International Centre for Allied Health Evidence

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Systematic Review of the Literature

The Effectiveness of Injection of Botulinum Toxin for Myofascial Pain

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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	**PICO**	Population, Intervention, Comparator, Outcome
BTx-A	Botulinum Toxin A	**PLA2**	Phospholipase A2
QALY	quality-adjusted life years	**RCT**	Randomised Controlled trial
Botox	Botulinum Toxin	**ROM**	Range Of Movement
MA	Meta-analysis		
MRI	magnetic resonance imaging	**SIGN**	Scottish Intercollegiate Guidelines Network
MPS	Myofascial pain syndrome	**SMD**	Standard Mean difference
NRS	Numerical Rating Scale	**SR**	Systematic Review
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs	**TMD**	Temporomandibular
RF	Radiofrequency	**TENS**	Transcutaneous Electrical Nerve Stimulation
		TrPS	Trigger Point
		US	Ultrasound
		VAS	Visual Analogue Scale
	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 review is to synthesise the evidence published since 2011 related to the effectiveness of injection of botulinum toxin as a form of interventional pain management for myofascial pain. 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 myofascial pain? 2. What is the evidence for the safety of botulinum toxin injections for myofascial pain?
Evidence sourced	The search yielded 606 articles. After scrutiny, 593 articles were excluded as duplicates or failing to meet the inclusion criteria (shown in Figure 1), leaving 13 studies for inclusion in this review including 5 systematic reviews (SRs) and 8 randomised controlled trials (RCTs).
What is the evidence for the effectiveness of botulinum toxin injection in relieving pain and/or improving functional outcomes in patients with pain?	**Myofascial Pain** 1. **The evidence indicates that for cervico-thoracic specific myofascial pain syndrome there is no statistically significant difference in pain reduction between botulinum toxin injections and saline solution injections.** Level A recommendation based on one HQ SR with Level 1+ evidence, one AQ SR with level 1+ evidence, one HQ RCT and one LQ RCT. 2. **The evidence indicates that for temporomandibular myofascial pain there is no statistically significant difference in pain reduction between botulinum toxin A injections and saline solution injections or fascial manipulation.** Level B recommendation based on results from one HQ RCT and one LQ RCT. 3. **The evidence indicates that for general myofascial pain syndrome botulinum toxin injections provide no statistically significant pain relief.** Level A recommendation based on one HQ SR with level 1++ evidence and one HQ SR with level 1 evidence. 4. **The evidence indicates that there is no difference in pain reduction when comparing dosages of 200 units to 480 units of botulinum toxin.** Level C recommendation based on one AQ RCT and one LQ RCT. 5. **The evidence indicates that there is no difference in pain reduction when using fixed point, intra-muscular or trigger point injection methods.** Level C recommendation based on three HQ RCTs and one LQ RCT.

	6. **The evidence indicates that there are no significant differences between injections of botulinum toxin and saline in terms of physical or emotional function or global or quality of life scores**. Level C recommendation based on one HQ RCT.
What is the evidence for the safety of botulinum toxin injection?	**The evidence suggests that botulinum toxin injections may be associated with more adverse events compared to placebo.** Level B recommendation based on one HQ SR (Soares et al 2014). **However, these adverse events are transient and resolve spontaneously.** Level A recommendation based on one HQ SR (Langevin et al 2011), one AQ SR (Desai et al 2014) and two HQ RCTs (Ernberg et al 2011, Kwanchuay et al 2015).
Does the evidence report any information about cost effectiveness?	No study identified within this search provided an economic analysis for the use of botulinum toxin injection in the treatment of myofascial pain.
Does the recent evidence change the 2011 recommendations?	**2005 Summary of Evidence** "The general use of botulinum toxin injection is not recommended for the treatment of myofascial pain. However, it may be considered in the research setting." **2011 Recommendation** The increasing body of evidence continues to support this recommendation.

1. Background

1.1 Objective of this Review

The objective of this review is to synthesise the evidence, published since 2011, related to the effectiveness of botulinum toxin injections for myofascial pain as a form of interventional pain management. 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 injections in relieving myofascial pain?
b) What is the evidence for the effectiveness of botulinum toxin injections in improving functional outcomes in patients with myofascial pain?
c) What is the evidence for the safety of botulinum toxin injections?

1.2 Description of the Intervention

Myofascial pain syndrome (MPS) is a condition where pain originates in the myofascial tissue (Rolan & Hu 2015) and is described as the sensory, motor and autonomic symptoms caused by myofascial trigger points (TrPs) (Sharan et al. 2014a). The myofascial trigger points are hypersensitive spots in skeletal muscles that are associated with a hypersensitive palpable nodule in a taut band. The spot is painful on compression and can give rise to characteristic referred pain, referred tenderness, motor dysfunction and autonomic phenomena (Rolan & Hu 2015; Simons 1997).

Low back pain (LBP) is one of the common manifestations in individuals with MPS (Sharan et al. 2014a) and other areas commonly affected are the Trapezius, Levator Scapulae, Infraspinatus and Scalenes muscles of the upper body (Sola 1995). Approximately 21-93% of patients with regional pain complaints have MPS (Sharan et al. 2014a) and overall the prevalence rates for MPS range from 10% to 80% (Wheeler 2004; Sharan et al. 2014b; Luo & Dun 2013; Gerwin 2001; Katz 2001).

A number of causal factors have been suggested for MPS such as acute physical overload, deep pain impulse, emotional tension, postural habits, fatigue, hypovitaminosis, infections, physical inactivity, poor physical conditioning, repetitive musculoskeletal microtrauma and trauma (Edwards 2005; Friction 1985; Friction 1994; Laskin 1969; Simons 1976; Simons 1999). The diagnosis of MPS is based on the identification of trigger points in the taut band through palpation of sensitive nodules, local twitch response and specific patters of pain referral associated with each trigger point (Friction 1985; Simons 1999). The contracted taut band can also be identified by ultrasound sonography (Ballyns 2011) and by MRI elastography (Chen 2007).

The treatment for MPS can be multidimensional and consists of trigger point inactivation, which can break the cycle of pain-spasm-pain (Simons 1999). It can also include patient reassurance, patient education, self-care and behaviour therapy, physiotherapy (ultrasound, mega-pulse, low level laser therapy, massage, transcutaneous electrical nerve stimulation (TENs), application of warm compressors,

exercise, stretching, acupuncture, dry needling, injections of anaesthetics, drug therapy and combined therapy (Baldry 2002; Bron et al. 2007; Esenyel, Caglar & Aldemir 2000; Flor & Birbaumer 1993; Han & Harrison 1997; Hong 1994; McMillan 1997, Roth, Horowitz & Bachman 1998; Simons 1999; Srbely & Dickey 2007; Talaat, el-Dibany & el-Garf 1986).

Currently, pharmacotherapy plays an important role in alleviating pain for patients with myofascial pain. Non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants and opioid analgesics are some of the most common classes of drugs provided (Zhang 2011). However, these drugs may not be effective in many patients (Charles 2004) and can also lead to serious health complications (Singh & Triadofilopoulos 1999).

Botulinum neurotoxin is a polypeptide protoxin synthesised by clostridium botulinum which is derived from the anaerobic bacterium C. botulinum (Alshadwi, Nadershah & Osborn 2015). This toxin interferes with the function of the neuromuscular junction (NMJ), binding to the presynaptic membrane of motor nerve endings inhibiting the release of acetylcholine (Ach) from pre-synaptic terminals (Alshadwi, Nadershah & Osborn 2015; Setler 2002). This inhibition and consequent suppression of acetylcholine leads to an induction of chemical denervation to paralyse muscle fibres (Setler 2002).

The clinical effects of Botulinum appear to be reversible weakness or paralysis of local skeletal muscles to the injection site (Freund & Schwartz 2003) and when an appropriate amount of Botulinum is injected into the muscle, partial chemical denervation is induced to reduce muscle contraction without complete paralysis (Freund & Schwartz 2003). With this effect, skeletal muscle strength generally weakens two to five days after the injection, which then minimises within two weeks and then recovers, the weakening effect then continuing from 6 weeks to 6 months (median 3-4 months). The injection dose influences the degree and the period of denervation. Changes to the muscular fibres (e.g. atrophy) also appear during the period where the effect is strong, with this gradually weakening after 2-3 months (Freund & Schwartz 2003; Setler 2002). These clinical effects make Botulinum injections useful for diseases or conditions which present with increased involuntary muscle activity or tension (Lew 2002).

1.3 Safety/Risk

While botulinum injections are quite safe and generally well tolerated across a wide range of therapeutuc uses (Naumann & Jankovic 2004), it is recommended that the minimum amount needed to achieve the desired effects is used (Apostol et al. 2009). Side effects such as pain in the injected area, bruises and muscular weakness are the most common, while fatigue, fever, dry mouth and ptosis can also appear one to two weeks after the injection. Headaches, lethargy and muscular pain can appear when an excessive dosage is used, but all of these side effects are temporary and reversible (Apostol et al. 2009). Rarely, an allergic reaction can be triggered and injection in areas near the neck and mouth can cause dysphagia (Apostol et al. 2009)

2. Methodology

2.1 Review question

What is the effectiveness of injection of botulinum neurotoxin as a form of interventional pain management for myofascial pain?

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 injections as a form of interventional pain management. 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	Injection of botulinum neurotoxin (BoNT) as a form of interventional pain management for myofascial pain
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 • Relationship to Imaging • 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,
  - AMED,
- ICONDA,
- CINAHL,
- PubMed,
- Pre-Medline,
- The Cochrane Library,
- Scopus,
- TRIP database

Table 2: Search terms for the review

Search term 1	Search terms 2	Search terms 3
• Myofascial Pain • Myofasc*	• Injection*	• Botulinum toxins • Botulinum neurotoxin • Clostridium botulinum • botulin* adj1 toxin* • Botox • Myobloc • Dysport • Xeomin • Neurobloc • Siax • Neuronox • abobotulinumtoxinA • abobotulinumtoxinB • abobotulinumtoxinC • abobotulinumtoxinD • abobotulinumtoxinE • abobotulinumtoxinF • abobotulinumtoxinG • incobotulinumtoxinA • rimabotulinumtoxinB • BTX-A • BTX • BoNT

The titles and abstracts identified from the above search strategy were assessed for eligibility by the *i*CAHE 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.

2.4 Study Selection

Inclusion Criteria

- Study Types: systematic reviews (SRs), all primary research designs (randomised controlled trials (RCTs), cohort studies (prospective or retrospective), case studies or case series).
- Participants: Patients with myofascial pain.
- Intervention: any serotype or preparation of BoNT
- Controls: any active treatment or placebo, or no intervention control
- Outcomes: Pain relief, functional outcomes, safety, and risk
- Publication criteria: English language, published in peer reviewed journal from January 2011 to current

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 published prior to 2011

2.5 Critical Appraisal

The SIGN (Scottish Intercollegiate Guidelines Network) checklist specific to the study design of each included studies was used to assess its methodological quality. The SIGN checklist asks a number of questions with yes, no, can't say or not applicable as responses; the appraiser gives an overall rating of quality, based on the responses to questions, of either high quality (++), acceptable quality (+), low quality (-) or unacceptable.

2.6 Data Extraction

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

- Evidence source (author, date, country)
- Level of evidence
- Characteristics of participants
- Interventions (BoNT preparation, dose, injection approach)
- Comparison treatment (if relevant)
- Outcome measures
- Adverse events and side-effects of treatment
- Results and study conclusion

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

In the formation of recommendations, the body of evidence 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 606 articles; following removal of duplicates 359 articles were identified for screening of title and abstract. After scrutiny, 346 articles were excluded for failing to meet the inclusion criteria (shown in Figure 1), leaving 13 studies for inclusion in this review. Figure 1 illustrates the process involved in study selection.

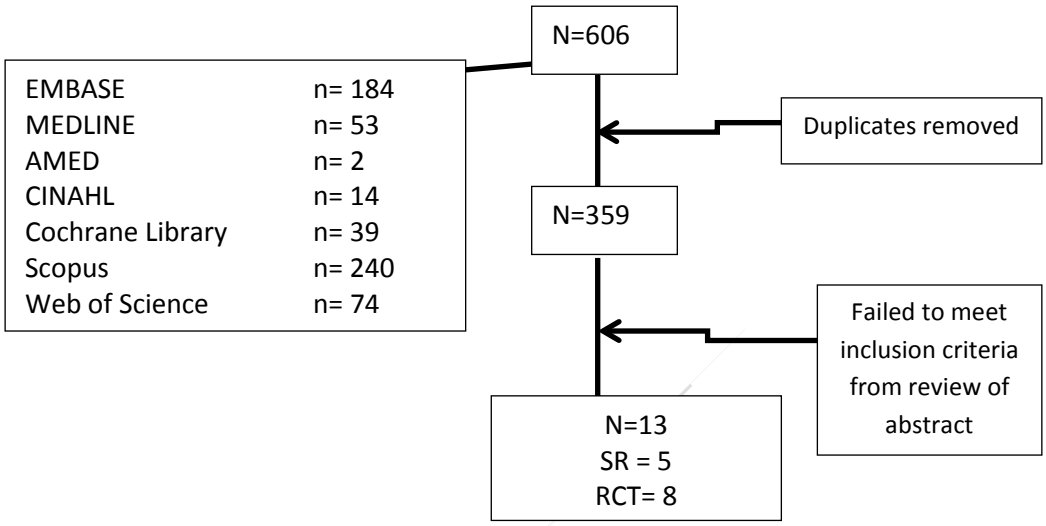

Figure 1: Flow chart of search results

3.2 Quality of the Evidence

The overall quality of the studies included in this review ranged from high to low. Four systematic reviews were of high quality (Langevin et al 2011; Mosshammer, Mayer & Joos 2013; Soares et al 2014; Zhang et al 2011) while Desai et al (2014) was of acceptable quality. Three RCTs were of high quality (Kwanchuay et al 2015; Benecke et al 2011; Ernberg et al 2011), one was of acceptable quality (Muller-Schwefe & Uberall 2011) and four were of low quality (Nicol, Wu & Ferrante 2014; Seo et al 2013; Guarda-Nardini et al 2012; Jerosch et al 2012).

3.3 Findings

Three systematic reviews of high quality focussed on general myofascial pain syndrome (Mosshammer, Mayer & Joos 2013; Soares et al 2014; Zhang et al 2011). One high and one acceptable quality review focussed on neck and cervico-thoracic myofascial pain respectively (Langevin et al 2011; Desai et al 2014).

Of the eight RCTs, five examined cervical, neck or shoulder girdle myofascial pain (Benecke et al 2011; Jerosch et al 2012; Kwanchuay et al 2015; Nicol, Wu & Ferrante 2014; Seo et al 2013). Two of these were of high quality. One high and one low quality study looked at temporomandibular myofascial pain (Ernberg et al 2011; Guarda-Nardini et al 2012). One acceptable quality study looked into myofascial back pain (Muller-Schwefe et al 2011).

3.4 Outcome Measures – Pain and Function

Systematic Reviews

Zhang et al. (2011)

Zhang et al (2011) (QS:HQ(++)) conducted a SR and MA to examine the effectiveness of botulinum toxin A injections versus non-active injection or other treatments in reducing chronic musculoskeletal pain, Twelve studies focusing on myofascial pain were included in the study (Ferrante et al. 2005; Guarda-Nordini et al. 2008; Lew et al. 2008; Kurtoglu et al. 2008; Nixdorf et al. 2002; Ojala, Arokoski & Partanen 2006; Qerama et al. 2006; Wheeler, Goolkasian & Gretz 2001b; Cheshire et al. 1994; Esenyel et al. 2007; Gobel et al. 2006; Wheeler, Goolkasian & Gretz 1998). The authors indicated that the general quality of the studies was high.

A meta-analysis was conducted with eight of the studies which found that, in the myofascial pain group, botulinum toxin A injection resulted in small pain relief which was not statistically significant (SMD = -0.16, 95% CI -0.39 to 0.06). No single study in the meta-analysis showed statistically significant results that botulinum was effective in pain reduction. Four studies were not included within the meta-analysis. One of these studies reported no statistically significant benefit over placebo after a follow up of 16 weeks. Another trial found that at week 5, significantly more people in the botulinum group experienced mild or no pain (baseline was moderate to severe pain). Another small study (6 participants), 4 of whom received botulinum toxin, reported at least 30% pain reduction compared to no pain relief in the placebo group. The last study found that botulinum toxin A and lidocaine were statistically more effective in relieving pain than other modalities.

The authors concluded that, based on a convincing number of RCTs, the results suggested that botulinum toxin A injections did not result in any significant pain relief for patients with myofascial pain syndrome.

Study	QS	Conclusions	Level of Evidence
Zhang et al. (2011)	HQ (++)	• Botulinum toxin provided no statistically significant pain relief in patients with myofascial pain syndrome	1++
		• Botulinum toxin A may be effective in reducing pain in patients with mild to severe myofascial pain syndrome	1-
		• Botulinum toxin A may be effective in reducing pain when combined with lidocaine	1-

Langevin et al (2011)

Langevin et al (2011) (QS:HQ(++)) conducted a SR to assess the effect of intra-muscular botulinum toxin type A injections on pain, function/disability, global perceived effect and quality of life in adults with neck pain, for which eight of the studies specifically looked at myofascial neck pain (Cheshire et al 1994; Esenyel et al 2007; Ferrante et al 2005; Gobel et al 2006; Kamanli et al 2005; Lew et al 2008; Ojala, Arokoski & Partanen 2006; Wheeler, Goolkasian & Gretz 1998).

The results from these studies predominantly showed no statistically significant difference between the botulinum toxin A injection and the comparator. Four pieces of high quality evidence showed no short term statistically significant difference between botulinum toxin A and a placebo intervention. Two low quality pieces of evidence found no short term difference between botulinum toxin A paired with exercise compared to lidocaine and exercise. One very low quality piece of evidence showed no short term difference in disability or quality of life with botulinum toxin A and exercise compared to lidocaine and exercise. Two very low quality pieces of evidence found no difference in the short term when botulinum toxin A was paired with exercise and medication compared to exercise and medication alone. One very low quality piece of evidence showed a short term difference in pain but not in disability or quality of life when comparing botulinum toxin A with exercise to dry needling and exercise. One low quality piece of evidence showed no difference up to 6 months when botulinum toxin A was compared to a placebo.

In conclusion, in the short term there was no statistically significant difference between botulinum toxin A and its comparator treatments; one low quality piece of evidence showed this lack of difference remained up to 6 months.

Study	QS	Conclusions	Level of Evidence
Langevin et al. (2011)	HQ (++)	• Botulinum toxin A injection had no statistically significant different effect on pain when compared to placebo, exercise and medication, lidocaine and exercise and exercise and dry needling	1+
		• Botulinum toxin A injection had no short term difference when combined with exercise compared to exercise and lidocaine	1+
		• Botulinum toxin A showed no difference in pain compared to placebo at six months	1-

Mosshammer, Mayer & Joo (2013)

Mosshammer, Mayer & Joo (2013) (QS:HQ(++)) conducted a SR into local anaesthetic injection therapies for musculoskeletal disorders. Three studies were included that used botulinum toxin A as a comparator, two in regard to myofascial pain syndrome and one for myofascial pain with headaches (Gul & Onal 2009; Kamanli et al 2005; Venancio et al 2009).

As one of the studies did not differentiate the results of two other comparators, we are unable to extract the botulinum toxin A data. The other two studies looking at pain and pain intensity showed no statistically significant difference between the local anaesthetic injection and the botulinum toxin A injection.

Study	QS	Conclusions	Level of Evidence
Mosshammer, Mayer and Joo (2013)	HQ (++)	Botulinum toxin A was equally effective at reducing pain compared to local anaesthetic injections in patients with myofascial pain syndrome	1-

Desai et al (2014)

Desai et al (2014) (QS:AQ(+)) conducted a SR to evaluate the utility of botulinum toxin injections in treating cervico-thoracic myofascial pain syndrome. Seven prospective, double blind RCTs were identified and included within their review (Ojala, Arokoski & Partanen 2006; Ferrante et al. 2005; Wheeler, Goolkasian & Gretz 2001; Wheeler, Goolkasian & Gretz 1998; Gobel et al. 2006; Qerama et al. 2006; Lew et al. 2008). These studies were assessed for quality using the Cochrane assessment scale and the Agency for Healthcare Research and Quality (AHRQ) scale. On the Cochrane assessment scale, one study scored 3/11, two scored 4/11, three scored 7/11 and one scored 11/11. As for the AHRQ scale, four studies scored 7/10, two scored 8 and one scored 9.

The results from this review were mixed. No significant difference was found in six of the seven studies in regard to pain. One high quality RCT found that significantly more of the botulinum toxin A group reported mild or no pain compared with the placebo group at week five. The botulinum group also showed a significantly greater change from baseline score during weeks five to eight and reported significantly fewer days per week with pain between weeks five and twelve.

The authors of this review concluded that, even though the study of the highest quality produced positive findings, a greater number of higher quality studies are needed in order to reach a conclusion regarding the efficacy of this treatment modality.

Study	QS	Conclusions	Level of Evidence
Desai et al. (2014)	AQ (+)	• 6 of the 7 included studies found no statistical difference between Botulinum and the saline solution	1+
		• One study of high quality found that at week 5 the botulinum patients showed mild or no pain compared to the placebo group	1-
		• One study showed that botulinum group also had significantly greater change from baseline scores during week 5-8 and significantly fewer days per week with pain between weeks 5 and 12.	1-

Soares et al. (2014)

Soares et al. (2014) (QS:HQ(++)) conducted a systematic review looking into the effectiveness and safety of botulinum toxin A in the treatment of myofascial pain. Four studies were identified to be included in the review (De Andres 2010; Gobel 2006; Ojala, Arokoski & Partanen 2006; Qerema 2006). Overall, the authors deemed the studies to have good methodological quality.

The results showed that in one study (Gobel 2006), there was a significant improvement rate in the botulinum toxin A group for pain intensity and duration of pain scores compared to the placebo group. The other three studies showed no statistical difference in pain outcome when compared to the comparator. The treatments administered did not result in a significant improvement in participants' daily life activities or psychological status.

The authors concluded that there is limited evidence to support the use of botulinum toxin injections in the treatment of myofascial pain syndrome. However, some evidence shows some improvement in pain intensity and duration of daily pain in participants who received botulinum toxin A.

Study	QS	Conclusions	Level of Evidence
Soares et al. (2014)	HQ (++)	• 3 of the 4 studies showed no statistical difference in pain outcome when compared to the comparator	1
		• One study found a significant improvement rate with botulinum toxin A in pain intensity scores and duration of daily pain	1-

Randomised Controlled Trials

Eight RCTs that were not included in the previously reported systematic reviews were identified that investigated the effectiveness of botulinum toxin injections for myofascial pain. For this analysis we have reviewed the effectiveness of the botulinum toxin injections against baseline measures and then against other interventions or different techniques.

Intervention	Study	QS	Outcome measure	Result
Botulinum toxin Injection compared to placebo				
Botulinum toxin A 10 (400 units) fixed predetermined injection locations in head, neck and shoulders	Benecke et al. (2011)	HQ	Daily pain intensity, pain on palpation of cervical and shoulder muscles @ baseline 4, 8, 12 weeks	• @ 5/52 49% of BoNT-A group responded compared to 38% placebo – no statistical difference • @ 8/52 change in baseline pain intensity greater in BoNT-A group (P=0.008) • Duration of daily pain reduced @ 5/52 in BoNT-A group (p=0.04) • BoNT-A group sig more days per week without pain @ 4/52 and more days per week with mild pain @ week 8 • No difference between groups in duration of tension type headaches, time per week with migraine, duration of sleep
Botulinum toxin A (50 units) injected with EMG guidance for intra-muscular administration into 3 standardised points in each masseter muscle	Ernberg et al. (2011)	HQ	McGill pain Questionnaire, graded chronic pain scale, jaw disability checklist, symptom checklist-90 revised, RDC/TMD questionnaire, pain free jaw opening capacity, pain relied scale and 7 point PGIC scale. SCL-90R questionnaire, adverse events @ baseline, 1 month and 3 months	• No sig difference in pain reduction between botulinum toxin A and saline injection • botulinum had a clinically sig pain reducing effect (30%) at the one month follow up but this was not statistically different from saline. • no sig difference between groups regarding the effect on physical or emotional function, global improvement or other clinical measures
Botulinum Toxin A injection (20 Units) in most painful trigger points	Kwanchuay et al. (2015)	HQ	VAS (Pain) and pressure pain threshold (PPT) @ baseline, week 3 and week 6 post injection	• Mean VAS score (SD) = Botox group @ baseline 6.7 (1.2), 3/52 6.3 (1.2) 6/52 2.4 (2) • Saline group @ baseline 6.3 (1.2), 3/52 = 3.3 (2.8) 6/52 3.4 (3.6) • Mean PPT @ baseline, 3 and 6 week = Botox group 1.6 (0.4), 2.1 (0.6) and 2.6 (0.8) • Control group 1.7 (0.4), 2.0 (0.5) and 2.2 (0.7) • Within botox group, the data demonstrated sig VAS reduction and increased PPT and 3 and 6 week compared with before treatment ($p<0.05$) • control group also showed sig VAS reduction and increased PPT at 3 and 6 weeks compared with before treatment

Botulinum Toxin A - 25 units - maximum of 300 units per subject – fixed pattern	Nicol, Wu and Ferrante (2014)	LQ	pain (0-10 point scale) - brief pain inventory, postural analysis, health related quality of life, disability, headache, SF-36 (health related QoL) @ baseline, 6, 12 after first injection then 14,26 weeks phase two	• Week 26 compared to baseline, BoNT-A subjects had improved average pain scores (P=0.019) as measured by BPI • Trend toward improvement in worst BPI pain scores (p=0.052) no sig changes in 'best' VNS pain score or NDI were found • no sig difference between BoNT-A and placebo group using the SF-36 - BoNT-A group had improvement in the interference scores for general activity (p=0.046, 0.038,3.7) and sleep (p=0.02, 0.37, 4.33) • no sig findings found between treatment groups and physical examination findings • BoNT subjects had a reduction in the number of headaches experienced per week (p=0.04) • Both groups mean pain score decreased over time the botulinum toxin A group deceased sig more than the placebo group over time.

Botulinum toxin compared to placebo

- **No difference was found in pain reduction between placebo and botulinum toxin A for myofascial pain (2xHQ)**
- Botulinum Toxin A injections may be effective at reducing pain more than a placebo at 8 weeks (1xHQ)
- Botulinum Toxin A injections may be effective at reducing the duration of daily pain at 5 weeks (1xHQ)
- Botulinum Toxin A injections may be able to increase the days per week without pain or mild pain (1xHQ)
- There was no significant difference when comparing botulinum toxin A and a placebo in terms of effects on physical or emotional function, global improvement or other clinical measures (1xHQ, 1xLQ)
- Botulinum Toxin A may be able to reduce the frequency of headaches per week when compared to a placebo (1xLQ)

Intervention	Compar-ator	Study	Quality Score	Results
Botulinum compared to other intervention				
Botulinum toxin (150 units per side) minimum of 5 injections	Fascial manipulation	Guarda-Nardini et al. (2012)	LQ	• Botulinum group - VAS pain levels decreased from 7.3 @ baseline to 5.2 immediately post injection and 4.8 @ 3/12 • Fascial manipulation @ baseline VAS 6.0 reduced to 2.1 and 2.5 @ 3 months • Botulinum group showed slight increases in Jaw ROM parameters
Botulinum compared to other interventions				
• Both fascial manipulation and botulinum toxin injections were effective at reducing pain in individuals with fascial myofascial pain (1xLQ) • Botulinum toxin injections may be more effective at increasing jaw range of motion compared to fascial manipulation (1xLQ)				
Botulinum Toxin Dosage parameters				
Intramuscular injections in most painful trigger points (4 injections)	Dysport 200U compared to 320U	Jerosch et al (2012)	LQ	• Pain intensity scores= Dysport 200U @ baseline = 3.27, 7/52 = 2.36, @12/52 = 2.26 • Dysport 320U @baseline = 3.26 @ 7/52 = 2.28 12/52 = 2.02 • Mean duration of muscle pain per week (hours) = Dysport 200U @ baseline = 53.6, @ 7/52 = 36.4 @ 12/52 = 27.8

				• Dysport 320U = baseline 56.3, 7/52 = 35 12/52 = 24.7 • QoL scores (Sf-36) • Dysport 200U = 32.6 baseline, 6/52 = 38.4, 12/52 = 42.4 • Dysport 320U @ baseline = 32.5, 6/52 = 38.9, 12/52 = 43 • No sig differences were found between groups • More adverse events in Dysport 320U group compared to 200U
Treatment administered by injection at four trigger points - two different muscles on one or both sides of the body	Botulinum Toxin (240U, 320U and 480U Dysport)	Muller-Schwefe & Uberall (2011)	AQ	• Percentage change in weekly median pain intensity scores at rest and on movement decreased after injection in all treatment groups and in all groups combined - no sig difference among the three dose group. • PDI median percentage change score from baseline was -23.4% for the combined group and was similar in all treatment groups. • Pain intensity score percentage decreased was -17.9% (-100.00% to +425.0%) and on movement -17.6% (-100.00% to +100.00%) at week 6. • Adverse events by dosage: 240U = 12; 320U = 21; 480U = 12
Botulinum Toxin Dosage Parameters • Botulinum Toxin Injections ranging from 200 Units to 480 units were effective at reducing pain with no significant difference between the groups (1xAQ, 1xLQ) • Botulinum toxin dosages of 320U may produce more adverse events than lower dosages (1x AQ, 1xLQ)				
Botulinum toxin – As an adjunct therapy (i.e. exercise with and without botulinum toxin)				
Botulinum toxin with low intensity electrical stimulation	Botulinum toxin with high intensity electrical stimulation	Seo et al. (2013)	LQ	• The VAS scores were sig lower at weeks 4,8,12 and 16 than at baseline in both the groups ($p<0.05$) • treatment success rates were sig higher in the group with a lower electrical stimulation intensity than in the higher intensity group at week 12 (78.9% vs 58.8%, p = 0.039) and week 16 (76.3% vs 51.4%, p=0.024) • Sig changes in the NPAD score over time where noted only in the sensory group at weeks 8, 12 and 16 ($p<0.05$) • The NPAD score at week 16 was sig lower in the lower intensity group (15.44%; 95% CI 12.16 - 18.72) than in higher intensity group 21.21%; 95% CI 16.60 - 25.82) (p=0.041)
Botulinum toxin – As an adjunct therapy (i.e. exercise with and without botulinum toxin) • Botulinum toxin with electrical stimulation at lower intensities was more effective at decreasing pain and decreasing scores on the neck pain and disability index than botulinum toxin with higher intensities of electrical stimulation (1xLQ)				

3.5 Outcome Measures – Safety and Risk

Desai et al (2014) conducted a SR into the evidence for botulinum toxin type A in the treatment for cervico-thoracic myofascial pain syndrome. One of the studies (Ojala, Arokoski & Partanen 2006) reported no significant differences in the prevalence of side effects between the saline and the botulinum toxin A group. Most of these side effects were minor and short lived. Pain at the injection site was reported and other side effects included vertigo, sweating, fatigue of the hands, headache and swelling of the eyelids. Three subjects in the Ferrante trial experienced flu-like symptoms. Wheeler, Goolkasian & Gretz (1998) reported that more adverse events occurred in the botulinum group compared to the saline group. The most frequent events were weakness of the injected muscles, pain or soreness in the

injection site and flu like symptoms. Wheeler, Goolkasian & Gretz (2001) reported mild adverse events in the botulinum group. Two subjects reported transient ipsilateral arm heaviness and numbness, which resolved after one week. Two further subjects noted transient discomfort opposite the injection site and two others reported a shift in their pain. The last study reported a total of 65 adverse events, 31 of those being in the botulinum group. Most were mild or moderate, the most common being muscle soreness, but this was the same in both groups.

Langevin et al (2011) pooled the data from their SR and reported an estimated 30% adverse event rate. Adverse events reported included transient effects of injection site soreness, shoulder or arm weakness, fatigue, heaviness, numbness, flu-like symptoms, systemic fever, shivering, generalised muscle soreness, vertigo and headache.

Soares et al (2014) conducted a SR into botulinum toxin for myofascial pain syndrome in adults. The authors reported that there were significantly more adverse events from botulinum toxin A than placebo in one of the studies (Gobel 2006). The most common adverse event was sore muscles, of mild to moderate severity, and one participant in each treatment arm withdrew from the study due to adverse events. In the other studies, the adverse event rates were similar in both groups (De Andres 2010; Ojala, Arokoski & Partanen 2006; Qerama et al 2006).

Zhang et al (2011) found that most studies reported either no side effects following botulinum toxin injection, or transient side effects that resolved spontaneously. In one of the included trials (Nixdorf et al 2002), three patients who received botulinum toxin injections dropped out of the study due to paralysis and increased pain.

Benecke et al (2011), during a RCT looking at efficacy of botulinum type A injection for myofascial pain syndrome affecting the cervical muscles of the back and shoulders, found that 24 of the patients treated with BoNT-A experienced 33 adverse events. This number was not statistically different from the placebo group. The majority of the adverse events were mild or moderate in severity. The most commonly experienced were musculoskeletal, connective tissue and bone disorders (42%). No serious events occurred during the study and no patients withdrew from the study due to adverse events.

Ernberg et al (2011) conducted a RCT looking at botulinum toxin type A for temporomandibular myofascial pain. The authors found that patients reported side effects in the first week, but these were unrelated to the drug. The most frequently reported side effect was headache, with seven botulinum and nine saline patients reporting this. Two patients reported tiredness or fatigue, three patients reported jaw pain, two patients reported influenza-like symptoms and one patient reported dry mouth. All side effects resolved at the one month follow up.

Jerosch et al (2012) conducted a study using intramuscular injections of two different dosages of botulinum toxin (Dysport). They found that at least one treatment-emergent adverse event, judged as possibly or probably related to the study medication, was experienced by 24% of Dysport 200U and 33% of Dysport 320U participants. The most frequent adverse events were injection site pain (4.9% and 6.1% respectively), muscular weakness (1.2% and 6.1%). From these events, injection site pain was considered to be severe in three patients and muscular weakness severe in two patients. No serious or significant adverse events that occurred were considered to be related to the study treatment.

Kwanchuay et al (2015) conducted a RCT using botulinum type A injections for chronic myofascial pain syndrome of the upper trapezius muscle and reported that 45.8% of the patients in the treatment group had non-severe adverse effects after a few days of the injection. One patient had 2cm of skin redness around the injection site, two patients felt feverish for one day, four patients felt tight on the injection site for one day, three patients felt stiff on the injected shoulder for two days and one patient had skin redness and felt stiff. 41.7% of the placebo group (saline injection) also had non-severe adverse events.

Muller-Schwefe & Uberall (2011), within their RCT comparing three different dosages (Botulinum 240, 320 and 480U), found that 31.7% of patients reported an adverse event; this proportion was higher in the medium dose group (36.8%) compared to the low dose group (28.1%) and high dose group (30.7%). The most frequently reported adverse events were influenza-like symptoms, which occurred in eight patients. A total of 16 adverse events were considered possibly or probably related to treatment and included back pain, dizziness, eye irritation, headache, infection, influenza-like symptoms, ischial neuralgia, lumbo-sacral pain, nausea, pain, pain in legs, photophobia, tiredness, blurred vision and vomiting. One serious adverse event (severe lumbosacral pain in the medium dose group) was considered to be possibly related to the study treatment.

Nicol, Wu and Ferrante (2014) conducted a two-phase RCT using botulinum toxin A with individuals with cervical and shoulder girdle myofascial pain syndrome. The authors found that there was a low incidence of adverse effects including nine individuals with a flu-like illness, one case of arthralgia and four of fatigue. Twenty nine patients reported a mild and vague sensation of weakness in the neck; four of these reported it to be a significant weakness, where the description of weakness was such that when the participant bent forward to brush their teeth they would have a sensation that their head was flopping forward. All patients who reported weakness had their symptoms resolve in 7-10 days.

Seo et al (2013) conducted a RCT using botulinum toxin A and two different intensities of electrical stimulation for patients with chronic myofascial pain syndrome of the neck and shoulders. A total of seven adverse events occurred, with one reported as being possibly due to a relationship with the treatment: this was a spontaneous abortion. There were some minor symptoms of short duration after the treatment, such as pain at the injection site. All patients recovered from the adverse events.

3.6 Economic analysis

This review found no evidence published since 2011 investigating cost-benefits associated with use of botulinum toxin injections as a interventional pain management technique for people with myofascial pain.

4. Recommendations

1. **The evidence indicates that for cervico-thoracic specific myofascial pain syndrome there is no statistically significant difference in pain reduction between botulinum toxin injections and saline solution injections.** Level A recommendation based on one HQ SR with Level 1+ evidence (Langevin et al 2011), one AQ SR with level 1+ evidence (Desai et al 2014), one HQ RCT and one LQ RCT.

2. **The evidence indicates that for temporomandibular myofascial pain there is no statistically significant difference in pain reduction between botulinum toxin A injections and saline solution injections or fascial manipulation.** Level B recommendation based on results from one HQ RCT (Ernberg et al 2011) and one LQ RCT (Nicol, Wu and Ferrante 2014).

3. **The evidence indicates that for general myofascial pain syndrome botulinum toxin injections provide no statistically significant pain relief.** Level A recommendation based on one HQ SR with level 1++ evidence (Zhang et al 2011) and one HQ SR with level 1 evidence (Soares et al 2014).

4. **The evidence indicates that there is no difference in pain reduction when comparing dosages of 200 units to 480 units of botulinum toxin.** Level C recommendation based on one AQ RCT (Muller-Schwefe & Uberall 2011) and one LQ RCT (Jerosch et al 2012).

5. **The evidence indicates that there is no difference in pain reduction when using fixed point, intra-muscular or trigger point injection methods.** Level C recommendation based on three HQ RCTs (Benecke et al 2011, Ernberg et al 2011, Kwanchuay et al 2015) and one LQ RCT (Nicol, Wu and Ferrante 2014).

6. **The evidence indicates that there are no significant differences between injections of botulinum toxin and saline in terms of physical or emotional function or global or quality of life scores.** Level C recommendation based on one HQ RCT (Ernberg et al 2011).

7. **The evidence suggests that botulinum toxin injections may be associated with more adverse events compared to placebo.** Level B recommendation based on one HQ SR (Soares et al 2014). **However, these adverse events are transient and resolve spontaneously.** Level A recommendation based on one HQ SR (Langevin et al 2011), one AQ SR (Desai et al 2014) and two HQ RCTs (Ernberg et al 2011, Kwanchuay et al 2015).

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6. Appendices

Appendix 1 – 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 □ No □ Not applicable □ **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 □ No □ Can't say □ 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 2 – Quality scores for articles used in this review
SIGN Critical Appraisal Tool scores for Systematic Reviews

Quest	Reference (Author, year)	Desai 2014	Langevin (2011)	Mosshammer, Mayer & Joas (2013)	Soares et al 2014	Zhang et al 2011
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	Y	Y	Y	Y
1.2	A comprehensive literature search is carried out?	Y	Y	Y	Y	Y
1.3	At least two people should have selected studies	CS	Y	Y	Y	Y
1.4	At least two people should have extracted the data	Y	Y	Y	Y	Y
1.5	The status of publication was not used as an inclusion criterion	N	Y	N	Y	N
1.6	The excluded studies are listed	N	N	N	Y	Y
1.7	The relevant characteristics of the included studies are provided	Y	Y	Y	Y	Y
1.8	The scientific quality of the included studies was assessed and reported.	Y	Y	Y	Y	Y
1.9	Was the scientific quality of the included studies used appropriately?	Y	Y	N	Y	N
1.10	Appropriate methods are used to combine the individual study findings	NA	Y	Y	NA	Y
1.11	The likelihood of publication bias was assessed appropriately	N	N	Y	N	Y
1.12	Conflicts of interest are declared	N	N	N	N	Y
2.1	What is your overall assessment of the methodological quality of this review?	A	HQ	HQ	HQ	HQ

SIGN Critical Appraisal Tool scores for controlled trials

Quest	Reference (Author, year)	Benecke et al. 2011	Ernberg et al. 2011	Guarda-Nardini et al 2012	Jerosch et al 2012
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	Y	CS	CS
1.3	An adequate concealment method is used.	Y	Y	N	N
1.4	The design keeps subjects' and investigators 'blind' about treatment allocation.	Y	Y	N	N
1.5	The treatment and control groups are similar at the start if the trial.	Y	Y	CS	CS
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.	CS	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?	0%	Case: 0% Control: 8% (1 drop out)	0%	Dysport 200U 7% Dysport 320U 6%
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	CS	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	CS	CS	NA	CS
2.1	How well was the study done to minimise bias?	HQ	HQ	LQ	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	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	10 fixed location injection of 40U of BoNT A produced improvements in pain control for 8 weeks	BoNT A is not efficacious as adjunct to conservative treatment in patients withTMJ pain.	BoNT A and fascial manip both improved pain levels. In the short term both treatments equally effective.	Both Dysport 200U and 320U provided relief from chronic MPS in neck and shoulder girdle for at least 3 months.

Quest	Reference (Author, year)	Kwanchuay et al 2015	Muller-Schwefe & Uberall 2011	Nicol et al 2014	Seo et al 2013
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	Y	CS	CS
1.3	An adequate concealment method is used.	Y	N	N	CS
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	Y	Y	Y
1.6	The only difference between groups is the treatment under investigation.	Y	CS	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?	0%	Dysport 240U = 2% Dysport 320U = 5% Dysport 480 = 5%	3 of 57 – no details for which group	Motor Group = 13% Sensory Group = 11%
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	CS	Y	CS	Y
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	NA	CS	NA	NA
2.1	How well was the study done to minimise bias?	HQ	A	LQ	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	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	botulinum toxin A in VAS reduction was not statistically different from saline placebo. Botulinum was able to demonstrate statistically significant increase in pressure pain threshold at 6 weeks post injection	Treatment with BoNT-A using a four-trigger point injection protocol at 60U per trigger point was associated with a clinically relevant and statistically significant improvement in pain and pain related disability. Higher doses did not increase pain relieving effect.	Joint lavage combined with triamcinolone hexacetonide does not present a greater benefit over intra-articular injection with triamcinolone hexacetonide alone for primary osteoarthritis of the knee.	Short term electrical stimulation may affect pain reduction after botulinum toxin A injection at trigger point in patients with chronic MPS of the neck. Unclear if electrical stimulation facilitates or attenuates the effect of botulinum on MPS

Appendix 3 – Data Extraction table used in this review

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Benecke et al	2011	prospective, randomised, double blind placebo controlled RCT	10 fixed predetermined injection sites in head, neck and shoulders	Botulinum toxin type A (400 units of dysport) compared to placebo (saline)	No anaesthetic	Daily pain intensity, pain on palpation of cervical and shoulder muscles, adverse events @ baseline, week 4,8, 12	@ week 5 49% of BoNT-A group had responded compared to 38% placebo (p=0.1873) from week 4 to 11 no statistically significant differences in responders @ week 8, improvement in change from baseline in pain intensity over time were significantly greater for BoNT-A than placebo (p=0.008) duration of daily pain was reduced in the BoNT-A group from week 5 - statistically significant difference @ week 9 and 10 (p=0.04) for both BoNT-A group experienced significantly moer days per week without pain at week 4 (p=0.04) and significantly more days per week with no or mild pain at week 8 (p=0.03)	Patients with upperback myofascial pain syndrome using BoNT-A at predetermined injections sites rather than trigger points can produce pain improvements and the injections were well tolerated	no differences were found between groups in duration of tension type headaches, time per week with migraine, duration of sleep	62 adverse events reported during the study with no statistical difference between the treatment and the placebo group		N= 154 Age (standard error) = 48 (13) BoNT-A group and 45 (10) placebo group	myofascial pain syndrome affecting cervical muscles of the back and shoulders

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Ernberg et al.	2011	double blind, placebo controlled, crossover multicenter RCT	EMG guided intramuscular injections - 3 standardised points in each masseter muscle	Botulinum toxin A (50 units)	No Anaesthetic	McGill pain Questionnaire, graded chronic pain scale, jaw disability checklist, symptom checklist-90 revised, RDC/TMD questionnaire, pain free jaw opening capacity, pain relied scale and 7 point PGIC scale. SCL-90R questionnaire, adverse events @ baseline, 1 month and 3 months	No significant difference in pain reduction between botulinum toxin A and saline injection botulinum had a clinically significant pain reducing effect (30%) at the one month follow up but this was not statistically different from saline.	Authors concluded that botulinum type A is not efficacious as an adjunct to conservative treatments in patients with persistent myofascial TMD pain	no significant difference between groups regarding the effect on physical or emotional function, global improvement or other clinical measures	14 adverse reactions were reported for the botulinum group compared to 14 in the saline group		N=21 Age (SD) = 38 (12), study didn't differentiate between groups	temporomandibular disorder - myofascial TMD pain

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Guarda-Nardini et al.	2012	Randomised Controlled Trial	5 injections minimum -	Botulinum Toxin (approx 150 units)	No Anaesthetic	VAS (pain)@ baseline, 1 hour post intervention and 3 month follow up.	Both treatments provided significant improvement over time as to pain symptoms. Botulinum group - VAS pain levels decreased from 7.3 @ baseline to 5.2 immediately post injection and 4.8 @ 3/12 Fascial manipulation @ baseline VAS 6.0 reduced to 2.1 and 2.5 @ 3 months Botulinum group showed slight increases in Jaw ROM parameters	Both treatments may be useful in reducing pain symptoms in patients with myofascial pain of the jaw muscles between group differences were not significant Jaw ROM - both groups of patients had mouth opening, laterotrusion and protrusion values within the physiological range - Botulinum toxin group showed more marked positive changes but not relevant enough for clinically orientated discussion	Jaw ROM @ baseline and 3 month follow up	Nil reported		N = 30 Age (SD) = 47.7 (14.3) botulinum group and 43.2 (13.9) Myofascial manipulation group	temporomandibular disorder - myofascial TMD pain

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Jerosch et al.	2012	Open label, multicentered, randomised controlled trial	Intramuscular injections (4) into most painful trigger points on each side of the body	Two dosages - Dysoport 200U or Dysport 320U	Nil	Pain intensity (four point scale) rated daily @ one week prior to treatment to 12 weeks post treatment	pain intensity scores= Dysport 200U @ baseline = 3.27, 7/52 = 2.36, @12/52 = 2.26 Dysport 320U @baseline = 3.26 @ 7/52 = 2.28 12/52 = 2.02 Mean duration of muscle pain per week (hours) = Dysport 200U @ baseline = 53.6, @ 7/52 = 36.4 @ 12/52 = 27.8 Dysport 320U = baseline 56.3, 7/52 = 35 12/52 = 24.7 QoL scores (Sf-36) Dysport 200U = 32.6 baseline, 6/52 = 38.4, 12/52 = 42.4 Dysport 320U @ baseline = 32.5, 6/52 = 38.9, 12/52 = 43 No significant differences were found between groups	Authors concluded that Dysport 200U and 320U provided effective relief from chronic MPS in the neck and shoulder girdle	QoL Sf-36	24% of Dysport 200 and 33% of Dysport 320 experienced a adverse event that was possibly or probably related to the treatment medication		N=163 Mean age 51	Myofascial pain syndrome in the neck

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Kwanchuay et al.	2015	Randomised, double blind, placebo controlled trial	single injection into most painful myofascial trigger point	Botulinum toxin type A (20 units)	Nil	VAS (Pain) and pressure pain threshold (PPT) @ baseline, week 3 and week 6 post injection	Mean VAS score (SD) = Botox group @ baseline 6.7 (1.2), 3/52 6.3 (1.2) 6/52 2.4 (2) Saline group @ baseline 6.3 (1.2), 3/52 = 3.3 (2.8) 6/52 3.4 (3.6) Mean PPT @ baseline, 3 and 6 week = Botox group 1.6 (0.4), 2.1 (0.6) and 2.6 (0.8) Control group 1.7 (0.4), 2.0 (0.5) and 2.2 (0.7) Within botox group, the data demonstrated statistically significant VAS reduction and increased PPT and 3 and 6 week compared with before treatment ($p<0.05$) control group also showed statistically significant VAs reduction and increased PPT at 3 and 6 weeks compared with before treatment	No statistically significant difference in VAS reduction (mean difference) from baseline between the two groups, at 3 and 6 week after treatment Statistically significant difference in higher PPT (mean difference) from baseline and 6 week after botox compared with saline group (-0.5 95% CI = -0.9, -0.1 p = 0.036)	Nil	45.8% of botox and 41.7% of saline group had non-severe adverse events		N= 33 Mean age (SD) = 39.8 (10.1) botox group and 38.8 (10.8) Placebo group	Chronic myofascial pain syndrome of upper trapezius muscles

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Muller-Schwefe & Uberall	2011	open-label, prospective randomised controlled trial	Treatment adminsitered by injection at four trigger points - two different muscles on one or both sides of the body	Botulinum Toxin (Dysport) three different dosages - 240U, 320U and 480U	Nil	Pain diary, pain disability index, patient and investigator global assessment of efficacy, pain pressure threshold and tissue compliance	Percentage change in weekly median pain intensity scores at rest and on movement decreased after injection in all treatment groups and in all groups combined - no significant difference among the three dose group. PDI median percentage change score from baseline was -23.4% for the combined group and was similar in all treatment groups. Pain intensity score percentage decreased was -17.9% (-100.00% to +425.0%) and on movement -17.6% (-100.00% to +100.00%) at week 6.	results showed a significant reduction in patient reported pain intensity after injection at four trigger points, for all three doses investigated (4x60, 4 x 80, 4 x 120 units of Dysport). Reduction in pain of approximately 20% at rest and on movement were reported by patients 6 weeks after treatment assessed using the pain diary. reduction of pain were evident after the first week of dosingm with the positive effect of treatment maintained until week 6 and up to the study endpoint (week 12)	Nil	31.7% of patients reported an adverse event, proportion was higher in the medium dose group (36.8%) comapred to the low dose group (28.1%) and high dose group (30.7%)		N = 189 Mean age (SD) 55.2 (11.32) 240U Dysport, 55.2 (12.76) 320U Dysport, 52.7 (13.18) 480U Dysport	Myofascial back pain > 3 weeks

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Nicol, Wu and FErrante	2014	Enriched Protocol two phase study second phase prospective, randomized double blind and placebo controlled trial	Fixed pattern, variable dose injection - painful muscles injected mid belly	Botulinum Toxin A - 25 units - maximum of 300 units per subject	nil	pain (0-10 point scale) - brief pain inventory postural analysis, health related quality of life, disability, headache, SF-36 (health related QoL) @ baseline, 6, 12 after first injection then 14,26 weeks phase two	Week 26 compared to baseline, subjects who received BoNT-A had improved average pain scores (P=0.019, 0.26, 2.78) as measured by the BPI there was a trend toward improvement in worst BPI pain scores (p=0.052, -0.019, 3.46) no significant changes in 'best' VNS pain score or NDI were found no significant difference between BoNT-A and placebo group using the SF-36 - BoNT-A group had improvement in the interference scores for general activity (p=0.046, 0.038,3.7) and sleep (p=0.02, 0.37, 4.33) no significant findings found between treatment groups and physical examination findings BoNT subjects had a reduction in the number of headaces experienced per week (p=0.04, 0.07, 4.55) both groups mean pain score decreasd over time the botulinum toxin A group deceased significnatly more than the placebo group over time.	results suggest that injection of BoNT-A into painful muscle groups of the neck ad shoulder area improves pain relief in subjects with cervical and shoulder girdle myofascial pain syndrome subjects who received a second dose of BoNT-A in the second phase of the study had continued dramatic improvement in their pain scores, which was statistically significant compared to those who received placebo	Reduction over the 26 week time period in the interferance of chronic pain for general activity and sleep in the BoNT-A group second phase of the study was anaylzed for QoL measures , there was worsening in physical functioning in those subjects who received placebos compared to BoNT-A	Low incidence of adverse effects		N=114 57 deemed to be responders 29 received a second injection age = 47.8 for phase 1 phase 2 = 47.4 (14.9) for placebo group then 48.8 (16.2) BoNT-A group	Cervical and shoulder girdle myofascial pain syndrome

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES:	Safety and Risk	Imaging	Patient	Pathology
Seo et al	2013	Randomised double blinded study	3 (6 when bilateral) most painful and active trigger points were injected	Botulinum Toxin A (Dysport) injection approx 80 to 160U at each trigger point	Nil	VAS (pain), modified version of the neck pain diability scale, global assessment of improvement scale, pressure pain threshold @ baseline, 1 and 3 days and 1,3,4,8,12, 16 weeks post injection	The VAS scores were significantly lower at weeks 4,8,12 and 16 than at baseline in both the groups ($p<0.05$) treatment success rates were significantly higher in the group with a lower electrical stimulation intensity than in the higher intensity group at week 12 (78.9% vs 58.8%, $p = 0.039$) and week 16 (76.3% vs 51.4%, $p=0.024$) Significant changes in the NPAD score over time where noted only in the sensory group at weeeks 8, 12 and 16 ($p<0.05$)	Authors concluded that the results show that the intensity of pain was significantly reduced from week 4 to week 16 after botulinum toxin A injection at trigger points in patients with Chronic MPS of the neck and shoulder region	The NPAD score at week 16 was significantly lower in the lower intensity group (15.44%; 95% CI 12.16 - 18.72) than in higher intensity group 21.21%; 95% CI 16.60 - 25.82) ($p=0.041$)	total of 7 adverse events in 6 patients. Possible relationship between the treatment and a spontaneous abortion. Some minor symptoms of short duration after the treatment, such as pain at the injection site		N=76	Chronic myofascial pain syndrome of the neck and shoulder region

Appendix 4 – Systematic Review findings

Author and year	SIGN Score	Studies	Outcome	Conclusions	Evidence 1	2	3	4	Grade
Myofascial pain									
Desai et al. (2014) *Utility of Botulinum toxin in treating cervico-thoracic myofascial pain syndrome*	AQ	7 RCTs	Pain, QoL, Neck pain and disability	Five out of four trials showed no difference between botulinum injection or placebo injection	0	1	1	1	1+
				The role of botulinum injection in reducing pain was not supported	0	1	1	1	1+
				One study found that botulinum showed a trend toward improvement in ROM and reduction of pain at two weeks post injection and at four weeks there were statistically significant pain score differences in the botulinum group	0	1	0	0	1-
				One study botulinum group had significantly greater change from baseline scores during week 5-8 and significantly fewer days per week without pain between weeks 5 and 12	0	1	0	0	1-
Langevin et al. (2011) *Botulinum toxin intra-muscular injections for neck pain*	HQ	8 RCTs	Pain, disability, QoL, GPE	Botulinum toxin A injections had no statistical differenece in pain when compared to placebo, exercise and medication, lidocaine and exercise and dry needling	0	1	1	1	1+
				Botulinum toxin A injections had no short term difference when combined with exercise compared to exercise and lidocaine	0	1	1	1	1+
				Botulinum toxin A showed no difference in pain compared to placebo at 6 months	0	1	0	0	1-
Masshammer, Mayer & Joo (2013) *Comparing botulinum toxin injections to local anaesthetics in patients with myofascial pain syndrome*	HQ	3 RCTs (2 with extractable data)	Pain	Botulinum was equally as effective at reducing pain compared to local anaesthetic injections in patients with myofascial pain syndrome	0	1	0	0	1-

Author and year	SIGN Score	Studies	Outcome	Conclusions	Evidence				Grade
					1	2	3	4	
Soares et al. (2014) *Effectiveness and safety of botulinum toxin A in the treatment of myofascial pain*	HQ	4 RCTs	Pain, Pressure pain detection threshold in trigger point, pressure pain tolerance in trigger point, ROM	3 of 4 studies showed no statistical difference in pain outcome when compared to the comparator	0	1	0	1	1
				One study found a significant improvement rate with botulinum toxin A in pain intensity scores and duration of daily pain	0	1	0	0	1-
Zhang et al. (2011) *Effectiveness of botulinum toxin type A injection versus non-active injection or other treatment in reducing myofascial pain*	HQ	12 RCTs	Pain	• Bptulinum toxin provided no statistically significant pain relief in patients with myofascial pain syndrome	1	1	1	1	1++
				• Botulinum toxin A may be effective at reducing pain in patients with mild to severe myofascial pain syndrome	0	1	0	0	1-
				• Botulinum toxin A maybe effective in reducing pain when combined with lidocaine	0	1	0	0	1-