International Centre for Allied Health Evidence

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Systematic Review of the Literature

The Effectiveness of Injection of Botulinum Toxin for Neck 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	**NSAIDs**	Non-Steroidal Anti-Inflammatory Drugs
ACH	Acetylcholine	**PICO**	Population, Intervention, Comparator, Outcome
AHRQ	Agency for Healthcare Research and Quality	**QALY**	Quality-Adjusted Life Years
BoNT-A	Botulinum Toxin A	**QoL**	Quality of Life
BoNT-B	Botulinum Toxin B	**RCT**	Randomised Controlled trial
Botox	Botulinum Toxin	**ROM**	Range Of Movement
BPI	Brief Pain Inventory	**RR**	Risk Ratio
CD	Cervical Dystonia	**SF-36**	36-Item Short Form Health Survey
EMG	Electromyography	**SIGN**	Scottish Intercollegiate Guidelines Network
EUR	Euro	**SMD**	Standard Mean difference
GRADE	Grading of Recommendations Assessment, Development and Evaluation	**SR**	Systematic Review
MA	Meta-Analysis	**TrPS**	Trigger Point
MPS	Myofascial Pain Syndrome	**TWSTRS**	Toronto Western Spasmodic Torticollis Rating Scale
MRI	Magnetic Resonance Imaging	**US**	Ultrasound
NDI	Neck Disability Index	**USA**	United States of America
NMJ	Neuromuscular Junction	**VAS**	Visual Analogue Scale
NPAD	Neck Pain and Disability Scale	**VNS**	Visual Numerical Scale
NRS	Numerical Rating Scale	**WAD**	Whiplash-Associated Disorder
	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 neck 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 neck pain? 2. What is the evidence for the safety of botulinum toxin injections for neck pain?
Evidence sourced	The search yielded 277 articles. After scrutiny, 257 articles were excluded as duplicates or for failing to meet the inclusion criteria (shown in Figure 1), leaving 20 studies for inclusion in this review including 13 systematic reviews (SRs) and 7 randomised controlled trials (RCTs).
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?	***Cervical Dystonia*** • **Botulinum toxin injection showed higher improvement from baseline than placebo in the short term for cervical dystonia** (Level A Recommendation) • **Botulinum toxin A and botulinum toxin B are equally effective and safe for the treatment of cervical dystonia** (Level B recommendation) • **A single botulinum toxin B treatment session is associated with a significant and clinically relevant reduction of cervical dystonia impairment across all outcomes when compared with placebo** (Level A recommendation) • **Botulinum toxin B treatment for cervical dystonia is associated with a higher risk of dry mouth compared to botulinum toxin A** (Level A recommendation) • **240U and 120U incobotulinum toxin injections were comparable at four weeks post** injection (Level C recommendation) ***Myofascial Pain*** • **No short-term pain relieving benefit for botulinum toxin-A compared to saline for neck pain** (Level A recommendation) • **Botulinum toxin A injection had no statistical difference in pain when compared to placebo, exercise and medication, lidocaine and exercise and exercise and dry needling** (Level A recommendation) • **Botulinum toxin injections ranging from 200 units to 480 units were effective at reducing pain with no significant difference between the groups** (Level D recommendation) • **There was no significant difference when comparing botulinum toxin A and a placebo for the effect on physical or emotional function, global improvement or other clinical measures for myofascial pain** (Level D recommendation)

	Whiplash-associated Disorder • **Botulinum toxin injection type A failed to confirm a clinical or statistically significant benefit for whiplash-associated disorder when compared with placebo and other treatments** (Level A recommendation)
What is the evidence for the safety of botulinum toxin injection?	**Adverse events reported included: injection site soreness, dry mouth, dysphagia, fatigue, heaviness, numbness, flu-like symptoms, systemic fever, shivering, generalised muscle soreness, vertigo and headache** (Level A recommendation) **Most adverse events were considered mild or moderate. Serious adverse events were transient and rare** (Level A recommendation)
Does the evidence report any information about cost effectiveness?	**There is a lack of evidence related to the cost- effectiveness of the use of botulinum toxin A or B for cervical dystonia, myofascial pain syndrome and whiplash associated disorder.**
Do the recommendations differ from the 2011 report?	**2005 Summary of Evidence** "The routine use of botox injections for the treatment of neck pain cannot be recommended due to conflicting evidence." **2011 Recommendation** "The evidence suggests that Botox injections are effective for short term relief of pain associated with cervical dystonia, however they cannot be recommended for the management of neck pain associated with myofascial pain syndrome or whiplash associated disorders".

1. Background

1.1 Objective of this Review

The objective of this review is to synthesise the evidence 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 neck pain?
b) What is the evidence for the effectiveness of botulinum toxin injections in improving functional outcomes in patients with neck pain?
c) What is the evidence for the safety of botulinum toxin injections?

1.2 Description of the Intervention

A range of conditions have been reported in the literature related to the use of botulinum toxin injections for neck pain. These include cervical dystonia, myofascial pain syndrome and whiplash-associated disorder.

Cervical Dystonia:

After Parkinson's disease and essential tremor, dystonia is the third most common movement disorder (Steeves et al 2012). This movement disorder is characterised by involuntary muscle contractions which occur in the face, neck, trunk, or limbs (Albanese et al 2013).

Cervical dystonia is the most common form of focal dystonia, being a dystonia focused on one body region, with up to 280 patients per million in the USA (Jankovic et al 2006). Specifically, cervical dystonia can be characterised as abnormal movement or posturing of the head, neck, and shoulders (Foltz et al 1959) and may be accompanied by spasm, jerking, tremors. Cervical dystonia is almost always accompanied by pain (Chan et al 1991; Marques et al 2016).

Cervical dystonia may be classified into common postures of muscle spasm – torticollis (head rotated), laterocollis (head tilted to the side), anterocollis (head tilted forward; flexion), and retrocollis (head tilted backward; extension) (Mordin et al 2014). Diagnosis of cervical dystonia generally is based on the deviation from normal neck posture and clinical symptoms such as involuntary neck movements (Geyer & Bressman 2006). It is mostly a life-long disorder (Jahnanshani et al 1990) and there are currently no curative or disease-modifying treatments available (Marques et al 2016). The exact cause of cervical dystonia is unknown, though it is thought to be caused by abnormal sensorimotor integration from the central nervous system (Hallett et al 1998), brain injury, infection, drugs, toxins, other disorders such as a vascular disorder, or possibly even inherited (Albanese et al 2013; Balint et al 2015).

Myofascial Pain Syndrome:

Myofascial pain syndrome (MPS) is a condition where pain originates in the myofascial tissue (Roldan & 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 (Roldan & Hu 2015; Simons 1997).

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 patterns 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).

Whiplash-associated disorder:

Whiplash-associated disorder (WAD) is a common source of neck pain which can be diagnosed as localized spasm and tenderness of the neck which limits active range of motion (van Suijlekom et al 2011). It is most commonly caused by a sudden acceleration or deceleration motion, and is therefore often associated with car accidents (van Suijlekom et al 2011).

Botulinum Toxin Injection:

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 around 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, this weakening effect then continuing from 6 weeks to 6 months (median 304 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 botulinum injections in patients with neck 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.

2.3 Search strategy

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 with or without local anaesthetic as a form of interventional pain management for neck 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

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,
- TRIP database

Table 2: Search terms for the review

Search term 1	Search terms 2	Search terms 3	Search terms 3
• Neck pain • Cervical pain • Neckache • Neck-ache	• 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, all primary research designs - randomised controlled trials (RCTs), cohort studies (prospective or retrospective), case studies or case series.
- Participants: Patients with neck pain.
- Intervention: Botulinum toxin injections
- Controls: Any active treatment or placebo, or no intervention control.
- Outcomes: Pain 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 non-English language material
- Studies involving healthy volunteers or experimentally induced pain
- Studies on interventions involving other techniques where neck pain 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 their 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 these questions, of either high (++), acceptable (+), low (-) or unacceptable quality. As there is no SIGN checklist for case studies, these study designs will not be quality scored

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 was extracted from individual studies:

- Evidence source (author, date, country)
- Level of evidence
- Characteristics of participants
- Interventions
- Outcome measures
- Results

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 potential 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 277 articles; following removal of duplicates 174 articles were identified for screening of title and abstract. After scrutiny, 154 articles were excluded for failing to meet the inclusion criteria (shown in Figure 1), leaving 20 studies for inclusion in this review. Figure 1 illustrates the process involved in study selection.

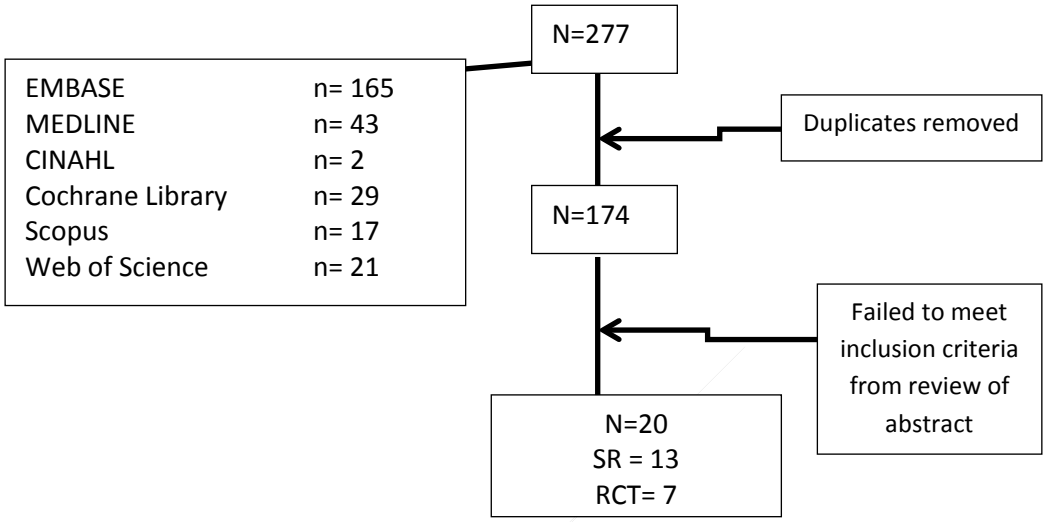

Figure 1: Flow chart of search results

3.2 Quality of the Evidence

The overall quality of the studies included in this review ranged from high to low:

	N=	HQ(++)	AQ(+)	LQ(-)	R(0)
Systematic reviews	13	6	2	3	2
RCTs	7	3	1	3	0

Appendices 1 presents the SIGN critical apprasial tools used in this review. Appendices 2 and 3 present the critical appraisal scores for the SRs and RCTs included in this review

Systematic reviews (SRs): common quality and design flaws

A) Studies did not address the potential for publication bias in reporting their reviews.
B) Conflicts of interest were often not identified or reported.
C) Excluded studies were not listed.

Randomised controlled trials (RCTs): common quality and design flaws

A) With the small numbers reported in the RCTs it was difficult to ensure that the effect of confounders was dealt with. This was particularly important when considering the effect of secondary outcomes.
B) A number of studies failed to report the use of intention to treat analysis when reporting the study's findings.
C) Studies rarely controlled for participants' involvement in co-interventions such as exercise/medication etc.

3.3 Findings

Eight systematic reviews focused on cervical dystonia, of which two were high quality (Marques et al 2016; Duarte et al 2016), one was acceptable quality (De Pauw et al 2014), three were low quality (Jimenez-Shahed 2012; Colosimo et al 2012; Hallett et al 2013), and two were of very low quality (Kamm & Benecke 2011; Zoom et al 2012). Five systematic reviews focused on myofascial pain, of which four were of high quality (Langevin et al 2011a; Langevin et al 2011b; Peloso et al 2013; Khalifeh et al 2016) and one of acceptable quality (Desai et al 2014). One systematic review focused on whiplash-associated disorder (Langevin et al 2011a) and was of high quality. One review (Peloso et al 2013) only examined systematic reviews, and reported on two included reviews (Langevin et al 2011a/2011b). These reviews were reported separately to allow for more detailed examination which focused specifically on botulinum injection for neck pain.

In regards to RCTs, three studies examined cervical dystonia, of which two were high quality (Poewe et al 2016; Evidente et al 2013) and one was acceptable quality (Mordin et al 2014). Four studies examined myofascial pain, of which one was high quality (Benecke et al 2011) and three were low quality (Jerosch et al 2012; Seo et al 2013; Nicol et al 2014). There were no RCTs for whiplash-associated disorder.

3.4 Outcome Measures – Pain and Function

This review took a pragmatic approach to the presentation of the literature, sub-dividing the studies into the most common major clinical presentations reported in the literature. For the neck, these were cervical dystonia, myofascial pain syndrome, and whiplash related pain. Where systematic reviews reported studies involving a range of pathologies, if possible the data for each pathology was extracted from the individual systematic review and is presented separately below. Appendix 4 presents the findings from the systematic reviews included in this review. Appendix 5 presents the studies included in these systematic reviews. Appendix 6 presents the data extraction from the RCTs included in this review.

Cervical Dystonia:

Systematic Reviews

Kamm & Benecke (2011)

Kamm & Benecke (2011) (QS:R(O)) conducted a review of the clinical evidence and ongoing clinical trials for botulinum toxin therapy for cervical dystonia. While this review was not conducted in a systematic manner, it does provide a detailed list of all clinical trials involving botulinum toxin therapy for cervical dystonia, including ongoing trials, up until the date of publication.

In examining these trials, the authors concluded that botulinum toxin A is an effective and safe treatment of cervical dystonia and has a sustained long-term efficacy, and was most likely more efficacious and better tolerated for patients with cervical dystonia than alternative treatments, such as trihexyphenidyl, as suggested by the American Academy of Neurology (Simpson et al 2008). They also concluded that botulinum toxin B appeared to be comparable to botulinum toxin A, though it has a higher chance of negative side effects such as dry mouth. It is important to note that the authors did not conduct any meta-analysis or

combination of the available studies to reach these conclusions, and while they have collected a large number of studies, there is no description of how they found, selected, and included these studies.

Study	QS	Conclusions	Level of Evidence
Kamm & Benecke (2011)	R(0)	BoNT-A is an effective and safe treatment of cervical dystonia and should be offered as a treatment option	1
		BoNT-A appears to have sustained long-term efficacy (more than 12 years)	1
		BoNT-B is safe and effective, but has a more disadvantageous profile of side effects than BoNT-A	1
		BoNT-A is best option, while BoNT-B is recommended for patients who have developed BoNT-A antibodies.	1

Colosimo et al (2011)

Colosimo et al (2011) (QS:LQ(-)) performed a SR to investigate the long-term efficacy and safety of botulinum toxin injection for craniocervical dystonia. Of the included studies, 12 case series were related to cervical dystonia and were graded I-IV as per the evidence classification scheme for therapeutic interventions issued by the European Federation of Neurological Societies (Brainin et al 2004). Ten of the twelve included studies were grade IV, being low quality, while the other two studies were grade I, being high quality.

The authors noted that while the evidence was mostly positive for the long-term efficacy of botulinum toxin A injection for cervical dystonia, some patients demonstrated a lack of response to botulinum toxin A injection beyond the initial injection (Hatheway and Dang 1994). The authors suggested that this was due to the presence of neutralizing antibodies which prevent botulinum toxin A from producing a secondary response. There was also no evidence of specific side effects of botulinum toxin A for cervical dystonia.

Study	QS	Conclusions	Level of Evidence
Colosimo et al., (2012)	LQ(-)	Subgroup of cervical dystonia patients failed to maintain a sustained response after the first or second injection	1-
		No specific side effect due to long-term use of BoNT-A	1-

Jimenez-Shahed (2012)

Jimenez-Shahed (2012) (QS:R(0)) conducted a review examining the effectiveness of a newly developed type of botulinum neurotoxin, incobotulinumtoxinA (or Xeomin®), for focal dystonias. Within this review, four RCTs (n = 796) were relevant to cervical dystonia. Statistical comparisons between studies were made without separating pathologies, and therefore conclusions cannot be accurately drawn from these analyses. It is possible to comment that incobotulinumtonixA showed significant improvement when compared to other botulinum toxins, baseline, and placebo, however the quality of these included studies are not assessed, and cannot be properly evaluated.

Study	QS	Conclusions	Level of Evidence
Jimenez-Shahed, (2012)	R(0)	IncobotulinumtonixA demonstrates significant improvements in cervical dystonia for primary and secondary measures compared to other botulinum toxins, baseline, and placebo	1-
		IncobotulinumtoxinA showed no direct complications	1-

Zoons et al (2012)

Zoons et al (2012) (QS: R(0)) performed a systematic review for the pharmaco-therapeutic and pharmaco-economic value of botulinum treatment for focal dystonia. However, the authors failed to differentiate between the different types of focal dystonia when assessing study outcomes. While they concluded that botulinum toxin was the most effective treatment for reducing dystonic symptoms measured with dystonia-specific and general questionnaires, and for reducing pain, it is not clear if this has a specific impact on neck pain. Zoons et al (2012) failed to critically appraise or assess the evidence and has therefore not been included in this review.

Hallett et al (2013)

Hallett et al (2013) (QS:LQ(-)) conducted an evidence-based SR of botulinum neurotoxin for the treatment of movement disorders. Of the 51 studies included in this review, 13 studies were related to cervical dystonia, with eight being placebo controlled studies (Brashear et al 1999; Brin et al 1999; Comella et al 2011; Lew et al 1997; Poewe et al 1998; Truong et al 2005; Truong et al 2010) and five being active comparator or multiple doses studies (Benecke et al 2005; Brans et al 1996; Comella et al 2005; Odergren et al 1998; Pappert et al 2008). All 13 studies were classified as a Class 1 study by the American Academy of Neurology Classification of Quality of Evidence for Clinical Trials, indicating highest level evidence.

These studies examined four types of botulinum toxin injection for cervical dystonia: onabotulinum (Benecke et al 2005; Comella et al 2005; Odergren et al 1998; Pappert et al 2008), rimabotulinum (Brashear et al 1999; Brin et al 1999; Comella et al 2005; Lew et al 1997; Pappert et al 2008), incobotulinum (Benecke et al 2005; Comella et al 2011), abobotulinum (Brans et al 1996; Odergren et al 1998; Poewe et al 1998; Truong et al 2005; Truong et al 2010). All placebo-controlled evidence supported the efficacy of botulinum toxin for cervical dystonia, with a duration ranging from eight to 20 weeks. One study (Brans et al 1996) compared abobotulinum injection to trihexyphenidyl in 66 patients, showing that botulinum injection resulted in greater improvement with fewer adverse events than trihexyphenidyl. There were no significant differences between botulinum types when compared with each other for efficacy, although dry mouth was reported more frequently in the rimabotulinum groups than in onabotulinum groups.

The authors stated that the published evidence supported level A recommendations for all four botulinum toxin formulations for the treatment of cervical dystonia, and found that all types of botulinum toxin injections were comparable to one another in terms of efficacy, though they did not combine the results of included studies with any kind of analysis.

Study	QS	Conclusions	Level of Evidence
Hallett et al., (2013)	LQ(-)	Evidence supports Level A recommendations for all four BoNT formulations for the treatment of cervical dystonia	1

De Pauw et al (2014)

De Pauw et al (2014) (QS:AQ(+)) conducted a SR of physiotherapy for cervical dystonia. While a majority of this study focused on physiotherapy, five studies including four RCTs (Tassorelli et al 2006; El-Bahrawy et al 2009; Queiroz et al 2012; Boyce et al 2013) and one case report (Ramdharry 2006) involved botulinum toxin injection in combination with physiotherapy. Both botulinum injection alone and in combination with physiotherapy resulted in a decrease of severity of cervical dystonia on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), though in combination with physiotherapy also resulted in a significant decrease on the disability and pain subscales of the TWSTRS.

The authors concluded multimodal physiotherapy including botulinum toxin A injections appear to improve head position, decreasing pain and improving short-term functioning for patients with cervical dystonia.

Study	QS	Conclusions	Level of Evidence
De Pauw et al., (2014)	AQ(+)	A multimodal physiotherapy program in conjunction with BoNT-A injections may improve head position, decrease pain, and improve short-term function for patients with cervical dystonia	1

Duarte et al (2016)

Duarte et al (2016) (QS:HQ(++)) conducted a Cochrane SR and meta-analysis assessing the effectiveness of botulinum toxin type A verses botulinum toxin type B for the treatment of cervical dystonia. They identified three RCTs (Comella et al 2005; Pappert et al 2008; Tintner et al 2005) which met the inclusion criteria of comparing botulinum toxin types.

The authors found no difference between the two types of botulinum toxin for overall efficacy, with a mean difference of -1.44 (95% CI -3.58 to 0.70) lower on the TWSTRS for botulinum toxin B treated patients, or for adverse events (RR = 1.40; 95% CI 1.00 to 1.96). Botulinum toxin B had a slightly increased risk of sore throat/dry mouth than botulinum toxin A (RR = 4.39; 95% CI 2.43 to 7.91), but other than this, the two types of botulinum toxin were clinically non-distinguishable on all other outcomes, including severity, patient global response, pain, and quality of life. However, these studies were of low quality, and had a high risk of bias as all three studies were funded by drug manufacturers with a possible interest in the results.

Additionally, no definite conclusion can be drawn about the overall safety and long-term utility of botulinum toxin A compared with botulinum toxin B.

Study	QS	Conclusions	Level of Evidence
Duarte et al., (2016)	HQ(++)	Low-quality evidence to say that BtA and BtB are equally effective and safe for the treatment of cervical dystonia, and no evidence to support one botulinum toxin over the other.	1
		BtB presents higher risk of dry mouth compared to BtA.	1

Marques et al (2016)

Marques et al (2016) (HQ(++)) conducted a Cochrane SR and MA assessing the effectiveness of botulinum toxin type B for cervical dystonia. They included four RCTs (Brashear et al 1999; Brin et al 1999; Kaji et al 2013; Lew et al 1997).

Botulinum toxin B injection was associated with an improvement of 14.7% (95% CI 9.8 to 19.5) from the patients' baseline clinical status and a decrease of 6.8 points in the TWSTRS at four weeks after injection (95% CI; 4.54 to 9.01). Pain, measured by the TWSTRS-Pain subscale, was also reduced by 2.20 points at four weeks (95% CI: 1.25 to 3.15), and botulinum toxin B injection resulted in overall improvement of subjective clinical status as reported by both patients and clinicians.

Botulinum toxin B was associated with an increased risk of dry mouth (RR = 7.65; 95% CI: 2.75 to 21.32) and dysphagia (RR = 6.78; 95% CI: 2.42 to 19.05).

The authors concluded that a single botulinum toxin injection was associated with significant and clinically relevant reduction in cervical dystonia impairment, although there was no information available regarding repeat does of botulinum toxin B, appropriate treatment intervals and doses, guidance for injection technique, or impact on quality of life.

Study	QS	Conclusions	Level of Evidence
Marques et al., (2016)	HQ(++)	A single BtB-treatment session is associated with a significant and clinically relevant reduction of cervical dystonia impairment across all outcomes.	1+
		BtB presents higher risk of dry mouth	1+

Randomised Controlled Trials.

Three RCTs that were not included in the previously reported SRs were identified that investigated the effectiveness of botulinum toxin injections for cervical dystonia. For this analysis, the effectiveness of the botulinum toxin injections against baseline measures and then against other interventions or comparing different techniques was reviewed.

Intervention	Study	QS	Outcome measure	Result
Botulinum toxin Injection compared to placebo				
abobotulinumtoxin A solution for injection (ASI) 500U, abobotulinumtoxin A (dry formation) 500U, or placebo.	Poewe et al., (2016)	HQ(++)	Pain (VAS), TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain	• At 4 weeks, both BoNT-A types better than placebo for TWSTRS (mean decrease from baseline: ASI 500U = 212.5; Dry 500U = 214.0; Placebo = 23.9; p < .0001 vs placebo) • TWSTRS total score reduction maintained for 4 cycle of ASI during open label follow-up.
500U abotulinumtoxin A or placebo	Mordin et al., (2014)	AQ(+)	Pain (VAS), TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain; SF-36	• Patients treated with abobotulinumtoxinA reported sig greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health and Role Emotional domains than placebo patients (p≤0.03). • TWSTRS significantly correlated with Physical Functioning, Role Physical and Bodily Pain scores, on active treatment at 4 weeks
Botulinum toxin compared to placebo • **Botulinum toxin injection showed higher improvement from baseline than placebo at four weeks (1xHQ, 1xAQ)** • Botulinum toxin injection reported significantly better results than placebo on TWSTRS (1xHQ, 1xAQ) • TWSTRS-total score reduction was maintained during an open-label follow-up (1xHQ)				
Botulinum Toxin Dosage parameters				
240U incobotulinumtoxinA or 120U incobotulinumtoxinA for 5 or more injections	Evidente et al., (2013)	HQ(++)	TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain; Global Assessment (Symptomology)	• Sig. improvement for TWSTRS-Total scores at 4 wks (p<0.001 vs injection visit). • Sig. mean improvement for in TWSTRS-Total scores from first EP injection and TTV (240U (n = 81), –4.5 (7.82); 120U (n = 66), -6.7 (9.20); p<0.001.) • Similar results for disability, severity, and pain subscales for 4wks post each injection (p = 0.016). • Treatment diff. between 240U and 120U for TWSTRS-Total & subscales were non-sig. • Treatment efficacy was assessed as 'very good' or 'good' for a majority of subjects. • Moderate improvement in Patient Evaluation of Global Response reported at each injection interval.
Botulinum toxin dosage parameters • **240U and 120U incobotulinumtoxin injections were comparable at four weeks post injection (1xHQ)** • Differences between incobotulinumtoxin injections on TWSTRS-total and subscales were non-significant (1xHQ) • Treatment efficacy of both dose parameters were rated as good and very good by a majority of subjects (1xHQ)				
Botulinum toxin formulation				
Abobotulinumtoxin A solution for injection (ASI) 500U, Abobotulinumtoxin A (dry formation) 500U, or placebo.	Poewe et al., (2016)	HQ(++)	Pain (VAS), TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain	• At 4 weeks, both BoNT-A types better than placebo for TWSTRS (mean decrease from baseline: ASI 500U = 212.5; Dry 500U = 214.0; Placebo = 23.9; p < .0001 vs placebo) • Noninferiority limit of 3 points for TWSTRS at 4 weeks was not met for ASI vs Dry.

				• TWSTRS total score reduction were maintained for 4 cycle of ASI during open label follow-up.
Botulinum toxin formulations • **Abobotulinumtoxin A solution for injection was comparable to Abobotulinumtoxin A as a dry formulation at four weeks (1xHQ)** • Both abobotulinumtoxin A formulations (dry and injection) were more effective than placebo at four weeks (1xHQ) • TWSTRS score reduction was maintained during follow-up injections regardless of initial abobotulinumtoxin formulation (1xHQ)				

Myofascial Pain Syndrome:

Systematic Reviews

Peloso et al 2013

Peloso et al 2013 (QS: HQ(++)) performed a SR examining pharmacological interventions, including medical injection, for neck pain. Inclusion criteria for this review were systematic reviews of RCTs. Of the 26 reviews, two reviews involved Botulinum toxin injections (Langevin et al 2011a; Langevin et al 2011b). These reviews are included separately in this review as Peloso et al (2013) was not focused solely on botulinum injection.

Overwhelmingly, there was no evidence of benefit for botulinum injection when compared to a control or placebo group for pain for any condition. The authors finally concluded no short-term pain relief benefit for botulinum toxin-A compared to saline (strong GRADE; 5 trial meta-analysis) nor for subacute/chronic whiplash (moderate GRADE; 4 trial meta-analysis) in reducing reduced pain, disability or global perceived effect.

Study	QS	Conclusions	Level of Evidence
Peloso et al., (2013)	HQ(++)	No short-term pain relieving benefit for botulinum toxin-A compared to saline for chronic neck pain.	1

Langevin et al (2011a)

Langevin et al (2011a) (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 predominately showed no statistically significant difference between botulinum toxin A injection and the comparator. Four pieces of high quality evidence showed no short-term statistically significant difference between botulinum toxin A versus a placebo intervention. Two low quality pieces of evidence found no short-term difference when 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 compared to its comparator and one low quality piece of evidence showed this lack of difference persisted up to 6 months.

Study	QS	Conclusions	Level of Evidence
Langevin et al. (2011a)	HQ (++)	BoNT-A injection had no statistical difference in pain when compared to placebo, exercise and medication, lidocaine and exercise and exercise and dry needling	1+
		BoNT-A injection had no short-term difference when combined with exercise compared to exercise and lidocaine	1+
		BoNT-A showed no difference in pain compared to placebo at six months	1-

Langevin et al (2011b)

Langevin et al (2011b) (QS:HQ(++)) performed a Cochrane SR and MA of botulinum toxin for subacute/chronic neck pain. Of the nine included RCTs, seven were related to myofascial 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 et al 2006), and two were related to cervicogenic headache (Schnider et al 2002; Zhang et al 2003), which is not discussed in this review.

There was high quality evidence to suggest that, at both four weeks and six months post-injection, there was no difference between botulinum injection and saline (SMD -0.07; 95% CI -0.36 to 0.21). Similar results were reported for botulinum injection verses placebo (four weeks: SMD 0.16; 95% CI -0.53 to 0.86. Six months: SMD 0.00; 95% CI -0.69 to 0.69). Two very low quality studies showed no difference in pain between botulinum injection and saline when combined with physiotherapeutic exercise and analgesics at four weeks (SMD pooled 0.09; 95% CI -0.55 to 0.73). There was one very low quality study which reported a difference in global perceived effect at four weeks in favour of botulinum injection (SMD -1.12; 95% CI: -1.89 to -0.36)

Overall, the authors concluded that the evidence failed to confirm a clinical or statistically significant benefit for botulinum injection for chronic neck pain.

This review was withdrawn from the Cochrane database in 2015 due to non-compliance with The Cochrane Collaboration's Commercial Sponsorship Policy.

Study	QS	Conclusions	Level of Evidence
Langevin et al., (2011b)	HQ(++)	• Fails to confirm either a clinical or statistically significant benefit for BoNT-A injection for chronic neck pain	1++
		• Botulinum toxin A injections showed no short-term difference when combined with exercise compared to exercise plus lidocaine	1+
		• Botulinum toxin A showed no difference in pain relief compared to placebo at 6 months	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 scale. For the Cochrane assessment scale one study scores 3/11, two scored 4/11, three scored 7/11 and one scored 11/11. As for the AHRQ 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 patients on botulinum toxin A at week five showed mild or no pain compared with the placebo group; the treatment group also had a significantly greater change from baseline score during week 5-8 and significantly fewer days per week with pain between week five and twelve.

The authors concluded that even though the study of the highest quality produced positive findings, a greater number of higher quality studies need to be conducted to reach a conclusion regarding the efficacy of the treatment modality.

Study	QS	Conclusions	Level of Evidence
Desai et al. (2014)	AQ (+)	• 6 of the 7 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	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-

Khalifeh et al (2016)

Khalifeh et al (2016) (QS:HQ(++)) conducted a SR and MA examining the efficacy of botulinum toxin type A for the treatment of myofascial pain syndrome. They found 13 studies, of which nine (Cheshire, Abashian & Mann 1994; Ferrante et al 2005; Göbel et al 2006; Kwanchuay et al 2015; Lew et al 2008; Ojala, Arokoski & Partanen 2006; Qerama et al 2006; Wheeler,

Goolkasian & Gretz 1998, 2001) were related to neck pain. The remaining four (Ernberg et al 2011; Guarda-Nardini et al 2008; Kurtoglu et al 2008; Nixdorf, Heo & Major 2002) were related to the temporalis and masseter muscles.

The pooled results showed that while there was an improvement in the intensity of pain for the botulinum toxin group compared with the placebo group at four to six weeks, it was non-significant (SMD -0.110; 95% CI -0.344 to 0.124; p = 0.356). However, there was significant improvement at two to six months, (SMD, –0.360; 95% CI, –0.623 to –0.096; p = 0.008), indicating that botulinum toxin injection has an effect in the intermediate term from moderate level evidence. The number of participants who responded to treatment did not statistically differentiate between groups (RR 1.346; 95% CI 0.922-1.964; p = .123).

Overall the authors concluded that botulinum toxin type A may influence pain intensity for myofascial pain at two to six months when compared to placebo, as indicated by moderate level evidence.

Study	QS	Conclusions	Level of Evidence
Khalifeh et al., (2016)	HQ(++)	• Non-significant improvement in the intensity of pain for the botulinum toxin group compared with the placebo group at four to six weeks	1++
		• Significant improvement in the intensity of pain for the botulinum toxin group compared with the placebo group at two to six months	1++
		• Non-significant difference in number of participants who responded to treatment between groups at two months	1++
		• Non-significant increase of pain threshold to pressure (algometry) at two months	1++

Randomised Controlled Trials.

Five RCTs that were not included in the previously reported SRs were identified that investigated the effectiveness of botulinum toxin injections for myofascial pain. For this analysis, the effectiveness of the botulinum toxin injections against baseline measures and then against other intervention or comparing different techniques was reviewed.

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 in pain intensity was 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 sig more days per week with no at 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 - 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, subjects who received BoNT-A had improved average pain scores (P=0.019, 0.26, 2.78) • Trend toward improvement in worst BPI pain scores (p=0.052, -0.019, 3.46) • No sig changes in 'best' VNS pain score or NDI were found • No sig diff 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 headaches experienced per week (p=0.04, 0.07, 4.55) • Both groups mean pain score decreased over time the botulinum toxin A group deceased significantly 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 (1xHQ)** • 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 for the effect on physical or emotional function, global improvement or other clinical measures (1 x LQ) • Botulinum Toxin A may be able to reduce the frequency of headaches per week when compared to a placebo (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 significant differences were found between groups • More adverse events in Dysport 320U group compared to 200U

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 (1xLQ) • Botulinum toxin dosages of 320U may produce more adverse events than lower dosages (1 x LQ)				
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	• 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 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 score on the neck pain and disability index than botulinum toxin with higher intensities of electrical stimulation (1xLQ)				

Whiplash-associated disorders:

Systematic Reviews

Langevin et al (2011a)

Langevin et al (2011a) (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 five were related to whiplash-associated disorder (Braker et al 2008; Carroll et al 2008; Padberg et al 2007; Freund & Schwartz et al 2000; Wheeler et al 2001). This was the only SR to report on the effect of botulinum injection for whiplash-associated disorder, and is further discussed elsewhere in the review in regards to myofascial pain.

There was moderate quality evidence to show that botulinum injection was no better than saline injection at four weeks for pain (SMD -0.21; 95% CI -0.57 to 0.15), disability, or quality of life. 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. However, very low-quality evidence from two trials showed a small difference at six months in favour of botulinum injection plus exercise and medication for pain (SMD -0.66; 95% CI -1.29 to -0.04) for subacute neck pain or whiplash disorder.

Overall, the authors concluded that current evidence does not confirm a clinically or statistically significant benefit of botulinum toxin injection used alone for whiplash-associated disorder.

Study	QS	Conclusions	Level of Evidence
Langevin et al., (2011a)	HQ(++)	• Fails to confirm either a clinical or statistically significant benefit for BoNT-A injection for whiplash-associated disorder	1++
		• BoNT-A injections had no short-term difference when combined with exercise compared to exercise and lidocaine	1+
		• BoNT-A showed slight difference in pain compared to placebo at 6 months when combined with exercise and medication	1

Randomised Controlled Trials.

There were no randomised controlled trials for whiplash-associated disorder post-2011 identified for this review that were not previously reported in systematic reviews.

3.5 Outcome Measures – Safety and Risk

Cervical Dystonia

Marques et al (2016) conducted a Cochrane SR assessing the effectiveness of botulinum toxin type B for cervical dystonia. They reported that adverse events were generally transient and either mild to moderate, or intermittent. They found that adverse events for botulinum toxin injection were 90.2% in comparison to placebo injections at 83.8%, though these adverse events were not specified.

Jimenez-Shahed (2011) conducted a SR examining the effectiveness of a newly developed type of botulinum neurotoxin, incobotulinumtoxinA (or Xeomin®), for focal dystonias. For cervical dystonia, one study reported on the long-term safety of botulinum injection. Of the 153 participants analysed, 118 patients (77.1%) experienced at least one adverse event, with the most frequent being dysphagia, neck pain, and sinusitis. The total incidence of adverse events reduced with each repeated injection interval, indicating no cumulative effect from repeated doses.

Hallett et al (2013) conducted an evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders, which examined four different botulinum neurotoxins for cervical dystonia: onabotulinum, rimabotulinum, incobotulinum, abobotulinum. They found that incobotulinum was generally well tolerated with only three patients discontinuing treatment due to adverse events. When compared together, rimabotulinum groups reported more dry mouth than onabotulinum groups. Abobotulinum appeared to have a greater effect than onabotulinum; however it also had a greater frequency of adverse events. Abobotulinum reported 36% adverse events, with 15.6-17.3% of these being the most frequent adverse event (dysphagia), compared to 17.6% adverse events for onabotulinum, with 3% of these being dysphagia.

Duarte et al (2016) conducted a Cochrane SR and MA assessing the effectiveness of botulinum toxin type A verses botulinum toxin type B for the treatment of cervical dystonia. They found that the most frequently reported adverse events were sore throat/dry mouth (24.5%) and dysphagia (18.2%). Dysphagia appeared to be equally likely in patients treated

with either botulinum types (RR 2.89; 95% CI 0.80 to 10.41; I2=74%), where sore throat/dry mouth appeared to be more likely among botulinum toxin type B patients than botulinum toxin type A (RR 4.39; 95% CI 2.43 to 7.91; I2=0%)

Poewe et al (2016) conducted a RCT which examined the efficacy and safety of abobotulinumtoxin A Liquid Formulation in cervical dystonia, which compared abobotulinumtoxin A solution for injection to abobotulinumtoxin A in a dry formation to a placebo in a double-blind phase, followed by abobotulinumtoxin A as injections in an open label phase. In phase one, adverse events were reported more frequently for the solution group (42.5%) than for the dry formation (37.8%) or placebo (25.5%) groups. Most of these treatment-emergent adverse events were considered unrelated to the study drug. Of those which were considered related to the study drug, dysphagia (3.3% solution, 7.1% dry, 0% placebo) was the most common, followed by injection-site pain (3.3% solution, 3.2% dry, 1.8% placebo). Adverse events reported in the open-label section of the study reflected the events reported in stage one, with dysphagia being the most commonly reported event.

Evidente et al (2013) conducted a RCT which examined repeated incobotulinumtoxinA injections for cervical dystonia at two different botulinum strengths. During the 68-week period of this study, adverse events were reported at each injection interval. Incidents ranged 38.8-61.3% per interval for the 240U group, and 29.7-47.6% in the 120U group. Adverse drug reactions were 5.4-20.4% per interval for the 240U group, and 10.0-28.8% in the 120U group. Adverse events were wide ranging; however, dysphagia was the most frequently reported event throughout the course of the study, with 3 patients remaining unresolved at study conclusion. Most adverse events were mild (n=58; 27.1%) or moderate (n=38; 17.8%), although severe adverse events were reported by seven subjects in the 240U group (6.3%) and eight subjects in the 120U group (7.8%). They were most frequently neck pain, musculoskeletal pain, dysphagia, and headache, with nine subjects remaining unresolved at study conclusion.

Ramirez-Castaneda & Jankovic (2014) presented a retrospective, longitudinal cohort study that analysed data on 89 patients who received botulinum toxin injection for dystonia. Of these, 51 patients with a total of 2370 injection visits received treatment for cervical dystonia. Approximately 10% (409) of the visits had adverse effects reported for cervical dystonia, with dysphagia (27.1%) and neck muscle weakness (17.1%) representing the most common side effects with cervical dystonia. Most patients demonstrated sustained therapeutic benefit when receiving repeat injections over the interval follow-up period (10-26 years).

Anton (2011) examined the adverse events of botulinum toxin injection, including for the treatment of cervical dystonia. They included a meta-analysis of 308 patients who received botulinum toxin type B injection for cervical dystonia (Costa et al., 2005), which reported more adverse reactions for the treatment group in comparison to placebo during a 16-week follow-up. These were most commonly dysphagia (OR 4.37; 95% CI 2.18– 8.79), and dry mouth (OR 5.19; 95% CI 2.69–10.03), with nonspecific adverse events, such as injection site pain, headache, nausea, flu-like symptom not reaching significance.

Myofascial Pain

Desai et al (2014) conducted a SR into the evidence for botulinum toxin type A in the treatment of 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 other subjects 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.

Benecke et al (2011), in 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 botulinum toxin 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.

Jerosch et al (2012) conducted a study using intramuscular injections of two different dosages of botulinum toxin (Dysport) and found that at least one treatment-emergent adverse event judged as possibly or probably related to 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) and muscular weakness (1.2% and 6.1%). Of 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.

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 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 symptoms resolve in 7-10 days.

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. 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. **Whiplash-associated disorder** No studies included discussed safety or adverse events for whiplash-associated disorder.
3.6 Economic analysis	Only one study was identified that examined cost-effectiveness. This study was in relation to cervical dystonia. Zoons et al (2012) conducted a SR on the pharmaco-therapeutic and pharmaco-economic value of botulinum treatment for focal dystonia. While the authors did not differentiate between types of focal dystonia for outcomes, they did for some limited elements when examining economic value. They concluded that the cost of treating cervical dystonia was the highest of all the focal dystonias, requiring treatment on average five times a year. While most cost-effectiveness studies only looked at the cost of the toxin itself, one included study looked at the costs of treating patients with botulinum toxin, including costs of the toxin (EUR 154.36 for 100 IU Botox and EUR 215 for 500 IU Dysport); salaries of the treating physician, assisting nurse and secretary; needles; EMG equipment; and social costs (transportation by taxi with an accompanying person). The authors estimated that the daily costs were EUR 3.28 ± 0.86 for cervical dystonia. This leads to yearly costs of EUR 1,197.20 for botulinum toxin injection treatment for cervical dystonia. The authors concluded that for cervical dystonia, botulinum toxin was an expensive drug with good effects, and that the costs may weigh up to the regained quality of life; however, further research was required.

4. Recommendations

Summary of Recommendations

Cervical Dystonia

- **Botulinum toxin injection showed higher improvement from baseline than placebo in the short term for cervical dystonia** (Level A recommendation based on 1 x HQ SR with level 1+ evidence, 1 x HQ RCT and 1 x AQ RCT)
- **Botulinum toxin A and botulinum toxin B were equally effective and safe for the treatment of cervical dystonia** (Level B recommendation based on 1 x HQ SR with level 1 evidence)
- **A single botulinum toxin B treatment session was associated with a significant and clinically relevant reduction of cervical dystonia impairment across all outcomes when compared with placebo** (Level A recommendation based on 1 x HQ SR with level 1+ evidence)
- **240U and 120U incobotulinumtoxin injections were comparable at four weeks post** injection (Level C recommendation based on 1 x HQ RCT)
- **Botulinum toxin B treatment for cervical dystonia was associated with a higher risk of dry mouth compared to botulinum toxin A** (Level A recommendation based on 2 x HQ SR with level 1 and 1+ evidence)

Myofascial Pain

- **There was no short-term pain relieving benefit from botulinum toxin A injections compared to saline for neck pain** (Level A recommendation based on 2 x HQ SR with level 1++, 1 x HQ SR with level 1 evidence, 1 x AQ SR with level 1+ evidence).
- **Botulinum toxin A injections had no statistically different effect on pain when compared to placebo, exercise and medication, lidocaine and exercise and exercise and dry needling** (Level A recommendation based on 1 x HQ SR with level 1+ evidence).
- **Botulinum toxin injections ranging from 200 units to 480 units were effective at reducing pain with no significant differences between the groups** (Level D recommendation based on 1 x LQ RCT).
- **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 for myofascial pain** (Level D recommendation based on 1 x LQ RCT).

Whiplash-associated Disorder

- **Botulinum toxin injection type A failed to confirm a clinical or statistically significant benefit for whiplash-associated disorder when compared with placebo and other treatments** (Level A recommendation based on 1 x HQ SR with level 1++ evidence).

Safety and adverse events

- **Adverse events reported included: injection site soreness, dry mouth, dysphagia, fatigue, heaviness, numbness, flu-like symptoms, systemic fever, shivering, generalised muscle soreness, vertigo and headache** (Level A recommendation)
- **Most adverse events were considered mild or moderate. Serious adverse events were transient and rare** (Level A recommendation).

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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 systematic reviews used in this review

Reference (author, year)		Question													
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**1.11**	**1.12**	**2.1**	**2.2**
Colosimo et al	2012	Y	Y	CS	CS	Y	N	Y	Y	N	N/A	N/A	Y	LQ(-)	Y
De Pauw et al	2014	Y	Y	CS	Y	N	N	Y	Y	Y	N	N	Y	AQ(+)	Y
Duarte et al	2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	HQ(++)	Y
Hallett et al	2013	Y	Y	CS	CS	N	N	Y	Y	Y	N	CS	Y	LQ(-)	Y
Jimenez-Shahed	2012	Y	N	CS	CS	N	N	Y	N	N	N	CS	Y	LQ(-)	Y
Marques et al	2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	HQ(++)	Y
Kamm & Benecke	2011	N	N	CS	CS	Y	N	Y	N	N	N/A	N	N	R(0)	Y
Langevin et al	2011a	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	CS	N	HQ(++)	Y
Langevin et al	2011b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CS	Y	HQ(++)	Y
Peloso et al	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	HQ(++)	Y
Desai et al	2014	Y	Y	CS	Y	N	N	Y	Y	Y	NA	N	N	AQ(+)	Y
Khalifeh et al	2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	HQ(++)	Y

Appendix 3: Quality scores for randomised controlled trials used in this review

Reference (author, year)		Question												
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**2.1**	**2.2**	**2.3**
Myofascial Pain														
Benecke et al.	2011	Y	Y	Y	Y	Y	Y	CS	0%	Y	CS	HQ (++)	Y	Y
2.4	10 fixed location injection of 40U of Botulinum Toxin A produced improvements in pain control for at least 8 weeks following treatment.													
Jerosch et al.	2012	Y	CS	N	N	CS	Y	Y	200: 7% 320: 6%	Y	CS	LQ(-)	Y	Y
2.4	Both Dysport 200U and 320U provided effective relief from chronic MPS in the neck and shoulder girdle and this was maintained for at least 3 months.													
Seo et al.	2013	Y	CS	CS	CS	Y	Y	Y	MG:13% SG:11%	Y	NA	LQ(-)	Y	Y
2.4	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													
Nicol et al.	2014	Y	CS	N	CS	Y	Y	Y	Total 5.26%	CS	NA	LQ(-)	Y	Y
2.4	BoNT-A injected directly into painful muscle groups improves average pain scores and certain aspects of quality of life in patients experiencing severe cervical and shoulder girdle myofascial pain													
Cervical Dystonia														
Evidente et al.	2013	Y	Y	Y	Y	Y	Y	Y	240: 19% 120: 23%	Y	Y	HQ(++)	Y	Y
2.4	Both 240 U (n = 111) and 120 U doses of incobotulinumtoxinA provided statistically significant and clinically relevant improvements in mean TWSTRS-Total, -Severity, -Disability, and -Pain scores, from each injection session to respective 4-week follow-up visits													
Mordin et al.	2014	Y	Y	Y	Y	Y	Y	Y	BT: 18% CG: 38%	N	CS	AQ(+)	Y	Y
2.4	CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL													
Poewe et al.	2016	Y	Y	Y	Y	Y	Y	Y	BTI: 2% BTP: 2% CG: 4%	Y	CS	HQ(++)	Y	Y
2.4	Abobotulinumtoxin A solution for injection was comparable to Abobotulinumtoxin A as a dry formulation at four weeks. Both abobotulinumtoxin A formulations (dry and injection) were more effective than placebo at four weeks.													

Appendix 4: Data Extraction of systematic reviews included in this review

Author and year (condition)	SIGN Score	Condition	Studies (Patient No)	Outcome	Conclusions	Evidence				Grade
						1	2	3	4	
Colosimo et al., (2012)	LQ(-)	Cervical Dystonia	12 Case Series (n = 1317)	Adverse events, long-term effects	• Subgroup of cervical dystonia patients failed to maintain a sustained response after the first or second injection	0	0	0	1	1-
					• No specific side effect due exclusively to long-term use of BoNT-A	0	0	0	1	1-
De Pauw et al., (2014)	AQ(+)	Cervical Dystonia	4 RCTs; 1 Case Report (n = 121)	Pain, QoL, severity of condition, depression, function	• A multimodal physiotherapy program in conjunction with BoNT-A injections may improve head position, decrease pain, and improve short-term function for patients with cervical dystonia	0	1	0	1	1
Duarte et al., (2016)	HQ(++)	Cervical Dystonia	3 RCTs (n = 270)	Pain, disability, severity of condition, and safety	• Low-quality evidence to say that BtA and BtB are equally effective and safe for the treatment of cervical dystonia, and no evidence to support one botulinum toxin over the other.	1	1	0	1	1+
					• BtB presents higher risk of dry mouth compared to BtA.	1	1	0	1	1+
Hallett et al., (2013)	LQ(-)	Cervical Dystonia	13 RCTs (n = 1834)	Physical changes, QoL, & perceived improvements.	• Evidence supports Level A recommendations for all four BoNT formulations for the treatment of cervical dystonia	0	0	1	1	1
Jimenez-Shahed, (2012)	R(0)	Cervical Dystonia	4 RCTs (n =796)	Severity of condition, pain; Safety and efficacy	• IncobotulinumtonixA demonstrates significant improvements in cervical dystonia for primary and secondary measures compared to other botulinum toxins and baseline	0	0	0	1	1-
					• IncobotulinumtoxinA also improved significantly compared to placebo	0	0	0	1	1-
Kamm & Benecke (2011)	R(0)	Cervical Dystonia	25 RCTs (n =2685)	Severity of condition	• BoNT-A is an effective and safe treatment of cervical dystonia and should be offered as a treatment option	0	0	1	1	1
					• BoNT-A appears to have sustained long-term efficacy (more than 12 years)	0	0	1	1	1
					• BoNT-B is safe and effective, but has a more disadvantageous profile of side effects than BoNT-A	0	0	1	1	1
					• BoNT-A is recommended as frontline, while BoNT-B is recommended for patients who have developed BoNT-A antibodies.	0	0	1	1	1

Author and year (condition)	SIGN Score	Condition	Studies (Patient No)	Outcome	Conclusions	Evidence				Grade
						1	2	3	4	
Langevin et al., (2011a)	HQ(++)	Myofascial Pain, Whiplash	13 RCTs (n = 1285)	Pain, function/disability, global perceived effect, QoL	• Does not confirm a clinically or statistically significant benefit of BoNT-A used alone on chronic neck pain in the short-term or subacute/chronic whiplash disorder	1	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 slight difference in pain compared to placebo at 6 months when combined with exercise and medication	0	1	0	1	1
Langevin et al., (2011b)	HQ(++)	Myofascial Pain	7 RCTs (n = 307)	Pain, disability, global perceived effect, QoL	• Fails to confirm either a clinical or statistically significant benefit for BoNT-A injection for chronic neck pain	1	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-
Marques et al., (2016)	HQ(++)	Cervical Dystonia	4 RCTs (n = 441)	Pain, disability, severity of condition, and safety	• A single BtB-treatment session is associated with a significant and clinically relevant reduction of cervical dystonia impairment across all outcomes.	1	1	0	1	1+
					• BtB-treated patients at an increased risk of dry mouth and dysphagia.	1	1	0	1	1+
Peloso et al., (2013)	HQ(++)	Whiplash, myofascial pain	2 SRs containing 9 RCTS (n = 441)	Pain, disability, perceived global effect	• No short-term pain relieving benefit for botulinum toxin-A compared to saline for chronic neck pain or for whiplash.	0	1	0	1	1

Author and year (condition)	SIGN Score	Condition	Studies (Patient No)	Outcome	Conclusions	Evidence				Grade
						1	2	3	4	
Desai et al., (2014)	AQ(+)	Myofascial pain	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-
Khalifeh et al., (2016)	HQ(++)	Myofascial pain	9 RCTs (n = 488)	Intensity of Pain (VAS), response to treatment, increase of pain threshold	• Non-significant improvement in the intensity of pain for the botulinum toxin group compared with the placebo group at four to six weeks	1	1	1	1	1++
					• Significant improvement in the intensity of pain for the botulinum toxin group compared with the placebo group at two to six months	1	1	1	1	1++
					• Non-significant difference in number of participants who responded to treatment between groups at two months	1	1	1	1	1++
					• Non-significant increase of pain threshold to pressure (algometry) at two months	1	1	1	1	1++

Appendix 5: Randomised controlled trials within systematic reviews

	Langevin et al., (2011a)	Langevin et al., (2011b)	Marques et al., (2016)	Duarte et al., (2016)	de Pauw et al., (2014)	Hallett et al., (2013)	Jimenez-Shahed (2011)	Desai et al., (2014)	Kamm & Benecke (2011)	Khalifeh et al., (2016)	Colosimo et al., (2012)	**Total**
Benecke et al., (2005)						1	1		1			**3**
Benecke, (2009)							x		1			**1**
Blackie & Lees (1990)									1			**1**
Botox [Package Insert] (2010)						1						**1**
Boyce et al., (2013)					1							**1**
Braker et al., (2008)	1											**1**
Brans et al., (1996)						1			1			**2**
Brashear et al., (1999)			1			1			1			**3**
Brin et al., (1999)			1			1			1			**3**
Carroll et al., (2008)	1											**1**
Cheshire et al., (1994)	1	1								1		**3**
Comella et al., (2005)				1		1			1			**3**
Comella et al., (2011)						1	1					**2**
El-Bahrawy et al., (2009)					1							**1**
Esenyel et al., (2007)	1	1										**2**
Ferrante et al., (2005)	1	1						1		1		**4**
Freund & Schwartz (2000)	1											**1**
Gelb et al., (1989)									1			**1**
Gelb et al., (1991)									1			**1**
Göbel et al., (2006)	1	1						1		1		**4**
Grafe et al., (2009)							1		1			**2**
Greene et al., (1990)									1			**1**
Jankovic & Schwartz (1990)									1			**1**
Kaji et al., (2013)			1									**1**
Kamanli et al., (2005)	1	1										**2**
Kessler et al., (1999)									1			**1**
Koller et al., (1990)									1			**1**
Kwanchuay et al., (2015)										1		**1**
Lew et al., (1997)			1			1			1			**3**
Lew et al., (2008)	1	1						1		1		**4**
Lorentz et al., (1991)									1			**1**
Naumann et al., (2002)									1			**1**
Odergren et al., (1998)						1						**1**
Ojala, Arokoski, & Partanen (2006)	1	1						1		1		**4**
Padberg, de Bruijn, & Tavy, (2007)	1											**1**
Pappert & Germanson (2008)				1		1			1			**3**
Poewe et al., (1992)									1			**1**
Poewe et al., (1998)						1			1			**2**
Qerama et al., (2006)								1	1	1		**3**
Queiroz et al., (2012)					1							**1**
Stell, Bronstein & Marsden (1989)									1			**1**
Tassorelli et al., (2006)					1							**1**
Tintner et al., (2005)				1					1			**2**
Truong et al., (2005)						1			1			**2**
Truong et al., (2010)						1			1			**2**
Tsui et al., (1986)									1			**1**
Wheeler, Goolkasian, & Gretz, (1998)	1							1		1		**3**
Wheeler, Goolkasian, & Gretz, (2001)	1							1		1		**3**
Wissel et al., (2001)									1			**1**
Total	**13**	**7**	**4**	**3**	**4**	**13**	**3**	**7**	**27**	**9**	**0**	**90**

Appendix 6 – Data Extraction table for randomised controlled trials used in this review

Author	Year	Study design	Approach	Botulinim	+/- Local Anaesthetic	Outcome Measures	Results	Findings	FUNCTIONAL OUTCOMES: Range of Movement (ROM), Disability, Return To Work (RTW), Quality of Life (QoL), OR other	Safety and Risk	Imaging	Patient	Pathology
Myofascial Pain													
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 more 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
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
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
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 headaches experienced per week (p=0.04, 0.07, 4.55) both groups mean pain score decreased over time the botulinum toxin A group deceased significantly more than the placebo group over time.	Results suggest that injection of BoNT-A into painful muscle groups of the neck and 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: Range of Movement (ROM), Disability, Return To Work (RTW), Quality of Life (QoL), OR other	Safety and Risk	Imaging	Patient	Pathology
uervical Dystonia													
Evidente et al.	2013	Randomised, double blind, controlled trial	Repeated injections	Incobotulinumtoxin A (Xeomin®)	Nil	TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain; Global Assessment (Symptomology); Over 48 weeks; min every 6 weeks + 20 weeks after final injection. Adverse events	Sig. improvement for mean TWSTRS-Total scores at 4 wks post each injection (p<0.001 vs injection visit). Sig. mean improvement for in TWSTRS-Total scores from first EP injection and TTV (240U (n = 81), –4.5 (7.82); 120U (n = 66), -6.7 (9.20); p<0.001 for both groups.) Similar results for disability, severity, and pain subscales for 4wks post each injection (p = 0.016). Treatment diff. between 240U and 120U for TWSTRS-Total & subscales were non-sig. Treatment efficacy was assessed as 'very good' or 'good' for a majority of subjects. Moderate improvement in Patient Evaluation of Global Response reported at each injection interval.	Both 240 U (n = 111) and 120 U doses of incobotulinumtoxinA provided statistically significant and clinically relevant improvements in mean TWSTRS-Total, -Severity, -Disability, and -Pain scores, from each injection session to respective 4-week follow-up visits	Disability, severity, and pain, Global response.	AEs per injection interval were 38.8–61.3% in the 240U group and 29.7–47.6% in the 120U group. Dysphagia was the most frequently reported ADR, with a greater incidence per injection interval in the 240U group (ranging from 3.8 to 13.5%) than the 120U group (ranging from 1.3 to 5.8%).		N = 213 240U = 111; 120U = 103 Mean age (SD) = 52.4 (12.0) 240U and 53.6 (11.2) 120U. Patients must have completed the main phase of the treatment and have a need for reinjection	Cervical Dystonia
Mordin et al.	2014	Randomised, double blind, placebo controlled trial	Single injection	Abobotulinumtoxin A	Nil	Pain (VAS), TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain; SF-36; @ baseline, 4, 8 & 12 wks; SF-36 @ baseline and 4 wks	Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health and Role Emotional domains than placebo patients (p≤0.03 for all). The TWSTRS was significantly correlated with Physical Functioning, Role Physical and Bodily Pain scores, for those on active treatment.	CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL	SF-36 was assessed in 83 patients (botox = 45; placebo = 38) and it was found that treatment with BoNT-A sig. improved quality of life.	No adverse events reported.		N = 116 BNoT-A: 55 Placebo: 61 Mean age (SD) = 51.9 (13.4) botox group and 53.9 (12.5) Placebo group	Cervical Dystonia lasting more than 18 mths + minimum score 30 on TWSRS-Total
Poewe et al.	2016	Randomized, double blind, placebo controlled trial	Single injection verses oral intake. Repeat follow-up injection in open label	Abobotulinumtoxin A liquid vs. dry formulation	Nil	Pain (VAS), TWSTRS-Total; TWSTRS-Disability; TWSTRS-Severity; TWSTRS-Pain; baseline & 1, 2, 4, 8, 12 wks post-injection	At 4 weeks, both BoNT-A types were better than placebo for TWSTRS (mean decrease from baseline: ASI 500U = 212.5; Dry 500U = 214.0; Placebo = 23.9; p < .0001 vs placebo). Noninferiority limit of 3 points for TWSTRS at 4 weeks was not met for ASI vs Dry. TWSTRS total score reduction were maintained for 4 cycle of ASI during open label follow-up.	Abobotulinumtoxin A solution for injection was comparable to Abobotulinumtoxin A as a dry formulation at four weeks. Both abobotulinumtoxin A formulations (dry and injection) were more effective than placebo at four weeks.	Severity of symptoms assessed by TWSTRS-disability subscale	Safety profiles of abobotulinumtoxinA solution for injection and abobotulinumtoxinA were similar, with dysphagia and injection-site pain the most frequent drug-related adverse events		N = 369 BTI: 156, BTP: 156; CG: 52. 51.9 (13.4) Mean age (SD) = BTI: 51.6 (12.4); BTP: 49.1 (12.0) CG: 49.7 (10.8)	Cervical Dystonia lasting more than 18 mths, untreated with Botox in prior 14 wks + minimum score 30 on TWSRS-Total