, worse)	baseline	3 ± 0 (n=50)	3 ± 0 (n=50)	NR	NS
		4 wks. from end of tx	1.57 (n=47)	2.25 (n=48)	NR	P<0.0001
	Functional disability (0-3, worse)	baseline	3.26 ± 0.44 (n=50)	3.24 ± 0.43 (n=50)	NR	NS
		4 wks. from end of tx	1.24 (n=47)	2.06 (n=48)	NR	P<0.0001
	Proportion of patients who were satisfied	4 wks. from end of tx	78.7% (37/47)	29.2% (14/48)	NR	P<0.0001
Teepker 2010 5 day treatment period	Headache frequency (mean attacks/8 wks.; days)	baseline (8 wks. prior to tx)	9.36 ± 2.82	9.2 ± 2.6* (estimated from graph)	NR	NR
		8 wks. from end of tx	6.79 ± 4.28	7.7 ± 4.2* (estimated from graph)	NS	NR
	Headache frequency (mean headache days/8 wks.)	baseline (8 wks. prior to tx)	14.3 ± 5.07	17.69 ± 11.63	NR	NR
		8 wks. from end of tx	9.50 ± 6.80	13.15 ± 9.27	NR	NS
	Headache frequency (mean headache hrs./8 wks.)	baseline (8 wks. prior to tx)	125.93 ± 80.31	134 ± 100* (estimated from graph)	NR	NR
		8 wks. from end of tx	85.36 ± 72.27	103 ± 77* (estimated from graph)	NS	NR
	Headache severity (mean pain intensity/8 wks.; VAS 0-10)	baseline (8 wks. prior to tx)	6.26 ± 1.33	5.52 ± 1.72	NR	NR
		8 wks. from end of tx	6.11 ± 1.26	5.17 ± 2.51	NR	NS
	Headache severity (mean number of pills)	baseline (8 wks. prior to tx)	15.15 ± 11.24	14.21 ± 10.13	NR	NR
		8 wks. from end of tx	11.81 ± 9.89	12.50 ± 14.65	NR	NS

Appendix Table G9. Efficacy Outcomes Results from RCTs Evaluating Trigger Point Injections for Chronic Tension-Type Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
TPI vs. Placebo						
Karadas 2013 1 wk (1 session every 3 days for a total of 3 sessions)	Number of painful days/mo.	baseline	20.2 ± 3.9 (n=24)	19.1 ± 3.5 (n=23)	NR	NR
		12 wks. (3 mos.) after tx	7.5 ± 3.7 (n=24)	17.6 ± 4.0 (n=23)	NR	P<0.001
	Δ from baseline, Number of painful days/mo.	12 wks. (3 mos.) after tx	–12.7 ± 3.6 (n=24)	–1.5 ± 3.1 (n=23)	NR	P<0.001
	Pain severity (VAS 0-100)	baseline	77.5 ± 6.1 (n=24)	76.2 ± 6.1 (n=23)	NR	NR
		12 wks. (3 mos.) after tx	38.7 ± 11.0 (n=24)	70.0 ± 10.3 (n=23)	NR	P<0.001
	Δ from baseline, Pain severity (VAS 0-100)	12 wks. (3 mos.) after tx	–38.8 ± 10.5 (n=24)	–6.2 ± 9.0 (n=23)	NR	P<0.001
	Medication use (no. analgesic drugs/mo., tablets)	baseline	9.8 ± 2.1 (n=24)	10.1 ± 2.6 (n=23)	NR	NR
		12 wks. (3 mos.) after tx	3.9 ± 2.1 (n=24)	9.0 ± 1.9 (n=23)	NR	P<0.001
	Δ from baseline, Medication use (no. analgesic drugs/mo., tablets)	12 wks. (3 mos.) after tx	–5.9 ± 1.4 (n=24)	–1.1 ± 1.6 (n=23)	NR	P<0.001
	Hamilton Depression Scale scores	baseline	20.0 ± 7.9 (n=24)	20.2 ± 7.3 (n=23)	NR	NR
		12 wks. (3 mos.) after tx	14.8 ± 5.9 (n=24)	19.2 ± 7.3 (n=23)	NR	P<0.001
	Δ from baseline, Hamilton Depression Scale scores	12 wks. (3 mos.) after tx	–5.2 ± 4.0 (n=24)	–1.0 ± 1.8 (n=23)	NR	P<0.001
	Hamilton Anxiety Scale scores	baseline	21.9 ± 5.6 (n=24)	21.7 ± 4.2 (n=23)	NR	NR
		12 wks. (3 mos.) after tx	14.6 ± 4.5 (n=24)	20.3 ± 4.1 (n=23)	NR	P<0.001
	Δ from baseline, Hamilton Anxiety Scale scores	12 wks. (3 mos.) after tx	–7.3 ± 4.0 (n=24)	–1.4 ± 2.2 (n=23)	NR	P<0.001

CI, confidence interval; F/U, follow-up; Mo., month; mos., months; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; SD, standard deviation; tx, treatment; VAS, visual analog scale; wk., week; wks., weeks.

APPENDIX H. Data Abstraction Tables: Safety Outcomes

NOTE Additional safety outcomes information can be found in the report text. See section that follows these tables for safety information from unpublished trials from clinicaltrials.gov.

Appendix Table H1. Safety Outcomes from RCTs Evaluating BoNTA in Included Studies

			Results n/N (%)		Effect Size (95% CI)	p-value
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Comparator**		
BoNTA vs. Placebo						
Freitag 2008 16 week study period	Fever	16 wks.	0 (0.0)	2/21 (9.5%)	NR	NR
	Backache	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Panic attack	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Heaviness of arms	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Confusion	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Chest heaviness	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Stiff neck	16 wks.	1/20 (5.0%)	1/20 (4.8%)	NR	NR
	Dizziness	16 wks.	0 (0.0)	1/20 (4.8%)	NR	NR
	Sinus infection	16 wks.	2/20 (10%)	0 (0.0)	NR	NR
	Hair loss	16 wks.	1/20 (5.0%)	0 (0.0)	NR	NR
	Amenorrhea	16 wks.	1/20 (5.0%)	0 (0.0)	NR	NR
Hamdy 2009 16 week study period	Hematoma at site of injection	12 wks.	1/14 (7.1%)	1/14 (7.1%)	NR	NR
	Blepharoptosis	12 wks.	1/14 (7.1%)	0/14 (0.0%)	NR	NR
	Itching at site of injection	12 wks.	0/14 (0.0%)	1/14 (7.1%)	NR	NR
	Pain at site of injection	12 wks.	1/14 (7.1%)	1/14 (7.1%)	NR	NR
Kokoska 2004 24 week study period	Ptosis	24 wks.	3/20 (15%)	0 (0.0)	NR	NR
	Diplopia	24 wks.	0 (0.0)	0 (0.0)	NR	NR
	Facial nerve/expression problems	24 wks.	0 (0.0)	0 (0.0)	NR	NR

			Results n/N (%)		Effect Size (95% CI)	p-value
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Comparator**		
	Autonomic/systemic side problems	24 wks.	0 (0.0)	0 (0.0)	NR	NR
	Keratopathy	24 wks.	0 (0.0)	0 (0.0)	NR	NR
	Idiosyncratic or allergic reactions	24 wks.	0 (0.0)	0 (0.0)	NR	NR
Padberg 2004 12 week study period	Hematoma at injection site	12 wks.	0 (0.0)	2/21 (9.5%)	NR	NR
	Frontal muscle weakness	12 wks.	1/19 (5.3%)	0 (0.0)	NR	NR
	Nausea	12 wks.	1/19 (5.3%)	1/21 (4.8%)	NR	NR
	Neck numbness	12 wks.	1/19 (5.3%)	0 (0.0)	NR	NR
Schmitt 2004 8 week study period	Increased headache	4 wks.	4/30 (13.3%)	4/29 (13.8%)	NR	NR
	Increased headache	8 wks.	3/30 (10.0%)	0 (0.0)	NR	NR
	Other	4 wks.	4/30 (13.3%)	2/29 (6.9%)	NR	NR
	Other	8 wks.	0 (0.0)	0 (0.0)	NR	NR
Silberstein 2006 8 week study period	All adverse events	8 wks.	150U: 29/47 (61.7%) 100U: 33/51 (64.7%) 100U 3s: 33/52 (63.5%) 86U 3s: 28/51 (54.9%) 50U: 25/49 (51.0%)	26/50 (52.0%)	NR	NR
Ondo 2004 8 week study period	All adverse events	12 wks.	33	39	NR	NR

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks;

Appendix Table H2. Safety Outcomes from RCTs Evaluating Acupuncture

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Chronic Migraine						
Vickers 2004 3 month treatment period	Headache after treatment	Unclear: "after treatment"	2.2% (4/186) (5 cases in 4 pts.)	NR	NR	NR
	Withdrawal at 3 months due to adverse effects (NOS) (unclear if this patient is included in the count above)	12 wks.	0.6% (1/173)	0% (0/140)	NR	NR
	No serious adverse events (assumed based on statement "Confirming the excellent safety profile of acupuncture, the only adverse event reported was five cases of headache after treatment in four subjects.")	36 wks.	0% (0/186)	0% (0/193)	NR	NR
Yang 2011	"Serious adverse events"	Immediate	0% (0/33)	0% (0/33)	NS	NR
	Death	Immediate	0% (0/33)	0% (0/33)	NS	NR
	"Non-serious adverse events/side effects" (primarily related to local insertion of needles, i.e., local pain after tx, ecchymosis, local paresthesia during tx)	Immediate	6% (2/33)	NR	NR	NR
	Any non-serious adverse event (mostly mild and self-limiting)	Immediate	NR	66% (22/33)	NR	NR
	Paresthesia	Immediate	NR	48.4% (16/33)	NR	NR
	Difficulty with memory	Immediate	NR	36.3% (12/33)	NR	NR
	Dyspepsia	Immediate	NR	36.3% (12/33)	NR	NR
	Fatigue	Immediate	NR	24.2% (8/33)	NR	NR
	Dizziness	Immediate	NR	21.2% (7/33)	NR	NR
	Somnolence	Immediate	NR	18.1% (6/33)	NR	NR
	Nausea	Immediate	NR	12.1% (5/33)	NR	NR
	Adverse events leading to withdrawl from treatment	Immediate	0% (0/33)	9.1% (3/33)	NR	NR
Chronic Tension-Type Headache						
Karst 2000	NR					
Soderberg 2006	NR					

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Tavola 1992	NR					
Carlsson 1990	"In a few patients, a slight vasovagal reaction was seen at the first treatment [in the acupuncture group]. Otherwise, no complications were noted."					

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks;

Appendix Table H3. Safety Outcomes from RCTs Evaluating Manual Therapy for Chronic Migraine and Chronic Tension-Type Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Nelson 1998 8 wk treatment period	Withdrawal due to side effects (NOS)	4 wks.	0% (0/58) ("Side effects in the SMT group were much more benign infrequent, mild and transitory (NOS); none required withdrawal from the study")	14.0% (7/50)	NR	NR
Castien 2011	"No adverse events were reported in both intervention groups."					

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks;

Appendix Table H4. Safety Outcomes from RCTS Evaluating Massage Therapy for Chronic Daily Headache

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
Chatchawan 2014	Mild fever/mild soreness/other mild discomfort	9 wks.	16.7% (6/36)	13.9% (5/36)	"All (both groups) resolved w/in 15-60 mins. without using meds."	NR

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks;

Appendix Table H5. Safety Outcomes from RCTs Evaluating Transcranial Magnetic Stimulation for Chronic Migraine

			Results (mean ± SD or % (n/N))		Effect Estimate (95% CI)*	p-value*
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**		
TMS vs. Sham						
Misra 2013 5 day treatment period	Drowsiness	4 wks.	2.1% (1/47)	0% (0/48)	NR	P=0.5
	Discomfort during treatment (mean on Face pain scale (0-5))	4 wks.	100% (47/47) (3.10 ± 0.71)	14.6% (7/48) (0.14 ± 0.35)	NR	P<0.0001
	Study withdrawal due to side effect (NOS; unclear if this is the same patient as above)	4 wks.	2.1% (1/47)	0% (0/48)	NR	NS
Teepker 2010 5 day treatment period	Assessment of visual motor threshold is uncomfortable	during tx	35.7% (5/14)	30.8% (4/13)	NR	NS
	Sitting is long-lasting and uncomfortable	during tx	7.1% (1/14)	7.7% (1/13)	NR	NS
	Sleepiness	during tx	7.1% (1/14)	7.7% (1/13)	NR	NS
	Headache	during tx	14.3% (2/14)	0% (0/13)	NR	NS
	Amyostasia	"after treatment"	7.1% (1/14)	7.7% (1/13)	NR	NS
	Testiness	"after treatment"	7.1% (1/14)	7.7% (1/13)	NR	NS
	Vigorous dreams	"after treatment"	0% (0/14)	7.7% (1/13)	NR	NS
	Phonophobia	"after treatment"	0% (0/14)	7.7% (1/13)	NR	NS
	Withdrawal due to side effect (NOS)	"after treatment"	7.1% (1/14)	7.7% (1/13)	NR	NS

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks;

Appendix Table H6. Safety Outcomes from RCTS Evaluating Trigger Point Injections for Chronic Tension-Type Headache

			Results (mean ± SD or % (n/N))			
Author	**Outcome**	**F/U post-tx**	**Intervention**	**Control**	**Effect Estimate (95% CI)***	**p-value***
TPI vs. Placebo						
Karadas 2013 1 week (1 session every 3 days for a total of 3 sessions)	"no serious side effects [in any patient] observed before or after the applications"	NR	0% (0/24)	0% (0/24)	NR	NR
	Injection site and injection pain	NR	12.5% (3/24)	16.7% (4/24)	NR	NR
	Dizziness	NR	8.3% (2/24)	8.3% (2/24)	NR	NR
	Back pain	NR	8.3% (2/24)	12.5% (3/24)	NR	NR
	Cervical muscle spasm	NR	0% (0/24)	4.2% (1/24)	NR	NR

CI, confidence interval; NOS, not otherwise stated; NR, not reported; NS, not statistically significant; tx, treatment; SD, standard deviation; SMT, spinal manipulation therapy; U, units; wks., weeks.

The following Tables contain safety information from unpublished trials from clinicaltrials.gov. Data in this section are included for completeness only and have not been addressed in this report as they do not meet the inclusion criteria.

NCT01432379: BOTOX® Prophylaxis in Patients with Chronic Migraine

Baseline n=1168
Completed n=783
Date completed: May 2015
155-195 U of BoNTA administered to the face, head, and neck areas approximately every 12 weeks for 1 year

Appendix Table H7. Unpublished Safety Outcomes from NCT01432379: BOTOX® Prophylaxis in Patients with Chronic Migraine, Primary and Secondary Outcomes.

Outcome Type	Follow-up	Outcome Title	Description	Incidence Rate* Number (95% CI)
Primary	64 weeks	Incidence rate of dysphagia	Incidence rates reported for subjects with events 1,000 person-months, based on the first reported occurrence of dysphagia from study enrollment up to 64 weeks. Dysphagia was defined as difficulty or discomfort in swallowing	0.4 (0.1, 0.9)
Secondary	64 weeks	Incidence rate of intractable migraine	Incidence rates reported for subjects with events 1,000 person-months, based on the first reported occurrence of intractable migraine from study enrollment to 64 weeks. Intractable migraine was defined as a migraine that does not seem to go away	1.6 (0.9, 2.4)

*units were events per 1,000 person-months

Appendix Table H8. Unpublished Safety Outcomes from NCT01432379: BOTOX® Prophylaxis in Patients with Chronic Migraine, Serious Adverse Events.

Adverse Event	**Rate of occurrence in BoNTA group n/N (%)**
Total # serious adverse events	61/1160 (5.26%)
Blood and lymphatic system disorders	1/1160 (0.09%)
Angina pectoris	1/1160 (0.09%)
Myocardial infarction	1/1160 (0.09%)
Pericarditis	1/1160 (0.09%)
Vertigo positional	1/1160 (0.09%)
Retinal detachment	1/1160 (0.09%)
Upper abdominal pain	2/1160 (0.17%)
Gastric Ulcer	1/1160 (0.09%)
Gastrointestinal pain	1/1160 (0.09%)
Incarcerated umbilical hernia	1/1160 (0.09%)
Inguinal hernia	1/1160 (0.09%)
Intestinal obstruction	1/1160 (0.09%)
Device malfunction	1/1160 (0.09%)
Cholecystitis	1/1160 (0.09%)
Cholecystitis chronic	1/1160 (0.09%)
Chronic sinusitis	1/1160 (0.09%)
Gastroenteritis viral	1/1160 (0.09%)
Herpes zoster	1/1160 (0.09%)
Meningitis	1/1160 (0.09%)
Pneumonia	1/1160 (0.09%)
Pneumonia pneumococcal	1/1160 (0.09%)
Urinary tract infection	1/1160 (0.09%)
Craniocerebral injury	1/1160 (0.09%)
Femoral neck fracture	1/1160 (0.09%)
Hip fracture	1/1160 (0.09%)
Post lumber puncture syndrome	1/1160 (0.09%)
Radius fracture	1/1160 (0.09%)
Intervertebral disc protrusion	1/1160 (0.09%)
Musculoskeletal chest pain	1/1160 (0.09%)
Rotator cuff syndrome	1/1160 (0.09%)

Adverse Event	**Rate of occurrence in BoNTA group n/N (%)**
Breast cancer	1/1160 (0.09%)
Gastrointestinal carcinoma	1/1160 (0.09%)
Leiomyoma	1/1160 (0.09%)
Lipoma	1/1160 (0.09%)
Lung neoplasm malignant	1/1160 (0.09%)
Metastases to central nervous system	1/1160 (0.09%)
Metastases to lymph nodes	1/1160 (0.09%)
Migraine	11/1160 (0.95%)
Headache	3/1160 (0.26%)
Intracranial pressure increased	2/1160 (0.17%)
Cerebrovascular accident	1/1160 (0.09%)
Hemiplegic migraine	1/1160 (0.09%)
Migraine with aura	1/1160 (0.09%)
Monoparesis	1/1160 (0.09%)
Vllth nerve paralysis	1/1160 (0.09%)
Abortion	1/1160 (0.09%)
Abortion spontaneous	1/1160 (0.09%)
Depression	3/1160 (0.26%)
Bipolar disorder	1/1160 (0.09%)
Post-traumatic stress disorder	1/1160 (0.09%)
Nephrolithiasis	1/1160 (0.09%)
Urge incontinence	1/1160 (0.09%)
Breast hematoma	1/1160 (0.09%)
Breast mass	1/1160 (0.09%)
Cervical dysplasia	1/1160 (0.09%)
Pulmonary embolism	1/1160 (0.09%)

NCT02147561: A Safety and Efficacy Study of BOTOX® in Korean Adults with Chronic Migraine

Baseline n=280

Completed n=276

Date completed: February 2015

BoNTA injected across specific head and neck muscles on day 0

Appendix Table H9. Unpublished Safety Outcomes from NCT02147561: A Safety and Efficacy Study of BOTOX® in Korean Adults with Chronic Migraine, Primary Outcome

Outcome Type	Follow-up	Outcome Title	Description	Results, % or Mean Δ ± SD
Primary	4 weeks	Percentage of patients with adverse events	An adverse event was considered any unfavorable or unintended sign, symptom, or diseases associated with the use of the study drug, whether or not considered related to the study drug	24.37%

Appendix Table H10. Unpublished Safety Outcomes from NCT02147561: A Safety and Efficacy Study of BOTOX® in Korean Adults with Chronic Migraine, Serious and Nonserious Adverse Events

Adverse Event	Rate of occurrence in BoNTA group n/N (%)
Total # serious adverse events	4/279 (1.43%)
Diarrhea	1/279 (0.36%)
Fever	1/279 (0.36%)
Common cold	1/279 (0.36%)
Migraine	1/279 (0.36%)
Hemoptysis	1/279 (0.36%)
Total # non-serious adverse events	38/279 (13.62%)
Muscle weakness	24/279 (8.60%)
Ptosis	14/279 (5.02%)

APPENDIX I. Clinical Experts

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