International Centre for Allied Health Evidence

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Systematic Review of the Literature

The effectiveness of botulinum toxin injection for the treatment of headache

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Abbreviations

The following abbreviations are used in this report and are collated here for readers' convenience

Abbreviation		Abbreviation	
CI	Confidence Interval	**RCT**	Randomised Controlled trial
BoNT	Botulinum Toxin	**ROM**	Range Of Movement
BoNT-A	Botulinum Toxin A	**RR**	Risk Ratio
Botox	Botulinum Toxin	**SADP**	Scale of attitudes toward disabled persons
FDA	(United States) Food and Drug Administration	**SF-36**	36-Item Short Form Health Survey
HIT	Headache Impact Test	**SIGN**	Scottish Intercollegiate Guidelines Network
ICER	Incremental Cost Effectiveness Ratio	**SMD**	Standard Mean difference
ICHD	International classification of headache disorders	**SR**	Systematic Review
IQOLA	International quality of life assessment	**WHO**	World Health Organisation
MIDAS	Migraine Disability Assessment Test	**US**	Ultrasound
OLBPDQ	Oswestry low back pain disability questionnaire	**USA**	United States of America
PICO	Population, Intervention, Comparator, Outcome	**UK**	United Kingdom
QALY	Quality-Adjusted Life Years	**VAS**	Visual Analogue Scale
QoL	Quality of Life		
	Quality Ratings		
AQ	Acceptable Quality	**LQ**	Low Quality
CS	Can't say	**NA**	Not Applicable
HQ	High Quality	**R**	Reject (Unacceptable Quality)
QS	Quality of Study		

EXECUTIVE SUMMARY

Objective of the Review	The objective of this systematic review is to synthesise the evidence related to the effectiveness of injection of botulinum toxin as a form of interventional pain management for headaches In order to review the evidence this review aims to answer the following research questions 1. What is the evidence for the effectiveness of botulinum toxin injections in relieving pain and/or in improving functional outcomes in patients with headaches? 2. What is the evidence for the safety of botulinum toxin injections for headaches?
Evidence sourced	The search yielded 1495 articles. After scrutiny, 1455 articles were excluded as duplicates or failing to meet the inclusion criteria (shown in Figure 1), leaving 36 studies for inclusion in this review.
What is the evidence for the effectiveness of botulinum toxin injections into the neck in relieving pain and/or in improving functional outcomes in patients with pain?	• **The evidence suggests that botulinum toxin A is effective in chronic daily headaches and chronic migraines when compared to placebo.** (Level B recommendation) • **The evidence suggests that botulinum toxin A is not effective in the treatment of episodic migraine or tension-type headaches.** (Level B recommendation) • **The evidence suggests that multiple treatment cycles (5) are more effective than fewer cycles (2 or 3) for multiple outcome measures over 52 weeks. A single dose appears to be ineffective in the treatment of migraine.** (Level B recommendation) • **Acupoint-site injection appears to be more efficient for migraine treatment than fixed-site application.** (Level B recommendation) • **Botulinum toxin A injections into the neck muscles do not appear to be effective in the treatment of cervicogenic headache.** (Level B recommendation) • **Botulinum toxin A has a more sustained effect than transcranial magnetic stimulation.** (Level C recommendation) • **Further research is required to determine the efficacy of combining Botulinum toxin A injections with other treatment modalities such as infrared polarised light therapy.** (Level D recommendation)

What is the evidence for the safety of botulinum toxin injection?	• **The evidence suggests that adverse events following the use of BoNT-A injection for headaches are mild or moderate. Serious adverse events are transient and rare, occurring in 5.4% of patients receiving any BoNT-A injections and in 3.0% of patients receiving placebo. Adverse events include neck pain (12.6%), muscle weakness (8.0%), musculoskeletal stiffness (6.1%) and eyelid ptosis (4.6%).** (Level A recommendation)
Does the evidence report any information about cost effectiveness?	• **The evidence suggests that BoNT-A injections reduce the frequency of headaches in patients with chronic migraine and can be considered a cost-effective use of resources (**Level C recommendation) **There is a lack of evidence related to the cost- effectiveness of the use of BoNT-A injections for other headache types.**
Do the recommendations differ from the 2011 report?	**2011 Summary of Evidence** "The general use of botulinum toxin injection is not recommended for the treatment of headache. However, the procedure may be considered in the research setting". **2017 Recommendation** The evidence suggest that botulinum toxin A may be considered for chronic daily headaches and chronic migraines, but not for the treatment of episodic migraine, tension-type headaches or cervicogenic headaches

1. Background

1.1 Objective of this Review

The objective of this review is to synthesise the evidence related to the effectiveness of injection of botulinum toxin for the treatment of headache or migraine. This review will carry out a systematic review of the best available research evidence.
This review aims to answer the following research questions:

a) What is the evidence for the effectiveness of botulinum toxin injection in relieving headache?
b) What is the evidence for the effectiveness of botulinum toxin injections in improving functional outcomes in patients with headache?
c) What is the evidence for the safety of botulinum toxin injections in patients with headache?

1.2 Description of the Intervention

Clinically, headaches are classified into two types including primary and secondary (Choi et al 2016). Primary headaches occur without underlying disease and are further classified into three main types including migraine, tension-type and cluster headaches (Choi et al 2016). The World Health Organization (WHO) reported that migraine is the most common neurological disorder and the third most prevalent condition globally (Mathers, Fat & Boerma 2008). Although migraines are not life threatening, they can severely impair everyday functioning and affect quality of life (Choi et al 2016).

Headaches are typically unilateral, pulsating and aggravated by physical activity. In addition, migraine headaches are associated with nausea and or/vomiting, photophobia or phonophobia (Becker & Amirlak 2012). The full diagnostic criteria, as presented by the Headache Classification Committee of the International Headache Society (2013), for the different types of headache are shown below.

Migraine without aura
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least two of the following four characteristics:

1. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
2. each individual aura symptom lasts 5-60 minutes
3. at least one aura symptom is unilateral
4. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Chronic migraine

A. Headache (tension-type-like and/or migraine-like) on 15 days per month for > 3 months and ful-filling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for Migraine with or without aura

C. On 8 days per month for > 3 months, fulfilling any of the following

1. criteria C and D for Migraine without aura
2. criteria B and C for Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

Chronic tension type headache

A. Headache occurring on 15 days per month on average for >3 months (180 days per year), full-filling criteria B-D

B. Lasting hours to days, or unremitting

C. At least two of the following four characteristics:

1. bilateral location
2. pressing or tightening (non-pulsating) quality
3. mild or moderate intensity
4. not aggravated by routine physical activity such as walking or climbing stairs

D. Both of the following:

1. no more than one of photophobia, phonophobia or mild nausea
2. neither moderate or severe nausea nor vomiting

E. Not better accounted for by another ICHD-3 diagnosis.

Cluster headache

A. At least five attacks fulfilling criteria B–D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)

C. Either or both of the following:

1. at least one of the following symptoms or signs, ipsilateral to the headache:
    a) conjunctival injection and/or lacrimation
    b) nasal congestion and/or rhinorrhoea
    c) eyelid oedema
    d) forehead and facial sweating
    e) forehead and facial flushing
    f) sensation of fullness in the ear
    g) miosis and/or ptosis
2. a sense of restlessness or agitation

D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis.

Botulinum toxin (BoNT), produced by the anaerobic bacterium *Clostridium botulinum,* is one of the most potent toxins in nature (Ashkenazi & Blumenfeld 2013). BoNT has been used to treat a number of disorders associated with increased muscle tone (Jankovic & Brin 1991), as the toxin causes reversible, dose-dependent muscle relaxation by blocking acetylcholine release from nerve terminals at the neuromuscular junction (Ashkenazi & Blumenfeld 2013).

Chemically BoNT consists of two polypeptide chains, linked by a disulphide bond (Ashkenazi & Blumenfeld 2013). There are seven antigenetically distinct serotypes (A-G), with Botulinium toxin A (BoNT-A) being the most widely used and investigated serotype (Ashkenazi & Blumenfeld 2013). The effect of the toxin is terminated within 2-6 months due to the process of axonal sprouting, which occurs as a result of the toxin entering the cell (Ashkenazi & Blumenfeld 2013). The specific mechanism by which BoNT-A relieves pain has not yet been established, it is hypothesized that the primary mechanism is the suppression of the diffusion of neurotransmitters across the peripheral nerve (Ashkenazi & Blumenfeld 2013).

1.3 Safety/Risk

Botulinium toxin A has been used clinically for several decades with a good overall safety profile (Ashkenazi, A, Levin & Dodick 2007). Symptoms related to the muscle relaxing effect of the toxin such as blepharoptosis and neck muscle weakness may develop after injection, as well as pain and tenderness at the injection site. The United States Food and Drug Administration (FDA) published a black box warning for botulinum toxin administration due to the potential risk of symptoms of botulism developing. Extreme caution should be exercised in patients with neuromuscular junction disorders (e.g. myasthenia gravis) and it should not be used in those on medications affecting neuromuscular transmission (e.g. aminoglycosides) (Ashkenazi & Blumenfeld 2013). BoNT-A injections have reportedly fewer side effects than other commonly prescribed drugs for headache and a single treatment can last up to four months (Choi et al 2016).

2. Methodology

2.1 Review question

What is the effectiveness of botulinum toxin injection in treatment of headache?

2.2 Methods

A Systematic review of published research literature was undertaken to provide a synthesis of the currently available research evidence related to the effectiveness of botulinum toxin as a form of interventional pain management for headache. A systematic and rigorous search strategy was developed to locate all published and accessible research evidence. The evidence base for this review included research evidence from existing systematic reviews, meta-analyses and high-level primary research (randomised controlled trials, prospective cohort studies). Where no systematic reviews, randomised controlled trials or prospective cohort studies were located, then other primary study designs (excluding commentary /expert opinion) were considered.

The search was developed using a standard PICO structure (shown in Table 1). Only English articles published, using human participants, which were accessible in full text were included.

Table 1: Criteria for considering studies in the review

Population	Humans
Intervention	Botulinum toxin injection as a form of interventional pain management for headache
Comparator	Any active treatment or placebo.
Outcomes	• Pain-related primary outcome; • Functional outcomes (range of motion, reduction of disability, return to work, quality of life) • Safety and Risk • Best Practice recommendations • Cost effectiveness

2.3 Search strategy

A combination of search terms (shown in Table 2) were used to identify and retrieve articles in the following databases:

- OVID
  - EMBASE,
  - MEDLINE,
- ICONDA,
- CINAHL,
- PubMed,
- Pre-Medline,
- The Cochrane Library,
- Scopus,
- Wed of Science

Table 2: Search terms for the review

Search terms 1	Search terms 2	Search terms 3	
headache*	Injection*	Botulinum toxins	abobotulinumtoxinA
migraine*		Botulinum neurotoxin	abobotulinumtoxinB
head ache*		Clostridium botulinum	abobotulinumtoxinC
cephalgia*		botulin* adj1 toxin*	abobotulinumtoxinD
cephalalgia*		Botox	abobotulinumtoxinE
head pain*		Myobloc	abobotulinumtoxinF
		Dysport	abobotulinumtoxinG
		Xeomin	incobotulinumtoxinA
		Neurobloc	rimabotulinumtoxinB
		Siax	BTX-A
		Neuronox	BTX
			BoNT

2.4 Study Selection

The titles and abstracts identified from the above search strategy were assessed for eligibility by the iCAHE researchers. Full-text copies of eligible articles were retrieved for full examination. Reference lists of included full-text articles were searched for relevant literature not located through database searching. The search string used in the Medline search is provided in Appendix 1.

Inclusion Criteria

- Study Types: Systematic Reviews, all Primary research designs (Randomised Controlled Trials (RCTs), Cohort studies (Prospective or Retrospective), Case Studies or Case Series.
- Participants: Patients with headache or migraine.
- Intervention: Botulinum toxin injections
- Controls: any active treatment or placebo, or no intervention control
- Outcomes: Pain or symptom relief (primary), functional outcomes, safety, and risk (secondary)
- Publication criteria – English language, full text available, in peer reviewed journal

Exclusion criteria

- Studies only available in abstract form E.g. conference presentations
- Grey literature and no-English language material
- Studies involving healthy volunteers or experimentally induced pain
- Studies on interventions where migraine or headache groups could not be differentiated.

2.5 Critical Appraisal

The SIGN (Scottish Intercollegiate Guidelines Network) checklist specific to the study design of the included studies was used to assess the methodological quality of the included studies (Appendix 2). The SIGN checklist asks a number of questions with yes, no, can't say or not applicable as responses with the appraiser giving an overall rating of quality, based on the responses to questions of either high quality (++), acceptable (+), low quality (-) or unacceptable/rejected. As there is no SIGN checklist for case studies or case series designs these study designs will not be quality scored. Each study was graded for overall methodological quality using the SIGN levels of evidence model.

2.6 Data Extraction

Data were extracted from the identified publications using a data extraction tool which was specifically developed for this review. The following information were extracted from individual studies:

- Evidence source (Author, date, country)
- Study design
- Level of evidence
- Characteristics of participants
- Headache type
- Interventions
- Outcome measures
- Results
- Safety and risk
- Authors conclusions

For this review the studies that met the inclusion criteria were assessed for internal validity using the Scottish Intercollegiate Guidelines network (SIGN) Checklist for the relevant study design. Each study was graded for overall methodological quality using the SIGN Levels of evidence model.

2.7 Data Synthesis

As described, for this review each study was graded for overall methodological quality using the SIGN checklist specific to the study design of the included studies.

Recommendations from the literature were made and scored according to a modification of the SIGN Evidence Grading matrix (see Table 3). The modification was to add levels 1 and 2 to differentiate between the 1+ and 1-, 2+ and 2- levels of evidence.

Table 3: Modified SIGN Evidence Grading Matrix

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias
1	Meta-analyses, systematic review of clinical trials or clinical trials with a moderate (acceptable) level risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2	Cohort or case and control studies with moderate risk of bias and potential risk that the relationship is not causal.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

To standardise the strengths of recommendations from the extensive literature used for this review a structured system was developed to incorporate a number of quality measures. Four measures were selected as important variables for the assessment of strength of recommendations from the primary and secondary research sources. These were

a) Combination of data via meta-analysis

b) Quality of systematic review/trials

c) Number of RCTs

d) Consistency of the evidence

A scoring system was developed, based on a 0 and 1 score for each of these variables.

1. Combination of data via meta-analysis : Yes = 1, No = 0
2. Quality of systematic review: HQ/AQ (+) =1, LQ(0)/R = 0
3. Number of RCTs: ≥ 5RCTs = 1, < 5=0
4. Consistency: ≥ 75% agreement = 1, < 75% agreement = 0

This allowed for a maximum potentials score of 4 and a minimum score of 0, which reflected a measure of the evidence strength across a range of studies. The resultant score was transferred to the SIGN Evidence Grading matrix

Total Score	SIGN Evidence Grading matrix score
4	1++
3	1+
2	1
1/0	1-

2.8 Grade of Recommendations

Recommendations will be graded according to the Scottish Intercollegiate Guidelines network (SIGN) Grades of Recommendations (Table 4).

Table 4: Scottish Intercollegiate Guidelines network (SIGN) Grades of Recommendations

Grades of Recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+

3. Results

3.1 Evidence Sources

The search yielded 1495 articles; following removal of duplicates 785 articles were identified for screening of title and abstract. After scrutiny, 745 articles were excluded for failing to meet the inclusion criteria (shown in Figure 1), leaving 36 studies for inclusion in this review. Figure 1 illustrates the process involved in study selection.

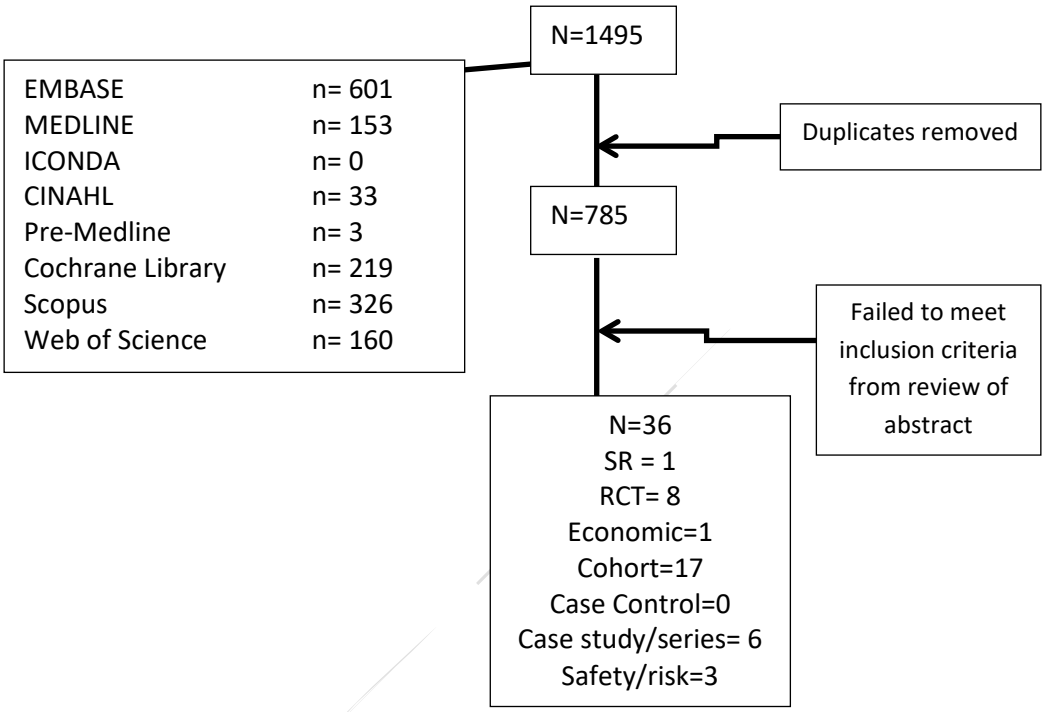

Figure 1: Flow chart of search results

One systematic review was located (Jackson, Kuriyama & Hayashino 2012). Randomised controlled trials were only included if they were published between 2011 and 2016 and were not already included in the systematic review. One economic study was located and three studies that specifically investigated the safety and risk or botulinum toxin injection for headache. In addition to the randomised controlled studies included in the systematic review (n=20), eight randomised controlled trials were located therefore lower levels of evidence (cohort, case control and case study/series) were not included in this review.

3.2 Quality of the Evidence

The overall quality of the studies included in this review ranged from high to low. The systematic review was of acceptable quality (1+), while the quality of the randomised controlled trials published between 2011 and 2016 that were not included in the systematic review were predominantly high quality with two of low quality.

3.3 Findings

One SR of acceptable quality was located that specifically investigated the efficacy of BoNT-A injections for the management of headaches (Jackson, Kuriyama & Hayashino 2012). A further eight randomised controlled trials published between 2011 and 2016 that were not included in the systematic review were also located (Aurora et al. 2011; Aurora et al. 2014; Hollanda, Monteiro & Melo 2014; Hou et al 2015; Jost 2011; Linde et al 2011; Shehata et al 2016; Song et al 2015). Only one economic study that specifically investigated BoNT-A in the treatment of headache was located (Batty et al 2013). Three studies were located that reported on the safety or unusual side effects following BoNT-A injection (Cho, Hwang & Kim 2013; Diener et al 2014; Russo et al 2016). Full details of individual studies can be found in Appendix 4 (Full data extraction).

It should be noted that there are a number of studies authored by Aurora et al. all relate the same study, the different publications report different aspects of the results however the included participants are the same (Aurora et al. 2011; Aurora et al. 2014).

3.4 Outcome Measures – Pain and Function

Systematic Reviews

Jackson et al (2012)

Jackson et al (2012) (QS:AQ(+)) systematically reviewed the literature to assess the association of BoNT- A with reducing headache frequency when used to prevent or treat migraine, tension or daily headaches in adults. The authors concluded that BoNT-A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but not associated with fewer episodic migraine or chronic tension-type headaches per month.

Study	QS	Conclusions	Level of Evidence
Jackson et al. (2012)	AQ (+)	Botulinum toxin A is effective in chronic daily headaches and chronic migraines when compared to placebo.	1+
		Botulinum toxin A was not effective in the treatment of episodic migraine or tension-type headaches	1+

Randomised Controlled Trials

Aurora et al (2011)

Aurora et al (2011) (QS:HQ(++)) evaluated the safety and efficacy of onabotulinumtoxin A (BOTOX®) as headache prophylaxis in adults with chronic migraine over 52 weeks. Researchers randomised 1,384 participants with chronic migraine to receive either BoNT-A or placebo. BoNT-A treatment was found to significantly reduce headache-day frequency vs placebo in patients with chronic migraine at week 56. Authors concluded that repeated treatments (≤5 cycles) was effective, safe, and well tolerated in adults with chronic migraine.

Study	QS	Conclusions
Aurora et al. 2011	HQ (++)	Botulinum toxin A is effective in reducing headache-day frequency when compared to placebo in people with chronic migraines.

Aurora et al (2014)

Aurora et al (2014) (QS:HQ(++)) evaluated the safety and efficacy of onabotulinumtoxin A (BOTOX®) as headache prophylaxis in adults with chronic migraine. This paper presents the secondary analysis of only the patients who received all five treatment cycles and therefore completed the study. As this was a secondary analysis 1,004 participants of the total 1,384 were included in the analysis. Authors concluded that in participants that completed all five treatment cycles on BoNT-A demonstrated improvements when compared to placebo (two cycles or three cycles) for multiple headache symptom measures. Continuing prophylaxis therapy with BoNT-A significantly reduced headache-related disability and improved functioning and overall quality of life over the 56-week period.

Study	QS	Conclusions
Aurora et al. 2014	HQ (++)	Multiple treatment cycles (5) was found to be more effective than fewer cycles (2 or 3) for multiple outcome measures over 52 weeks.
		Botulinum toxin A (5 cycles) significantly reduced head-ache related disability and improved quality of life over 56 weeks.

Hollanda et al (2014)

Hollanda et al (2014) (QS:HQ(++)) investigated the efficacy and safety of BoNT-A injections compared to placebo in the treatment of cephalic allodynia (central pain sensitisation, which can lead to a pain response being triggered by a stimuli that would not normally trigger pain), which is associated with chronic migraine. Researchers randomised 58 participants with migraine to receive either BoNT-A or placebo (saline). Authors concluded that BoNT-A injections were superior to saline solution in the treatment of cephalic allodynia in patients with migraine. Although authors urge caution in the interpretation of these results due to the small sample size included in this study which may limit the generalisation of study results.

Study	QS	Conclusions
Hollanda et al. 2014	HQ (++)	Botulinum toxin A injections were more effective than placebo (saline) in the treatment of cephalic allodynia, a common symptom of migraine headache.
		Due to the small sample size the results of this study should be interpreted with caution.

Hou et al (2015)

Hou et al (2015) (QS:HQ(++)) investigated the therapeutic effect of BoNT-A on migraine, and to evaluate fixed-site compared to acu-point injection of BoNT-A. Authors randomised 102 participants to one of three groups including placebo (n=19), fixed-site injection of BoNT-A (n=41) or to acu-point site injection of BoNT-A (n=42). Authors concluded that acupoint-site and fixed-site injection of BoNTA significantly reduced migraine attack frequency, intensity, duration and associated symptoms. Acupoint-site administration of BoNTA was found to be more efficient for migraines than fixed-site application in this study.

Study	QS	Conclusions
Hou et al. 2015	HQ (++)	Botulinum toxin A injection regardless of administration technique (fixed-site or acupoint) significantly reduced migraine attack, frequency, intensity and duration when compared to placebo.
		This study found that acupoint-site injection was more efficient for migraine treatment than fixed-site application.

Jost (2011)

Jost (2011) (QS:LQ(-)) investigated whether a single dose of BoNT-A compared to placebo would significantly reduce pain in patients with unilateral migraine. As this was a crossover study design, all participants (n=22) received both treatments. The authors randomised the participants to receive either BoNT-A or placebo in the first phase, and the participants then received the alternative treatment in the second phase. The authors found no significant differences between the BoNT-A and placebo in this study suggesting that a single dose of BoNT-A is ineffective in the treatment of migraine.

Study	QS	Conclusions
Jost 2011	LQ (-)	A single dose of botulinum toxin A was ineffective in the treatment of migraine.

Linde et al (2011)

Linde et al (2011) (QS:HQ(++)) investigated the effectiveness of BoNT-A injection into the neck of participants for the treatment of cervicogenic headache. As this was a crossover study design all participants (n=28) received both treatments. The authors randomised the participants to receive either BoNT-A or placebo in the first phase, and the participants then received the alternative treatment in the second phase. There were no significant differences between the BoNT-A and placebo at the completion of the trial. Authors concluded that BoNT-A injections in the neck muscles did not seem to be beneficial in cervicogenic headache.

Study	QS	Conclusions
Linde et al. 2011	HQ (++)	Botulinum toxin A injections into the neck muscles does not appear to be effective in the treatment of cervicogenic headache.

Shehata et al (2016)

Shehata et al (2016) (QS:AQ(+)) compared the effectiveness and safety of BoNT-A compared to repetitive transcranial magnetic stimulation in migraine prophylaxis. The authors randomised 29 participants to receive either BoNT-A injection or repetitive transcranial magnetic stimulation, a technique that uses magnets to target and stimulate specific areas of the brain. They found that both treatments were effective in the treatment of chronic migraine, however BoNT-A had a more sustained effect than repetitive transcranial magnetic stimulation.

Study	QS	Conclusions
Shehata et al 2016	AQ (+)	Both botulium toxin A and repetitive transcranial magnetic stimulation are effective treatments for chronic migraine.
		Botulinum toxin A had a more sustained effect than transcranial magnetic stimulation.

Song et al (2015)

Song et al (2015) (QS:LQ(-)) investigated the clinical value of the combination of ultrasound-and-hyponome-guided BoNT-A injection and infrared polarised light on treating chronic migraine. The authors randomised 91 participants to one of four groups including, control (nimodipine) (n= 22), infrared polarised light therapy (n= 22), botulinum toxin treatment (n=24), joint treatment group (n=23), botulinium toxin and infrared polarised light. They found that all groups improved in headache symptoms and quality of life scores following treatment, although it was unclear if there were statistically significant differences between groups. The authors concluded that combining ultrasound and hyponome guided type BoNT-A injection and infrared polarised light demonstrated a significant clinical effect in the treatment of chronic migraine. Although it should be noted that authors did not present data comparing the different treatment groups.

Study	QS	Conclusions
Song et al 2015	LQ (-)	Statistically significant effects were found in all four treatment groups (control, infrared polarised light therapy, botulinum toxin treatment, joint treatment group) in the treatment of chronic migraine.
		Authors suggested that combined botulinum toxin A and infrared polarised light demonstrated a significant clinical benefit although this was not clear from the data presented.

3.5 Outcome Measures – Safety and Risk

All of the RCTs reported that BoNT-A was safe and well tolerated with small numbers of adverse events (full details can be found in appendix 4). Reported adverse events were of mild to moderate severity and no participants reported the development of botulism. For studies that reported adverse events the most commonly reported neck were:

- Neck pain
- Muscular weakness- predominantly facial paresis
- Injection site pain
- Eyelid ptosis or blepharoptosis (drooping or falling of the upper eyelid)

- Neck stiffness
- Paraesthesia
- Skin tightness
- Impaired mobility of cervical spine
- Dizziness

Three studies were located that specifically reported on the safety or risk of BoNT-A injections for the management of headaches including two studies reporting on unusual side effects and one large pooled safety analysis. Cho et al (2013) reported on a possible side effect not reported by any of the intervention studies known as the "Mephisto sign" which can occur following injection into the frontalis muscle. Although not a serious or permanent adverse event it can leave patients with a "quizzical look", "Spock's eyebrow", "a sinister look" or "'joker' face", as it effects the eyebrow for up to three months. Russo et al (2016) reported another unusual side effect known as "rams horn sign" which is characterised by the appearance of two symmetrical bumps on the upper part of the forehead. Similarly to the "Mephisto sign" it is not a serious or permanent adverse event but may be concerning for patients.

Diener et al (2014) analysed the pooled safety data from the two exploratory phase 2 studies and the two PREEMPT trials. Of the 2,436 patients, a total of 1,997 received at least one BoNT-A injection, with 1,448 receiving three or fewer and 513 completing five cycles of BoNT-A injections. The authors found that BoNT-A was safe and well tolerated, with neck pain being the most commonly reported BoNT-A associated adverse event.

3.6 Economic analysis

Only one study reporting the cost-effectiveness of BoNT-A for the prophylaxis of headache in adults with chronic migraine in the United Kingdom (UK). Batty et al (2013) developed a state-transition (Markov) model comparing BoNT-A to placebo, using data from the PREEMPT trail (n=1384), to estimate the 2-year discounted costs and quality-adjusted life years (QALYs). Authors found that at 2 years, BoNT-A treatment was associated with an increase in costs of £1,367 and an increase in QALYs of 0.1 compared to placebo, resulting in an incremental cost-effectiveness ratio (ICER) of £15,028. The authors concluded that BoNT-A reduced the frequency of headaches in patients with chronic migraine and can be considered a cost-effective use of resources in the UK National Health Service.

4. Recommendations

Summary of Recommendations

- **The evidence suggests that botulinum toxin A injection is effective in chronic daily headaches and chronic migraines when compared to placebo** (Level B recommendation based on 1 x AQ SR with level 1+ evidence, 2 x HQ RCT).
- **The evidence suggests that botulinum toxin A is not effective in the treatment of episodic migraine or tension-type headaches** (Level B recommendation based on 1 x AQ SR with level 1+ evidence).
- **The evidence suggests that multiple treatment cycles (5) are more effective than fewer cycles (2 or 3) for multiple outcome measures over 52 weeks. A single dose appears to be ineffective in the treatment of migraine** (Level B recommendation based on 1 x HQ RCT and 1 x LQ RCT).
- **Acupoint-site injection appears to be more efficient for migraine treatment than fixed-site application** (Level B recommendation based on 1 x HQ RCT).
- **Botulinum toxin A injections into the neck muscles do not appear to be effective in the treatment of cervicogenic headache** (Level B recommendation based on 1 x HQ RCT).
- **Botulinum toxin A has a more sustained effect than transcranial magnetic stimulation** (Level C recommendation based on 1 x AQ RCT).
- **Further research is required to determine the efficacy of combining BoNT-A injection with other treatment modalities such as infrared polarised light therapy** (Level D recommendation based on 1 x LQ RCT).
- **The evidence suggests that adverse events following the use of BoNT-A injection for headaches are mild or moderate. Serious adverse events are transient and rare, occurring in 5.4% of patients who received any BoNT-A injections and 3.0% of patients receiving placebo. Adverse events include neck pain (12.6%), muscle weakness (8.0%), musculoskeletal stiffness (6.1%) and eyelid ptosis (4.6%)** (Level A recommendation).
- **The evidence suggests that BoNT-A injections reduce the frequency of headaches in patients with chronic migraine and can be considered a cost-effective use of resources** (Level C recommendation)..

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6. Appendices

Appendix 1 – Summary of studies included in this review

Study Design	Author	Year	Level of Evidence	N=	Outcomes	Conclusions
Systematic review	Jackson et al.	2012	1+	27 RCTs	Patient reported outcomes	Botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per month.
Randomised controlled trial	Aurora et al.	2011	1+	1,384	Frequency of headache days at 24 weeks, Headache Impact Test (HIT)-6 score, frequency of: migraine days moderate/severe headache days, headache episodes, migraine episodes, acute headache medication intakes	Repeated treatment with ≤5 cycles of onabotulinumtoxinA was effective, safe, and well tolerated in adults with chronic migraine.
Randomised controlled trial	Aurora et al.	2014	1+	1,004	Frequency of headache days at 24 weeks, Headache Impact Test (HIT)-6 score, frequency of: migraine days moderate/severe headache days, headache episodes, migraine episodes, acute headache medication intakes	This subgroup analysis demonstrated improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures and suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes.
Randomised controlled trial	Hollanda et al.	2014	1+	58	Headache diary, frequency of headache episodes with allodynia, intensity of headache pain, frequency of analgesics use for headache	This study suggests that Botx-A injections are superior to saline in the treatment of CA associated with CM, with mild self limited side effects.

Study Design	Author	Year	Level of Evidence	N=	Outcomes	Conclusions
Randomised controlled trial	Hou et al.	2015	1+	102	Headache diary (Frequency of migraine attack per month; Intensity of migraine (VAS); Duration of each attack; Migraine associated symptoms scale	It can be concluded that acupoint-site and fixed-site injection of BoNTA are able to significantly reduce migraine attack frequency, intensity, duration and associated symptoms. Acupoint-site administration of BoNTA is proved to be more efficient for migraines than fixed-site application, and thus is a potential method in clinical practices in treating patients who experienced six or more attacks per month, hemiplegic and basilar type migraines, and migraines with prolonged auras as well.
Randomised controlled trial	Jost	2011	1-	22	Pain (visual analog scale), SF-McGill Pain Questionnaire, Northwick Park Neck Pain Questionnaire, International quality of life assessment (IQOLA), SF 36, Scale of attitudes toward disabled persons (SADP) Oswestry low back pain disability questionnaire, (OLBPDQ) ,headache attacks and adjuvant medication	From the data published so far, the injection of BTX may be considered a promising approach in the management of chronic migraine. Optimum injection sites and appropriate doses, however, still need more exploration. One injection into the corrugator muscle alone must be considered as ineffective.
Randomised controlled trial	Shehata	2016	1+	29	Headache frequency (days/month) and headache severity assessed by VAS; secondary 25-item HDI, HIT-6, and number of acute medications.	BoNT-A injection and repetitive transcranial magnetic stimulation (rTMS) have favourable efficacy and safety profiles in chronic migraineurs. rTMS is of comparable efficacy to BTX-A injection in chronic migraine therapy, but with less sustained effect.
Randomised controlled trial	Song	2015	1-	91	Severity of chronic migraine, seizure duration, seizure frequency, use of painkillers, MIDAS, SF-36 score	The combination of ultrasound and hyponome guided type A botulinum toxin injection and infrared polarized light on treating chronic migraine demonstrated a significant clinical effect.

Appendix 2 – SIGN Checklists used in this review

SIGN Critical Appraisal Tool for Systematic Reviews and Meta-analyses

SIGN

Methodology Checklist 1: Systematic Reviews and Meta-analyses

SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*

Study identification (*Include author, title, year of publication, journal title, pages*)	
Guideline topic:	Key Question No:

Before completing this checklist, consider:

Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.

Checklist completed by:

Section 1: Internal validity

In a well conducted systematic review:		***Does this study do it?***	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes □	No □ **If no reject**
1.2	A comprehensive literature search is carried out.	Yes □ Not applicable □	No □ **If no reject**
1.3	At least two people should have selected studies.	Yes □	No □ Can't say □
1.4	At least two people should have extracted data.	Yes □	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes □	No □
1.6	The excluded studies are listed.	Yes □	No □
1.7	The relevant characteristics of the included studies are provided.	Yes □	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes □	No □
1.9	Was the scientific quality of the included studies used appropriately?	Yes □	No □
1.10	Appropriate methods are used to combine the individual study findings.	Yes □ Can't say □	No □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □	No □

		Not applicable □
1.12	Conflicts of interest are declared.	Yes □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) □ Acceptable (+) □ Low quality (-)□ Unacceptable – reject 0 □
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes □ No □
2.3	**Notes:**	

SIGN Critical Appraisal Tool for Controlled trials

Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias? *Code as follows:*	High quality (++)☐ Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

Appendix 3 – Quality scores for articles used in this review

SIGN Critical Appraisal Tool scores for Systematic Reviews

Quest	Reference (Author, year)		Jackson et al. 2012
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper. Does this study do it?	Y/N	Y
1.2	A comprehensive literature search is carried out?	Y/N/NA	Y
1.3	At least two people should have selected studies	Y/N/CS	CS
1.4	At least two people should have extracted the data	Y/N/CS	Y
1.5	The status of publication was not used as an inclusion criterion	Y/N	N
1.6	The excluded studies are listed	Y/N	N
1.7	The relevant characteristics of the included studies are provided	Y/N	Y
1.8	The scientific quality of the included studies was assessed and reported.	Y/N	Y
1.9	Was the scientific quality of the included studies used appropriately?	Y/N	Y
1.10	Appropriate methods are used to combine the individual study findings	Y/N/CS/ NA	Y
1.11	The likelihood of publication bias was assessed appropriately	Y/N/NA	Y
1.12	Conflicts of interest are declared	Y/N	Y
2.1	What is your overall assessment of the methodological quality of this review?	HQ/A/L Q/U	A
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y/N	Y

SIGN Critical Appraisal Tool scores for controlled trials

Quest	Reference (Author, year)	Aurora et al. 2011	Aurora et al. 2014	Hollanda et al. 2014
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y	Y	Y
1.3	An adequate concealment method is used.	Y	Y	CS
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y	Y	Y
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	Y
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Active: 25.4% Placebo: 29.3%	Subgroup analysis of only participants that completed the study.	0%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	CS	CS	N/A
2.1	How well was the study done to minimise bias?	HQ	HQ	HQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y
2.4	Summary of the author's conclusion	Repeated treatment with ≤5 cycles of onabotulinumtoxinA was effective, safe, and well tolerated in adults with chronic migraine.	This subgroup analysis demonstrated improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures and suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes.	This study suggests that Botx-A injections are superior to saline in the treatment of cephalic allodynia associated with chronic migraine, with mild self limited side effects.

Quest	Reference (Author, year)	Hou et al. 2015	Jost 2011	Linde et al. 2011	Shehata et al. 2016
1.1	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y	CS	Y	Y
1.3	An adequate concealment method is used.	Y	CS	Y	N
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y	CS	Y	N
1.5	The treatment and control groups are similar at the start if the trial.	Y	CS	Y	Y
1.6	The only difference between groups is the treatment under investigation.	Y	Y	Y	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y	Y	Y	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Not reported (assume 0%)	Not reported (assume 0%)	21% dropout (cross over study)	97%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y	CS	Y	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	N/A	N/A	N/A	N/A
2.1	How well was the study done to minimise bias?	HQ	LQ	HQ	A
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y	Y	Y	Y
2.4	Summary of the author's conclusion	BoNTA administration for migraines is effective, and at acupoint-sites shows more efficacy than at fixed-sites. Further blinded studies are necessary to establish the efficacy of a low dose toxin (25 U) introduced with this methodology in chronic and episodic migraines.	The injection of low-dosed Botulinumtoxin A did not show any relevant or significant effects in patients with unilateral migraine without aura. One injection into the corrugator muscle alone must be considered as ineffective.	Onabotulinum toxin A in neck muscles does not seem to be beneficial in cervacogenic heachache.	BTX-A injection and rTMS have favorable efficacy and safety profiles in chronic migraineurs. rTMS is of comparable efficacy to BTX-A injection in chronic migraine therapy, but with less sustained effect.

Quest	Reference (Author, year)		Song et al. 2015
1.1	The study addresses an appropriate and clearly focused question.	Y/N/CS	Y
1.2	The assignment of subjects to treatment groups is randomised.	Y/N/CS	CS
1.3	An adequate concealment method is used.	Y/N/CS	N
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y/N/CS	CS
1.5	The treatment and control groups are similar at the start if the trial.	Y/N/CS	CS
1.6	The only difference between groups is the treatment under investigation.	Y/N/CS	Y
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Y/N/CS	Y
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		88%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Y/N/CS/ NA	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Y/N/CS/ NA	N/A
2.1	How well was the study done to minimise bias?	HQ/A/ LQ/U	LQ
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Y/N	Y
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Y/N	Y
2.4	Summary of the author's conclusion		The combination of ultrasound-and-hyponome-guided type A botulinum toxin injection and infrared polarized light on treating chronic migraine demonstrated a significant clinical effect.

Appendix 4 – Data Extraction table used in this review

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Anand et al.	2006	Double blind RCT	Migraine	Botulinum Toxin type A	Placebo (saline)	10 sites of 3 cranial muscle regions (frontalis, temporalis, and glabellar muscles)	Electromyographic (EMG)	35	Diary with self-explanatory questionnaire. Headache severity, nausea and vomiting severity, other symptoms e.g. aura	The mean number of headache days per month in the study group decreased from 4 to 5 moderate to severe headaches per month to 1 to 2 (P<0.05) compared with 12.6 to 10.8 in the placebo group at 3 months. About 75% of patients reported marked improvement in intensity of headache from moderate to severe headache (grade 2/3) to complete relief mild headache (grade 0/1) after 3 months compared with none in the placebo group (P<0.05)	No adverse effects were reported in the study group	In the present study, pericranial injection of 50 U botulinum toxin type A was found to be a safe and effective treatment that significantly decreased frequency and severity of migraines, acute medication use, and migraine-associated symptoms compared with placebo.
Aurora et al.	2007	Double blind RCT	Episodic migraine	Botulinum Toxin type A	Placebo (saline)	Number of injection sites and units injected into each muscle area was defined by the physician based on the pain distribution pattern and pain severity.	Not reported	369	Migraine episodes (number and severity), disability assessment scale, headache specific quality of life	Change from baseline in the frequency of migraine episodes per 30 day-period was -2.4 in the botulinum toxin group compared with -2.2 in the placebo group (P>0.999). There were no statistically significant differences between treatment groups at any time point. There were no statistically significant differences in any of the other outcomes.	During the study a total of 70.7% (261/369) of patients experienced 1 or more adverse events, regardless of causality. The overall incidence was higher in the botulinum toxin group compared to placebo. 7 patients (6 botulinum, 1 placebo) discontinued the study due to adverse events. The majority of adverse events was transient and mild to moderate in severity.	There were no statistically significant between-group differences in the mean change from base-line in the frequency of migraine episodes per 30-day period. There were substantial, sustained improvements during the course of the study in all groups. Multiple treatments with botulinum were shown to be safe and well tolerated over an active treatment period lasting 9 months.
Aurora et al.	2010	Double blind RCT	Chronic migraine	OnabotulinumtoxinA	Placebo	31 fixed-site, fixed dose injections across 7 specific head/neck muscle areas	Not reported	679	Migraine episodes (number and severity), Headache Impact Test, Migraine specific quality of life questionnaire	No significant between-group difference for onbotulinumtoxinA versus placebo was observed for the primary endpoint, headache episodes (-5.2 vs. -5.3; p=0.344). Large within-group decreases from baseline were observed for all efficacy variables.	A total of 59.7% of onabotulinumtoxinA-treated patients experienced adverse events, compared with 46.7% of placebo-treated patients. Overall, few patients discontinued due to adverse events. Most adverse events were mild or moderate severity and resolved without sequelae. 2 cycles of treatment with 155-195 U were safe and well tolerated.	There was no between-group difference for the primary endpoint, headache episodes. However, significant reductions from baseline were observed for onabotulinumtoxinA for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine
Aurora et al.	2011	Double blind RCT	Chronic migraine	OnabotulinumtoxinA	Placebo	31 fixed-site, fixed dose injections across 7 specific head/neck muscle areas	Not reported	1384	Frequency of headache days at 24 weeks, Headache Impact Test (HIT)-6 score, frequency of: migraine days moderate/severe headache days, headache episodes, migraine episodes, acute headache medication intakes	OnabotulinumtoxinA treatment was found to significantly reduce headache-day frequency vs placebo in patients with chronic migraine at week 56; P = .019). Statistically significant reductions at week 56 were also found in frequencies of migraine days, P = .018) and moderate/severe headache days (P = .027) and cumulative headache hours on headache days (P = .018) when compared to placebo.	Only 4.6% of patients discontinued the study because of an adverse event 9 (AE). The only individual treatment-related AEs occurring at a rate >5% were neck pain in the onabotulinumtoxinA group (6.7%) and muscular weakness (5.5%, with facial paresis [2.2%] comprising nearly half of these reports). Neck pain did not occur consistently with repeated onabotulinumtoxinA treatment, as incidence rates declined with subsequent treatment cycles.	Repeated treatment with ≤5 cycles of onabotulinumtoxinA was effective, safe, and well tolerated in adults with chronic migraine.

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Aurora et al.	2014	Double blind RCT	Chronic migraine	Onabotulinumtoxin A	Placebo	31 fixed-site, fixed dose injections across 7 specific head/neck muscle areas	Not reported	1005	Frequency of headache days at 24 weeks, Headache Impact Test (HIT)-6 score, frequency of: migraine days moderate/severe headache days, headache episodes, migraine episodes, acute headache medication intakes	At Week 56, after all patients were treated with onabotulinumtoxinA, there continued to be significant between-group differences favouring the Active/Active vs Placebo/active group for the following headache symptom measures: frequencies of headache days, migraine days, and moderate/severe headache days.	The treatment-related adverse event (AE) rate was 28.5% for onabotulinumtoxinA vs 12.4% for placebo; it was 34.8% for patients treated only with onabotulinumtoxinA for all five cycles throughout the 56-week trials. The most frequently reported treatment-related adverse events in patients who received all five treatment cycles of onabotulinumtoxinA were neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%).	This subgroup analysis demonstrated improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures and suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes.
Cady & Schreiber	2008	Double blind RCT	Disabling headache	Botulinum Toxin Type A	Placebo (saline)	Muscles: Corrugator, Splenius capitis, Trapezius, Temporalis, Procerus, Frontalis	Not reported	61	Headache Diaries (number of headache episodes, days with headache, and headache-free days per 30 days; percentage of headache episodes with aura) and severity. Questionnaires (HIT-6, MIQ, MIDAS)	Headache diaries, did not reach statistical significance at months 1 to 3 for the number of headache episodes or days (primary endpoint). During the open-label study, BoNTA-treated subjects had a decrease in the number of headache episodes at months 5 and 6 and headache days at months 5 and 6. BoNTA did not affect maximum headache severity compared with baseline or placebo during the first 3 months of the study. A decrease in HIT-6 scores was significantly greater for BoNTA-treated subjects than for placebo-treated subjects at month 3. BoNTA was significantly better than placebo (P = .001) in the reduction of MIDAS total score. BoNTA-treated subjects showed improvement in 11 of 13 and 7 of 13 assessments of treatment satisfaction in MIQ at months 3 and 6, respectively, while the placebo group showed no improvement at any measured time interval in the study.	At month 3 (blinded period), there were no treatment-related AEs reported in both groups. However, there were 18 possible/probable occurrences of treatment-related adverse events (AEs) in the BoNTA group. At month 6 (open-label period), 4 treatment-related AEs were reported, along with 2 possible occurrences. The majority of treatment related AEs were transient and mild to moderate in severity, with no subjects discontinuing the study because of AEs.	BoNTA-treated subjects showed improvements from baseline in measures of headache frequency, and improvements from baseline and in comparison, with placebo treatment in headache impact and treatment satisfaction at multiple time points in this study. However, BoNTA-treated subjects did not differ from placebo-treated subjects in measures of headache frequency and severity.
Cady et al.	2011	Double blind RCT	Migraine	Onabotulinumtoxin A	Topiramate	Not reported	Not reported	59	Physician Global Assessment, headache days, migraine disability assessment, headache impact assessment, money spent on migraine medication	This study demonstrated positive benefit for both onabotulinumtoxinA and topiramate in subjects with CM. Overall, the results were statistically significant within groups but not between groups. By week 26, subjects had a reduction of headache days per month compared with baseline. This was a significant within-group finding.	The number of subjects who discontinued the study was 15, 8 topiramate subjects and 7 onabotulinumtoxinA subjects, half of whom listed adverse events as the reason for dropping out. Yet at baseline, before the study began, a majority of subjects from both groups had identified side effects.	OnabotulinumtoxinA and topiramate demonstrated similar efficacy for subjects with chronic migraine as determined by Global Physician Assessment and supported by multiple secondary endpoint measures.

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Chankrachang et al.	2011	RCT	Migraine	Botulinum Type A Toxin Complex (Dysport®)	Placebo (saline)	2 subcutaneous injections frontal and temporal regions of face, and 2 intramuscular injections occipital region	Not reported	128	Migraine attacks from the pre-treatment period to 8-12 weeks, intensity score, patient global assessments, MIDAS and SF-36	Change in number of migraine attacks from pre-treatment to weeks 8-12 was not significantly different. There was a greater improvement in total intensity score at weeks 8-12 with Dysport-240 (not significant), and interim visit data showed that this was significant at weeks 0-4 (P = .03 Dysport-240 vs placebo). The mean duration of headache during weeks 0-4 was lower with Dysport-240 (P = .04 vs placebo). Improvements in patient and investigator global assessments of change between weeks 0-4 and 8-12 were significant for the Dysport-240 group (both P < .05 vs placebo).	32 adverse events across all 3 treatment groups (10, 15, and 7 events in the placebo, Dysport-120, and Dysport-240 groups, respectively). the 3 that were reported in more than one patient per treatment group all occurred in the Dysport-120 group (muscle tightness, dizziness, and neck pain). Adverse events were considered by the investigator to be probably related to treatment in 4/10 (40.00%) events in the placebo group, 2/15 (13.33%) events in the Dysport-120 group, and 3/7 (42.86%) events in the Dysport-240 group. The majority of adverse events (22/32 [68.8%]) were mild or moderate and no serious adverse events occurred during the 12 weeks of follow-up.	This exploratory study suggests that Dysport may be beneficial in the treatment of migraine, particularly at a dose of 240 units. In this study of chronic migraine sufferers, the injections were well tolerated and adverse events were as expected with BoNT-A treatment. Although we found no effect on the primary efficacy end point, the frequency of migraine attacks, we found that the number of hours with migraine and the total intensity score at 4 weeks were both significantly improved in the Dysport-240 group compared with placebo.
Diener et al.	2010	Double blind RCT	Chronic migraine	Onabotulinumtoxin A	Placebo	Administered as 31, fixed-site, fixed-dose, intramuscular (IM) injections (minimum dose 155 U) across seven specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius)	Not reported	706	frequency of headache days in 28-days, frequency of moderate/severe headache days, monthly cumulative headache hours on headache days, proportion of patients with severe (60) Headache Impact Test (HIT)-6 score, and frequency of headache episodes, acute headache pain medication intakes	OnabotulinumtoxinA was statistically significantly superior to placebo for the primary endpoint, frequency of headache days per 28 days relative to baseline (-9.0 onabotulinumtoxinA/-6.7 placebo, p<.001). OnabotulinumtoxinA was significantly favoured in all secondary endpoint comparisons. OnabotulinumtoxinA was safe and well tolerated, with few treatment-related adverse events.	Patients receiving botulinum toxin A were more likely to report any adverse event than those injected with placebo (25 studies: RR, 1.25; 95% CI, 1.14-1.36), although they were not more likely to withdraw from the study (23 studies: RR, 1.04; 95% CI, 0.85-1.27). Some adverse effects were more common among patients receiving botulinum toxin A, including blepharoptosis (RR, 9.5; 95% CI, 4.7-18.9), muscle weakness (RR, 8.9; 95% CI, 2.5-30.9), neck pain (RR, 4.7; 95% CI, 3.2-6.9), neck stiffness (RR, 3.2; 95% CI, 1.9-5.6), parasthesia (RR, 3.3; 95% CI, 1.3-7.9), and skin tightness (RR, 3.6; 95% CI, 1.6-8.3).	Botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per month.
Elkind et al.	2006	3 sequnetial double blind RCTs	Migraine	Botulinum Toxin Type A (BoNTA; BOTOX®)	Placebo	Muscles: Frontal (4 sites), temporal (2 sites), glabellar (5 sites)	Not reported	401	Frequency and incidence of migraine headaches of any severity, migraine headache severity, acute migraine medication, migraine duration, days with aura, and days with migraine-associated symptoms, patient global assessment, SF-36, The Migraine-Specific Measure of Quality of Life, Migraine Impact Questionnaire	Migraine frequency was not different among treatment groups at any visit in any of the studies (assessed as change from baseline, all P≥ .201). At no time was there a statistically significant effect of BoNTA. A few statistically significant differences in other migraine-related variables were observed at several time points. For instance, in study I, average migraine headache severity was significantly more improved in the 7.5 U group than in the placebo group at day 120 (0.23 vs 0.07, respectively; among groups P = .028; pair-wise P = .017). However, none of the groups treated with BoNTA showed consistent, statistically significant improvements over placebo or other doses on any of the dependent variables assessed in these studies.	Adverse events were reported by 46.5% to 78% of patients in each group. The adverse events reported by 5% of patients in at least 1 of the treatment groups in all studies of the study were flu syndrome, respiratory infection, sinus infection, and blepharoptosis. Blepharoptosis was reported significantly more frequently with BoNTA 50 U than placebo in studies I and III, and with BoNTA 25 U than placebo in study I. Eyelid edema was reported significantly more frequently with BoNTA 50 U than placebo in study I, and dizziness was reported significantly more frequently with BoNTA 50 U than placebo in study III. Serious adverse events were reported for 18 patients and all were considered unrelated to treatment. No patient died during these studies.	In these exploratory studies of episodic migraine patients, repeated injections of low doses of BoNTA (50 U or less) into fixed frontal, temporal, and glabellar sites were not more effective than placebo. Up to 4 treatments with BoNTA were well tolerated.

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Evers et al.	2004	Double blind RCT	Migraine	Botulinum Toxin Type A	Placebo	Muscles: Frontalis (2 sites), temporalis, sternocleidomastoideus, trapezius, splenius capitis, semispinalis	Not reported	60	Migraine diary (intensity of migraine, the days with other headaches, accompanying symptoms, acute medication for treating migraine attacks, and any adverse events), German version of Beck's Depression Inventory and the German version of the Headache Disability Inventory	The rate of patients with at least 50% reduction of migraine frequency (primary efficacy parameter) was 30% in the group receiving 100 U, 30% in the group receiving 16 U, and 25% in the group receiving placebo (P = 0.921).There were no significant differences between the three treatment groups with respect to the reduction of migraine frequency, number of days with migraine, number of days with moderate or severe migraine, or number of acute drugs for the treatment of migraine attacks. The only significant difference that could be observed was in the sum score of all accompanying symptoms. In the group receiving 16 U botulinum toxin A, but not in the group receiving 100 U, the accompanying symptoms were significantly reduced by 29% in month 3 compared with a reduction of 5% in the group receiving placebo (P = 0.048; post hoc test). No significant differences between the three treatment groups could be observed for these efficacy parameters.	Adverse events included: Neck pain, ptosis, weakness of frontal muscles, weakness of neck muscles, frontal paraesthesia, impaired mobility of cervical spine. The total number of adverse events was significantly higher in the group receiving 100 U compared with the group receiving placebo (P < 0.05). All adverse events were mild and transient. There was no serious adverse event.	In conclusion, our study does not support the hypothesis that botulinum toxin A is effective in the prophylactic treatment of migraine. However, it might be that other injection sites and other doses of botulinum toxin A are effective in a defined sub group of patients. Furthermore, our study gives some evidence that a low dose of botulinum toxin A might have a mild effect on the accompanying symptoms of migraine.
Frietag et al.	2008	Double blind RCT	Chronic migraine	Botulinum Toxin Type A (BOTOX®)	Placebo (saline)	Muscles: Glabella (4), temporal (4), frontal (4), suboccipital (6), trapezius (4)	Not reported	86	Migraine episode frequency, total headache days, headache index (HAI), acute medication, MIDAS, Headache Pain Specific Quality of Life measure	Botulinum Toxin Type A was statistically superior to placebo for the primary endpoint of reduction in migraine headache episodes. Six patients on Botulinum Toxin Type A compared with 3 patients on Placebo had at least a 50% reduction in their migraine episodes. Active treatment was superior to placebo for the secondary endpoints of total headache days, headache index, and quality of life measures. It showed numerical superiority to placebo for acute medication use and Migraine Disability Assessment Scores.	There were relatively few adverse events reported in this study and there was little difference in the frequency or nature of adverse events reported between BoNTA and Placebo groups. Reported adverse events included: fever (n=2 placebo), backache (n=1 placebo), panic attack (n=1 placebo), heaviness of arm (n=1 placebo), confusion (n=1 placebo), chest heaviness (n=1 placebo), stiff neck (n=1 placebo, n=1 BoNTA), dizziness (n=1 placebo), sinus infection (n=2 BoNTA), hair loss (n=1 BoNTA), amenorrhea (n=1 BoNTA)	The use of Botulinum Toxin Type A may be an effective treatment for chronic migraine when the patient does not have concomitant medication overuse. It was well tolerated in this trial.

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Hollanda et al.	2014	Double blind RCT	Migraine	Botulinum Toxin Type A	Placebo (Saline)	Muscles: Frontal (2), temporal (2) and occipital (2)	Not reported	58	Headache diary, frequency of headache episodes with allodynia, intensity of headache pain, frequency of analgesics use for headache	There were no significant differences in baseline between active intervention or placebo groups regarding mean age, number of headache episodes [mean 12.1 (9.22) and 17.00 (9.69) respectively; P=0.12], pain severity as measured by the VAS or frequency of analgesic use for headache episodes. Efficacy analysis showed that Botx -A injections led to an important decrease from baseline in the mean migraine episodes associated with CA after 12 weeks (5.20 versus 11.17; P=0.01). Also, VAS scores and frequency of analgesics use for headache were significantly reduced in the Botx-A group.	A total of 16 subjects reported adverse events during the study protocol, the most common being pain in the site of injections, which were resolved without sequelae. There were no severe adverse events reported in this group.	This study suggests that Botx-A injections are superior to saline in the treatment of CA associated with CM, with mild self limited side effects.
Hou et al.	2015	Double blind RCT	Migraine	Onabotulinumtoxin A	Placebo (Saline)	frontal and occipital belly of occipitofrontalis, corrugator supercilii, temporalis and superior part of trapeziue muscle	Not reported	102	Headache diary (Frequency of migraine attack per month; Intensity of migraine (VAS); Duration of each attack; Migraine associated symptoms scale	BoNTA injection in both of the fixed-sites and acupoint-sites groups induced a significant decrease of the attack frequency of migraine for four months compared with placebo ($p < 0.01$). However, the reduction of attack frequency in acupoint-sites group was greater from month 1 to 4 ($p < 0.01$) compared with fixed-sites group. The mean duration of each attack after BoNTA treatment in both groups was significantly reduced compared to that in placebo ($p < 0.01$). In comparison between fixed-sites and acupoint-sites groups, the decrease of each attack duration in acupoint-sites group was greater for four months ($p < 0.01$).	Three cases (7%) of 41 subjects injected with BoNTA at fixed-sites appeared transient unilateral upper eyelid ptosis that lasted for three or five days. One patient in fixed-sites group after injection noted an acute pain at injection sites that disappeared after one night. These three subjects were among the cases of improvement in fixed-sites group. One patient in acupoint-sites group after injection felt an ethereal pain in local skin that lasted for four days, and BoNTA treatment was invalid for him.	It can be concluded that acupoint-site and fixed-site injection of BoNTA are able to significantly reduce migraine attack frequency, intensity, duration and associated symptoms. Acupoint-site administration of BoNTA is proved to be more efficient for migraines than fixed-site application, and thus is a potential method in clinical practices in treating patients who experienced six or more attacks per month, hemiplegic and basilar type migraines, and migraines with prolonged auras as well.
Jost	2011	Double blind RCT (cross over)	Unilateral migraine	Botulinum Toxin Type A	Placebo	Not reported	Not reported	22	Pain (visual analog scale), SF-McGill Pain Questionnaire, Northwick Park Neck Pain Questionnaire, International quality of life assessment (IQOLA), SF 36, Scale of attitudes toward disabled persons (SADP) Oswestry low back pain disability questionnaire, (OLBPDQ) ,headache attacks and adjuvant medication	We found no clinically relevant or statistically significant differences regarding the target parameters in both injection intervals.	Not reported	From the data published so far, the injection of BTX may be considered a promising approach in the management of chronic migraine. Optimum injection sites and appropriate doses, however, still need more exploration. One injection into the corrugator muscle alone must be considered as ineffective

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Linde et al.	2011	Double blind RCT (cross over)	Cervicogenic headache	Onabotulinumtoxin A	Placebo (saline)	fixed-site injections across six specific head/ neck muscle areas on the pain side: 20U divided upon two points in the occipital muscle insertions, 20U in the upper trapezius, 20U in the splenius capitis, 20U in the sternocleidomastoideus, and 20U in the levator scapulae.	Not reported	28	maximum intensity of head pain (scale 0–3), presence of neck pain, total duration of pain in head and neck (hours), analgesic medication (number of tablets), and sick leave, SF-36, neck range of motion, pain pressure thresholds.	There was no significant difference between verum and placebo in a mixed linear model analysis (p=0.084) with regard to the primary end-point, reduction of days with moderate to severe headache. Six patients withdrew from the study before the second injections, but an intention-to-treat (ITT) analysis gave a similar result (p=0.27). There were no significant differences favouring verum in any of the secondary efficacy measures.	There was no significant difference (p>0.2) in the proportion of participants experiencing any AE after onabotulinum toxin A (11/23, 48%) compared to placebo (8/24, 33%). The only AE that occurred in ≥5% of verum-treated patients was aggravated headache. AEs of onabotulinum toxin A were mild or moderate in severity and had resolved without sequelae within 4 weeks after injections. One serious AE (hospitalisation for heart operation) was reported during the study. This was considered to be unrelated to the study medication (onabotulinum toxin A).	Onabotulinum toxin A in neck muscles does not seem to be beneficial in cervicogenic headache
Magalhaes et al.	2010	RCT	Chronic daily migraine	Botulinum Toxin Type A	Amitriptyline	Not reported	Not reported	72	Number of days in pain, intensity of pain (VAS), pain drug doses used for migraines, self-assessment of improvement, impression of improvement by the physician.	A reduction of at least 50% in the number of days of pain was recorded in 67.8% of the patients in the BTX-A group and 72% (n= 23) of the patients in the AM group (p= 0.78; RR = 0.94; CI = 0.11–8). The reduction in the intensity of pain, as assessed using the visual analogical scale, was 50% in the BXT-A group and 55.6% in the AM group (p= 0.79; RR = 1.11; CI = 0.32–3.8). The reduction in the number of pain drug doses was 77% for the toxin group and 71% for the amitriptyline group (p= 0.76; RR = 0.92; CI = 0.45–1.88).	There was no correlation between adverse events and the dose of AM. Weight gain occurred in 11.8% of subjects in the BXT-A group and 58.3% of subjects in the AM (p= 0.0001). The occurrence of somnolence was 4% in the toxin group and 52.7% in the AM group (p= 0.0001). Fourteen percent of the toxin group and 44% of the AM group complained of dry mouth (0.0045). Constipation occurred in 0% of the toxin group and in 38.8% of the AM group (p=0.0001). At the site of injection in the toxin group, pain occurred in 35% of the subjects and edema in 14%.	Botulinum toxin type A was as effective as amitriptyline for the prophylactic treatment of chronic daily migraines.
Mathew et al.	2005	Double blind RCT	Chronic Daily Headache	Botulinum Toxin Type A (BOTOX®)	Placebo (saline)	The number of injection sites within each specified muscle area was determined by the physician. Muscles included: Frontal/glabellar, occipitalis, temporalis, masseter, trapezius, semispinalis, splenius capitis	Not reported	355	Headache-free days (30 days), frequency of headache free days (180 days), medication use, migraine disability assessment scale (MIDAS), Headache pain-specific quality of life questionnaire	at day 180, placebo nonresponders stratum treated with BoNT-A had an improvement from baseline of 6.7 headache-free days per 30 day period compared to a mean change from baseline of 5.2 headache-free days for placebo-treated patients. The between-group difference of 1.5 headache-free days favoured BoNT-A treatment, although the difference was not statistically significant.	During the study, a total of 72.4% (257/355) of patients experienced one or more adverse events. The most frequently reported treatment-related adverse events in the BoNT-A group were muscular weakness (22% (38/173)), neck pain (13.3% (23/173)), headache (6.9% (12/173)), and blepharoptosis (6.9% (12/173). boNT-A patients had significantly higher incidences of treatment-related neck pain, shoulder/arm pain, muscular weakness, skin tightness, and blepharoptosis	BoNT-A treatment resulted in patients having, on average, approx. 7 more headache-free days compared to baseline. Although at the primary time point (day 180) the BoNT-A treatment resulted in a 1.5 between-group difference compared to placebo, this difference was not statistically significant. The treatment met secondary efficacy outcome measures, including the percentage of patients experiencing a 50% or more decrease in the frequency of headache days, in addition to statistically significant reductions in headache frequency.

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Ondo et al.	2004	Double blind RCT	Chronic daily headache	Botulinum Toxin Type A	Placebo	The injection locations were at the discretion of the injecting physician, but generally employed a 'follow the pain' strategy. Masseter muscles were injected in some cases.	Not reported	60	The primary efficacy point was headache-free days. Secondary efficacy points included global impressions, headache medication use, palpation scores (rated 0–4 at 24 separate points around the head), the Beck Depression Inventory (BDI), the Psychosocial Adjustment to Illness Scale (PAIS), and adverse events (AEs).	Over a 12-week period after injections, headache-free days had improved in the BTX group from week 8 to 12 (P<0.05), and strongly tended to improve over the entire 12-week period, 33 ± 23 vs.24 ± 16 days without headache (P=0.07), but did not meet the a priori significance criteria. The subject global impressions (P<0.05), subject change in headache impressions (P<0.005), and investigator global impressions (P<0.001) all improved in the BTX group compared with placebo. Adverse events were mild and did not differ between groups. At week 24 (open label), headache-free days were less in the twice BTX injected group compared with the once injected group, 40 ± 26 vs. 26 ± 19 (P<0.05). BTX may help chronic daily headache and appears to have a cumulative effect with subsequent injections.	Adverse events (AEs) were mild and did not differ between groups. Only a single patient with eyelid ptosis was thought to have a definite BTX-related AE. Overall, 33 AEs were reported in the drug group and 39 were reported in the placebo group. None of these was rated as serious or resulted in discontinuation.	BTX may help chronic daily headache and appears to have a cumulative effect with subsequent injections.
Petri et al.	2009	Double blind RCT	Migraine	Botulinum Type A Toxin Complex (Dysport®)	Placebo (Saline)	Occipitalis, occipitofrontalis, temporalis, semispinalis capitis, splenius capitis, sternocleidomastoideus, trapezius, frontalis, depressor supercelli, lateral orbicularis, corrugator supercilli, procerus, levator scapulae	Not reported	127	Headache diary (incidence, duration and severity of migraine attacks, pain intensity), occurrence of aura or concomitant symptoms, and acute medication used for treatment of migraine attacks), Beck's Depression Inventory, Global rating of the treatment efficacy, Total Tenderness Score, use of analgesics, migraine-related disability.	There was a mean reduction of 0.54 and 0.94 attacks/month with placebo and BoNT-A, respectively, and absolute attack count was less in the verum group (3.6 vs. 4.2 attacks/month), but this was not statistically significant. The patients' global assessment of efficacy was significantly better than placebo in the high-dose group (p = 0.02) but no effects were seen for the other secondary efficacy parameters.	Treatment was generally well tolerated in the 127 patients analyzed for safety. Adverse events occurred in 38% (12/32) and 13% (4/32) of patients in the 210- and 80-unit groups, respectively, and in 17% (11/63) of patients receiving placebo. The most frequent adverse event was neck weakness in 8 patients (13%) who received verum and 1 patient (2%) receiving placebo (p <0.05, pooled analysis). Ptosis was reported for 2 patients who received verum (3%, pooled analysis; 1 patient for each dose).	Our study showed a trend towards a reduced attack rate with verum but did not show any statistically significant efficacy of BoNT-A in the prophylactic treatment of migraine.
Relja et al.	2007	Double blind RCT	Episodic migraine	Botulinum Toxin Type A	Placebo (Saline)	Frontalis (4), corrugator (2), temporalis (4), splenius capitis (2), trapezius (4), semispinalis capitis (2), suboccipital region (2)	Not reported	515	Frequency of migraine episodes, number of days with headache or migraine episode (in a 30-day period), the frequency of moderate-to-severe migraine episodes, acute headache pain medication use, Migraine Disability Assessment Scale (MIDAS), the Headache Pain-Specific Quality of Life Questionnaire.	All groups (N=495) improved, with no significant differences. At day 180, the frequency of migraine episodes was reduced from baseline means of 4.3,4.7, 4.7 and 4.4 by 1.6, 1.7, 1.5 and 1.4 for BoNTA 225 U, 150 U and 75 U and placebo, respectively. The primary end-point was not met.	One or more adverse events, regardless of causality, were reported for 76.7%, 77.6% and 77.2% of patients treated with BoNTA 225 U, 150 U and 75 U compared with 54.2% of patients treated with placebo. The overall incidence of adverse events was greater in each BoNTA group than in the placebo group (P<0.001). The majority of adverse events were transient and mild or moderate in severity. The most frequently reported treatment-related adverse events in the BoNTA groups were muscular weakness (in areas of injection sites), neck pain, neck rigidity, blepharoptosis, myalgia, skin tight-ness and injection site pain.	BoNTA treatment was safe and well tolerated but did not result in significantly greater improvement than placebo in this study. Several factors may have confounded the results.

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Sandrini et al.	2011	Double blind RCT	Medication over-use headache	Botulinum Toxin Type A	Placebo	16 (8 on the right and 8 on the left) intramuscular injections in the following muscles:frontalis (2), corrugators (1), temporalis (1), cervical paraspinal (2) and trapezius (2)	Not reported	68	Frequency of headache days for the 28-day period, acute headache pain medication use, intensity of headache pain, Headache Impact Test (HIT)-6 score and Migraine Disability Assessment Scale (MIDAS), pericranial muscle tenderness	No significant differences between onabotulinum toxin A and placebo treatment were detected in the primary (head-ache days) end point (12.0 vs. 15.9;p=0.81). A significant reduction was recorded in the secondary end point, mean acute pain drug consumption at 12 weeks in onabotulinum toxin A-treated patients when compared with those with placebo (12.1 vs. 18.0; p=0.03).	A total of 16 (28.5%) subjects in the randomized population experienced adverse events. Treatment-related adverse events were reported in 25.9% of the onabotulinum toxin A-treated (7 patients) and in 17.2% of the placebo-treated (5 patients) patients. Two patients randomized to onabotulinum toxin A (7.4%) discontinued due to adverse events (neck pain). No clinically significant serious adverse events were reported in any of the 56 subjects. Most common adverse events (<5%) were pain at the site of injection and muscular weakness, all of which resolved without sequelae.	Our data identified the presence of pericranial muscle tenderness as a predictor of response to onabotulinum toxin A in patients with complicated form of migraine such as MOH, the presence of pericranial muscle tenderness and support it as prophylactic treatment in these patients.
Saper et al.	2007	Double blind RCT	Episodic migraine	Botulinum Toxin Type A	Placebo	Patients were randomized in equal numbers to one of five groups for treatment with placebo or BoNTA injected into one of four muscle regions: frontal, temporal, glabellar, or all three areas (FTG). Patients randomized to placebo received placebo injections into frontal, temporal, and glabellar areas, and patients randomized to active treatment in only one specified muscle area received placebo injections into the remaining two areas	Not reported	232	Frequency (number/month) of migraine headaches, maximum migraine severity (mild, moderate, severe) and duration, occurrence of nonmigraine headaches, use of acute migraine medication, presence or absence of aura, presence or absence of associated symptoms (e.g., nausea, vomiting, photo/phonophobia), and patient global assessment of response to treatment, Headache Pain Specific Quality of Life Questionnaire, Migraine-Specific Measure of Quality of Life, and Migraine Impact Questionnaire, SF-36 Health Survey	BoNTA and placebo produced comparable decreases from baseline in the frequency of migraines (P≥0.411). In general, no statistically significant differences were observed for any efficacy variable. The overall rates of adverse events (any type) or treatment-related adverse events were similar among the groups.	A total of 47.0% (109 of 232) of patients experienced one or more adverse events during the study, regardless of causality, and the incidence was not significantly different among groups (P=0.589): 55.1% (27 of 49) FTG group, 45.5% (20 of 44) frontal group, 40.0% (18 of 45) temporal group, 42.9% (21 of 49) glabellar group, and 51.1% (23 of 45) placebo group. These were transient and mild to moderate in severity. Muscle weakness was the most frequently reported adverse event within a treatment group and flu syndrome was the most frequently reported adverse event across groups.	In this exploratory study of episodic migraine patients, low-dose injections of BoNTA into the frontal, temporal, and/or glabellar muscle regions were not more effective than placebo. BoNTA was safe and well tolerated. Future studies may examine higher BoNTA doses, flexible injection sites, multiple treatments, and disallow concomitant prophylactic medications.
Shehata et al.	2016	RCT	Migraine	Botulinum Toxin Type A (BOTOX®)	Repetitive transcranial magnetic stimulation	31 sites across seven specific head and neck muscles ± 8 sites (following the pain).	Not reported	29	headache frequency (days/month) and headache severity assessed by VAS; secondary 25-item HDI, HIT-6, and number of acute medications.	A reduction in all outcome measures was achieved in both the groups. However, this improvement was more sustained in the BTX-A group, and both the therapies were well tolerated.	No systemic reactions or serious adverse events were recorded. Injections-related adverse events included pain at the site of injection (n⍰5), hematoma (n⍰2), and blepharoptosis (n⍰1); these adverse effects were transitory and did not interfere with the patient activity, and did not need further management. In rTMS group (n⍰14), two patients (14.29%) experienced headache worsening which compelled them to withdraw their consent and one patient (7.14%) had transient tinnitus on the day of session which lasted for few hours and waned the continuation of sessions.	BTX-A injection and rTMS have favorable efficacy and safety profiles in chronic migraineurs. rTMS is of comparable efficacy to BTX-A injection in chronic migraine therapy, but with less sustained effect.

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Silberstein et al.	2000	Double blind RCT	Migraine	Botulinum Toxin Type A	Vehicle or BTX-A, 25 U or 75 U	symmetrical injections into the frontalis, temporalis, and glabellar (corrugator and procerus) muscles	Not reported	123	frequency (number per month) of moderate-to-severe migraines, frequency of migraines of any severity, the percentage of subjects with at least a 50% decrease in the frequency of any migraines, the percentage of subjects with a decrease of two or more migraines per month, maximum migraine severity (on a scale of 0 to 3), days with acute migraine medication use, and percentage of subjects with migraine-associated symptoms, 9-point Global Assessment Scale	Compared with vehicle treatment, subjects in the 25-U botulinum toxin type A treatment group showed significantly fewer migraine attacks per month, a reduced maximum severity of migraines, a reduced number of days using acute migraine medications, and reduced incidence of migraine-associated vomiting. Both the 25-U and 75-U botulinum toxin type A groups were significantly better than the vehicle group on subject global assessment. Botulinum toxin A treatment was well tolerated, with only the 75-U treatment group exhibiting a significantly higher rate of treatment-related adverse events than vehicle.	All treatments were generally well tolerated and there were no serious treatment-related adverse events. The incidence of treatment-related adverse events in the 25-U BTX-A treatment group was not significantly different from the vehicle group, but there was a higher incidence in the 75-U BTX-A group than the vehicle group (50% versus 24%; P=5.017). All treatment-related adverse events were transient and included blepharoptosis (vehicle, 0 cases; 25 U BTX-A, 6 cases; 75 U BTX-A,7 cases), diplopia (vehicle, 0 cases; 25 U BTX-A, 0 cases; 75 U BTX-A, 2 cases), and injection site weakness—an expected drug effect (vehicle, 1 case; 25 U BTX-A, 4 cases; 75 U BTX-A, 5 cases).	Pericranial injection of botulinum toxin type A, 25 U, was found to be a safe treatment that significantly reduced migraine frequency, migraine severity, acute medication usage, and associated vomiting.
Silberstein et al.	2005	Double blind RCT	Chronic daily headache	Botulinum Toxin Type A	Placebo (saline)	20 sites encompassing 7 muscle areas, including the frontalis, corrugator, temporalis, splenius capitis, trapezius, semispinalis capitis, and the suboccipital region	Not reported	702	Each headache episode was characterized by the recording in the diary of the headache start and stop time, characteristics, symptoms, and medications taken. A headache-free day was defined as a complete day during which no headache was recorded. Mean change frequency of headache-free days for the 30-day period ending on day 180 for the placebo nonresponder group.	The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed in the placebo nonresponder group treated with BoNTA at 225 U, 150 U, 75 U, or placebo, respectively (P=.44). An a priori–defined analysis of headache frequency revealed that BoNTA at 225 U or 150 U had significantly greater least squares mean changes from baseline than placebo at day 240 (–8.4, –8.6, and –6.4, respectively; P=.03 analysis of covariance).	Treatment-related adverse events were reported for 65.4% of patients (119/182) treated with BoNTA at 225 U, 54.8% (92/168) treated with BoNTA at 150 U, 55.7% (97/174) treated with BoNTA at 75 U, and 21.3% (38/178) treated with placebo. The overall incidence of treatment-related adverse events was greater in each BoNTA group than in the placebo group (P<.001). The most frequently reported treatment-related adverse events in the BoNTA groups were muscular weakness (in areas of injection sites), neck pain, neck rigidity, injection-site pain, hypertonia, headache, shoulder/arm pain, and hypesthesia.	Although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240. The placebo response was higher than expected. BoNTA was safe and well tolerated.
Song et al.	2015	RCT	Chronic migraine	Botulinum Toxin Type A	Infrared polarized light and placebo	frontal, temporal, and occipital muscles	Ultrasound	91	Severity of chronic migraine, seizure duration, seizure frequency, use of painkillers, MIDAS, SF-36 score	The MIDAS scores, quality of life rating scales, in group A, B, C and D were significantly lower than before the treatment. Hence, the differences were statistically significant ($p < 0.01$). The MIDAS scores and quality of life rating scale scores in group D were compared with those in group A, B, and C respectively, and the differences were statistically significant ($p < 0.05$).	Patients in group B showed no significant adverse reactions. Two cases reported dizziness in group C and recovered after one week without any treatment.	The combination of ultrasound and hyponome guided type A botulinum toxin injection and infrared polarized light on treating chronic migraine demonstrated a significant clinical effect.

Author	Year	Study design	Headache type	Botulinum toxin	Comparator	Injection site(s)	Guidance	Sample size	Outcome Measures	Results	Safety and Risk	Authors conclusions
Vo et al.	2007	Double blind RCT	Migraine	Botulinum Toxin Type A	Placebo	orrugator, frontalis, temporalis, sternocleidomastoid, occipitalis, and posterior neck muscles	Not reported	32	Onset and intensity of headache attacks based on the 10-point Visual Analog Scale (VAS), medication use, Migraine-Specific Quality of Life Questionnaire (MSQ)	Quadratic trends were noted for headache severity (F (2,29) =14.1, p=0.001) and headache indexes (F (2,29) = 4.5, p= 0.042) for both groups, suggesting changes in severity of head pain and overall intensity of headaches experienced over time; however, results were not significant for headache frequency and severity between groups. Paired t-tests of the headache index scores for the control group revealed a significant increase from the first to the third follow-up periods (t=-2.58, p=0.020). Such a trend was not observed for the BTX-A group. Both groups, however, reported similarly low to moderate quality of life as a result of their migraines.	Not reported	This controlled trial failed to demonstrate efficacy of BTX-A in reducing the frequency of migraine headaches. The pattern headache index in the botox group, however, suggested a protective effect for botox against the headache severity.