TITLE: Botulinum Toxin A for Myofascial Pain Syndrome: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Myofascial pain syndrome (MPS) is described as distinct type of regional musculoskeletal pain complaint that is caused by myofascial trigger points (TrPs) within muscles or their fascia. The trigger is identified as the presence of a taut band in the muscle, tenderness on compression in a point of the band.[1] There are variable estimates from epidemiologic studies on the incidence and prevalence of MPS due to the lack of universally accepted diagnostic criteria for the syndrome, in addition most of the epidemiologic data available pertain to musculoskeletal pain in general.[1,2] It has been estimated that in a general internal medicine practice 30% of patients complained primarily from myofascial pain, and that for 85% of patients admitted to a comprehensive pain center the primary diagnosis was myofascial pain.[2] Treatment of MPS involves treatment of TrPs and the removal of causative/perpetuating factors.[1] Muscle stretch, TrP injection (such as injection of botulinum toxin, or anaesthetic), acupuncture, therapeutic ultrasound, and drug therapy are treatments currently adopted for the deactivation of TrPs.[1] Correction of perpetuating factors include amending incorrect muscle activity and any abnormal postural issues, as well as, where possible, correcting all possible anatomical defects causing muscle imbalance.[1]

Botulinum Toxin A (BoNTA) is a purified neurotoxin complex produced from the fermentation of Clostridium botulinium type A.[3-5] BoNTA inhibits acetylcholine release into the neuromuscular junction, resulting in reduction in muscular contractions.[3-5] In Canada BoNTA is marketed in three distinct formulations, Botox, Dysport, and Xeomin.[3-5] BoNTA is used off-label for the treatment of MPS.[6] The objective of this review is to evaluate the clinical effectiveness of BoNTA in the treatment of MPS.

This report is an update to a CADTH Rapid Response report published in October 2008.[7]

RESEARCH QUESTION

What is the clinical effectiveness of botulinum toxin A for reduction in pain and improvement of functioning in myofascial pain syndrome?

KEY FINDINGS

One meta-analysis, two systematic reviews, and four randomized-controlled trials were included in this review. The current available evidence to support the use of botulinum toxin A in the treatment of myofascial pain syndrome is inconclusive.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and August 22, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with myofascial pain syndrome
Intervention	Botulinum Toxin Type A
Comparator	Usual care, methylprednisolone, placebo
Outcomes	Pain reduction, improved functioning, quality of life, safety
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT), and non-randomized studies (Non-RCTs)

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review/meta-analysis, or if were published prior to 2008. Systematic reviews/meta-analyses with a more recent update were considered duplicates and were excluded; the most recent update will be considered the primary publication.

Critical Appraisal of Individual Studies

The methodological quality of the included systematic reviews and meta-analyses was evaluated using the "assessment of multiple systematic reviews" (AMSTAR).[8] The Downs and Black Checklist[9] was used to assess included randomized controlled trials. For the included studies a numeric score was not calculated for quality assessment. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 100 citations were identified in the literature search. Following screening of titles and abstracts, 85 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons, leaving seven articles that reported three systematic reviews and meta-analyses and four unique randomized-controlled trials. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Two systematic review (SRs),[10,11] one SR with meta-analysis,[12] and four RCTs,[13-16] were included in this review. Detailed study characteristics are provided in Appendix 2.

Systematic Reviews

The SRs originated in Canada,[12] the United states,[11] and Brazil.[10] Zhang et al.[12] examined the efficacy of BoNTA versus placebo or other non-active therapies including exercise in reducing chronic musculoskeletal pain. Twelve RCTs evaluating BoNTA for MPS were included in this review, with eight of these trials included in the meta-analysis. Seven trials of the twelve included RCTs included in Zhang et al.[12] SR were also included either in Zhou et al.[11] SR (six RCTs in common) or Soares et al.[10] SR (three RCTs in common). Zhou et al.[11] evaluated the efficacy of BoNTA injection at active trigger points as a treatment for MPS. Eight double blinded RCTs were included in this review, with BoNTA compared to saline or bupivacaine in the included trials. Soares et al.[10] examined the effectiveness and safety of BoNTA versus placebo or other alternative drugs (not specified) in the treatment of MPS. Four RCTs were included in this review of which three trials were included in Zhang et al.[12] and two trials included in Zhou et al.[11] The primary outcome in the Zhang et al.[12] and Zhou et al.[11] SRs was reduction in pain intensity while that for Soares et al.[10] SR was frequency, intensity and duration of pain.

Randomized Controlled Trials

One RCT was conducted in each of the following countries: US,[13] Italy,[14] and Germany.[15] The fourth RCT was multinational, being conducted in Sweden and Denmark.[16] Nicol et al.[13] used an enriched protocol design where in phase I all patients received BoNTA then after six weeks patients were assessed and those who were considered responders were enrolled in the phase II of the study and were randomized to receive either BoNTA or placebo in a double-blind fashion. Patients diagnosed with myofascial pain of the neck and shoulders were enrolled in this trial. Pain intensity and health related quality of life were assessed six and twelve weeks after

randomization. Study by Benecke et al.[15] evaluate the efficacy and tolerability BoNTA (Dysport) 400U for the treatment of upper back MPS using standardized fixed location injections where the intervention and the comparator were injected into 10 fixed locations in predetermined injection sites in the head, neck, and shoulder. The proportion of patients with mild or no pain at week 5, change in pain intensity, and duration of pain were assessed in this study. Guarda-Nardini et al.[14] compared BoNTA (Dysport) 150U injections with fascial manipulation in patients with temporomandibular disorders (TMD) diagnosis of myofascial pain. This study was an open label randomized trial. Pain was assessed at baseline and at three months. Ernberg et al.[16] was a randomized double-blind cross-over trial comparing BoNTA with isotonic saline for the treatment of persistent myofascial TMD pain. After randomization, twelve patients received BoNTA (Botox) 50 U per muscle, while nine patients received saline. After 3 months those who received BoNTA received saline while those who received saline in the beginning of the study received BoNTA (Botox) 50 U per muscle after three months. Pain and side effects were assessed three month after receiving treatment.

Summary of Critical Appraisal

The strengths and limitations of the included systematic reviews and RCTs are summarized in Appendix 3.

Systematic Reviews

All three included SRs used comprehensive methods to search the literature.[10-12] Two of the three included SRs included a formal assessment of study quality,[10,12] but the results of the quality assessment in Zhang et al.[12] did not appear to be considered when formulating the conclusions. Publication bias was assessed in two of the three SRs,[10,12] but the results of the publication bias assessment was not presented in Soares et al.[10] while in Zhang et al.[12] no publication bias was detected. One of the three included SRs did not provide a detailed study characteristics,[11] though data extraction was not performed in duplicate in this study. In the other two SRs[10,12] literature selection and data extraction were conducted by two reviewers independently. In Zhang et al.[12] data were pooled, however that pooling might not be appropriate because the severity of MPS and the anatomic site of pain varied between included studies, also different dosages of BoNTA were used in each study.

Randomized Controlled Trials

In two studies, the method of randomization of participants to each treatment arm was not described.[13,14] Two studies stated that the allocation sequence was concealed,[15,16] whereas the other two studies did not. While three of the four studies were described as double-blind,[13,15,16] it was unclear in one of the studies if patients and study personnel were blinded.[13] The sample size was justified in three RCTs.[14-16] Two studies used intention-to-treat analysis.[15,16] Adverse events were only reported in one of the four studies.[15] One of the studies[13] used an enriched protocol design, where only patients who were responders to BoNTA in the first phase of the study were enrolled in the second phase, hence only patients who are most likely will respond to BoNTA were included. This may bias the results in favor of BoNTA. In addition one of the studies[16] used a cross-over design. Using such design might bias the results mainly because blinding might not have been maintained, hence potentially biasing the results in favor of BoNTA. On the other hand active treatment might have not completely washed out at the time of cross over.

Summary of Findings

Details on individual study findings are tabulated in Appendix 4.

Pain reduction

All included studies reported results for pain reduction.[10-16] The meta-analysis by Zhang et al.[12] reported a small amount of pain relief in BoNTA group which was not statistically significant when compared to placebo. The SR by Zhou et al.[11] reported that BoNTA showed statistically significant improvement in pain score when compared to placebo in three out of seven trials, while the SR by Soares et al.[10] reported that one study out of the four included trials reported significant improvement in pain intensity scores in favor of BoNTA when compared with placebo. The RCT by Nicol et al.[13] reported that BoNTA improved average visual numerical pain scores compared to placebo, while Benecke et al.[15] reported that pain intensity was significantly lower in the BoNTA group compared with placebo group from week 4 to week 12. On the other hand, significant improvement in pain symptoms were observed between BoNTA treatment and fascial manipulation techniques as reported by Guarda-Nardini et al.[14] The proportion of patients with 30% pain reduction was not significantly larger for BoNTA than saline at any follow-up visit as reported by Ernberg et al.[16]

Improved functioning

Two RCTs reported results on improved functioning.[13,16] Nicol et al.[13] reported that subjects who received BoNTA had a statistically significant improvement in the interference scores for general activity when compared to placebo, however in this study the physical functioning domain of the SF-36 was not significantly better in BoNTA group when compared with placebo group. Ernberg et al.[16] reported that there was no change in physical functioning scores after any treatment compared to baseline.

Quality of life

One RCT reported results on quality of life.[13] Nicol et al.[13] reported that there was no statistically significant improvement in quality of life between patients who received BoNTA and those who received placebo as measured by SF-36 questionnaire.

Safety

Two SRs and one RCT reported safety results.[10,12,15] Zhang et al.[12] indicated that most studies reported transient or no side effects. Soares et al.[10] indicated that significantly more adverse events were reported in BoNTA group when compared with placebo group in one of the studies, with the most common adverse event being sore muscle, while in the other three studies adverse event rates were similar in both treatment groups. The RCT by Benecke et al.[15] reported that there were no statistical differences in the number of adverse events experienced by the two groups, that no patients withdrew from the study due to adverse events, and no serious adverse events occurred during the study.

Limitations

The methodological quality of the included SRs was high in two of the reviews ,[10,12] and low in the third review.[11] There was overlap in included studies among the three SRs, with none of

them including all of the studies, this is mainly due to the year of publication and inclusion/exclusion criteria of each of the SRs this overlap. This overlap could lead to an overrepresentation of individual study results in the findings of this review. The main methodological limitation of RCTs were that the randomization method and allocation concealment were not clearly reported in two RCTs[13,14] and the sample size was small in two RCTs.[14,16] Blinding in Ernberg et al.[16] might have been broken due to the cross over design and the positive results of BoNTA could be due to the disclosure of the drug. Finally, in Nicol et al.[13] only patients who were responders to BoNTA in the first phase of the study were enrolled in the second phase, hence only patients who are most likely will respond to BONTA were included.

The major limitations of the overall body evidence are discussed as follows: Different diagnostic criteria for MPS was used in trials, with some studies applying inclusion criteria that would have led to the exclusion of their patients from other studies, this difference would limit comparability between trials. Different muscles were injected in different studies. The number of trigger points injected was different between studies. Similarly, the dose used differed from one study to another. There was a short span of follow-up period, where the length of follow-up was suboptimal in some of the studies. Small sample size, where many of the trials included in the SRs and two of the included RCTs had a small number of subjects. Different methodology to assess pain was used in different studies. Finally, variability in outcomes might be explained by the different chemical makeup of BoNTA preparations.

Only one study with 15 patients was conducted in Canada. This study was included in one of the of the SRs. In addition none of the chemical makeup of BoNTA preparations is approved for use in Canada for the treatment of MPS, and it seems that there is no standard dosing for these preparations. Given these limitations, generalizability of the study results to Canadian setting is uncertain.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In the previous Rapid Response[7] done by CADTH, one systematic review (SR) and five randomized controlled trial (RCTs) were identified. The SR concluded that evidence cannot support the use of BoNTA injection in trigger points for myofascial pain and four out of five included trials reported that BoNTA has no effect on pain, or the effect is not statistically significant. It was concluded in that Rapid Response that the clinical evidence does not suggest that BoNTA is effective for the treatment of MPS.

Based on the SRs and the RCTs that were identified,[10-16] the current clinical evidence to support the use of BoNTA in the treatment of MPS is inconclusive. One of the SRs concluded that BoNTA injections do not result in any significant pain relief for patients with MPS,[12] while the other two SRs concluded that results of BoNTA injection for MPS are mixed.[10,11] In two of the included RCTs[13,15] it was concluded that BoNTA significantly reduced pain when compared with placebo, while the other two included RCTs did not find significant differences. The discrepancy in the efficacy of different studies could be explained by the different chemical makeup of various BoNTA preparations, different diagnostic criteria in the included studies, heterogeneity of exclusion criteria, concomitant interventions, injection techniques, volume injected, sample size, short duration of studies, and different outcome measures. These variables and limitations make rendering a conclusion difficult. More high quality RCTs of BoNTA for the treatment of MPS are needed to be conducted in order to draw a firm conclusion on its effectiveness and safety.

The difference in finding from the previous Rapid Response report is mainly due to the fact that in 50% of the included RCTs, BoNTA significantly reduced pain when compared with placebo, and two of the included SRs concluded that results of BoNTA injection for MPS are mixed, This made it difficult to render a clear conclusion on the efficacy of BoNTA for MPS.

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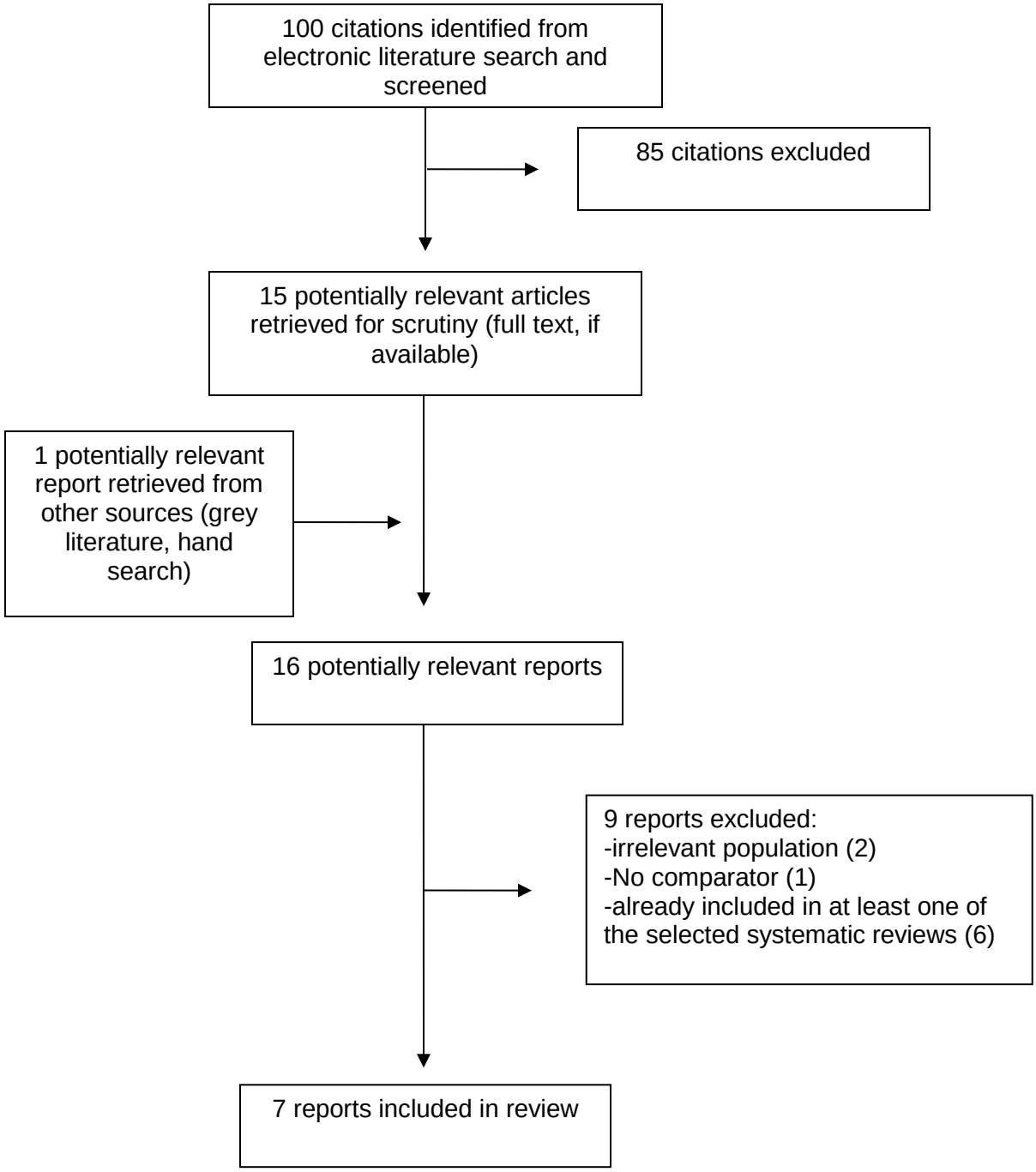
APPENDIX 1: Selection of Included Studies



APPENDIX 2: CHARACTERISTICS OF THE INCLUDED STUDIES

Table A2.1: Characteristics of the Included Systematic Reviews and Meta-analyses

Objectives/Scope	Type of primary studies	Population	Intervention	Comparator	Outcomes	Notes
Zhang et al. 2011,[12] Canada						
To evaluate the efficacy of BoNTA versus non-active injection or other treatment in reducing chronic musculoskeletal pain Systematic review and meta-analysis of randomized controlled trials	RCTs only • A total of 21 trials, were included in the review; of which, 12 trials evaluated BoNTA for MPS, 8 of these 12 trials were included in the meta-analysis • Trials were published between 1994 and 2008 • A total of 332 patients contributed to myofascial pain analysis	The review included trials on patients experiencing chronic musculoskeletal pain of all ages, gender and degree of severity	Intramuscular or subcutaneous BoNTA injections	• Placebo • other non-active therapies, including exercise	Reduction in pain severity through the period of follow-up	Four of the included studies in the review were not included in the statistical analysis due to inadequate data reporting The review included seven studies that are common with other systematic reviews (Gobel et al. 2006,[17] Ojala et al. 2006,[18] Qerama et al. 2006,[19] Cheshire et al. 1994,[20] Wheeler et al. 2001,[21] Ferrante et al. 2005,[22] and Wheeler et al. 1998[23])
Zhou et al. 2014,[11] US						
To evaluate the efficacy of BoNTA injection at active trigger points as a treatment for MPS Systematic review of randomized controlled trials	Double-blinded RCTs only • A total of 8 trials, were included in the review • Trials were published between 1994 and 2006	The review included trials on patients with MPS	BoNTA injections into trigger points for pain	• Saline • Bupivacaine	reduction in pain scores	The review included six studies that are common with other systematic reviews (Göbel et al. 2006,[17] Qerama et al. 2006,[19] Cheshire et al. 1994,[20] Wheeler et al. 2001,[21] Ferrante et al. 2005,[22] and Wheeler et al. 2001[23])
Soares et al. 2014,[10] Brazil						

Objectives/Scope	Type of primary studies	Population	Intervention	Comparator	Outcomes	Notes
To evaluate the effectiveness and safety of BoNTA in the treatment MPS Systematic review of randomized controlled trials	RCTs only • A total of 4 trials, were included in the review • Trials were published between 2006 and 2010	Male and female adult patients of with a clinical diagnosis of MPS Studies with MPS of the neck and head were excluded	BoNTA irrespective of dose	• Placebo • alternative drug (unspecified)	Frequency, intensity and duration of pain, pressure pain tolerance, and pain relief Adverse events	The review included three studies that are common with other systematic reviews (Göbel et al. 2006,[17] Ojala et al. 2006,[18] Qerama et al. 2006,[19])
BoNTA=Botulinum Toxin A; MPS=Myofascial pain syndrome; US=the United States of America						

Table A2.2: Characteristics of the Included Randomized Controlled Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Outcomes
Nicol et al. 2014,[13] US			
To evaluate the analgesic effect of BoNTA directly into painful muscle groups in the treatment of cervical and shoulder girdle myofascial pain Enriched protocol design was used, where subjects who were responders to BoNTA were entered in the second phase of the study which was randomized double-blind Patients were assessed six and twelve weeks after randomization	• Male and female patients in the age group 18 to 65 with myofascial pain of the neck and shoulders of at least 8 months duration were included • Patients had to have a Visual Numerical Scale pain score 4 or higher at baseline to be included • Patient with history of injection of BoNTA or with significant medical or psychiatric disease or were excluded • A total of 54 patients were randomized	**Intervention:** • BoNTA into each painful muscle, variable dose was used with a maximum dose of 300U, n=29 **Comparator:** • Placebo (Saline) into each painful muscle, n=25	• pain intensity using a Visual Numerical Scale • health-related quality of life • disability • headache
Guarda-Nardini et al. 2011,[14] Italy			

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Outcomes
To compare BoNTA injections with fascial manipulation in patients with TMD diagnosis of myofascial pain Parallel design open label RCT Patients were assessed at baseline and at three months	• Adult patients with a research diagnostic criteria for TMD diagnosis of myofascial pain with or without limited opening and bilateral pain of at least six months duration were included • Patients with TMD diagnosis of arthralgia and/or osteoarthritis were excluded • A total of 30 patients were randomized	**Intervention:** • BoNTA (Dysport®) 150U in the temporalis and masseter muscles. **Comparator:** • Fascial manipulation technique	• Pain assessed using VAS • Jaw range of motion
Benecke et al. 2011,[15] Germany			
To evaluate the efficacy and tolerability BoNTA for the treatment of upper back MPS using standardized fixed location injections Parallel design double-blind RCT Patients were followed-up for 12 weeks after treatment	• Patients in the age group 18 to 70 with MPS affecting cervical muscles of the back and shoulder and with moderate to severe intensity were included • Patient with history of injection of BoNTA for pain or had concurrent muscle disease, or had severe concomitant disease, or had specific back pain disorder were excluded • A total of 154 patients were randomized	**Intervention:** • BoNTA (Dysport®) 400U, n=81 **Comparator:** • Placebo (Saline), n=72 Intervention and the comparator were injected into 10 fixed locations in predetermined injection sited in the head, neck, and shoulder	• Proportion of patients with mild or no pain at week 5 • Change in pain intensity • Duration of pain • Number of pain free days per week • Time to reduction in pain • Safety
Ernberg et al. 2011,[16] Sweden and Denmark			
To compare BoNTA with isotonic saline for the treatment of persistent myofascial TMD pain. Randomized double-blind Cross-over design Patients were followed-up for three months after treatment	• Adult patients with a research diagnostic criteria for TMD diagnosis of myofascial pain with pain that persisted for at least 6 months in spite of conservative treatment were included • Patients with systemic inflammatory connective tissue diseases, fibromyalgia, pain of dental origin, whiplash-associated disorder, neuropathic pain or neurological disorders, or use aminoglycoside antibiotics, or muscle relaxants were excluded • A total of 21 patients were randomized	**Intervention:** • BoNTA (Botox®) the total dose of BoNTA was 50 U per muscle, if both muscles were treated a maximum dose of 100U received by the patient. **Comparator:** • Isotonic saline	• Pain • Physical function • Emotional function • Global improvement • Side effects

BoNTA=Botulinum Toxin A; MPS=Myofascial pain syndrome; TMD=Temporomandibular disorders; US=the United States of America; VAS=visual analog scale

APPENDIX 3: SUMMARY OF STUDY STRENGTHS AND LIMITATIONS

Table A3.1: Summary of Critical Appraisal of the Included Systematic Reviews and Meta-analyses

First Author, Publication Year, Country	Strengths	Limitations
Zhang et al. 2011,[12] Canada Systematic review and meta-analysis	• Comprehensive literature search based on pre-defined criteria • Detailed characteristics of the included studies were presented • Literature selection and data extraction were conducted by two reviewers independently. • Conflict of interest was stated • The methodological quality were evaluated systematically by two reviewers using Jadad scale	• For MPS no subgroup analyses were performed on dosage per injection, treatment period, severity of MPS. • Anatomic site of pain varied between included studies • Did not consider the results of the quality assessment when formulating conclusions
Zhou et al. 2014,[11] US Systematic review	• Comprehensive literature search based on pre-defined criteria • Conflict of interest was stated	• Lack of description of study characteristics • Study selection and data extraction were not performed in duplicate • No list of excluded studies was provided • Publication bias was not assessed • The quality of the included studies was not evaluated
Soares et al. 2014,[10] Brazil Systematic review	• Comprehensive literature search based on pre-defined criteria • Detailed characteristics of the included studies were presented • Literature selection and data extraction were conducted by two reviewers independently • The risk of bias and the methodological quality were evaluated systematically by the two reviewers using the Cochrane risk of bias tool. • list of excluded studies was provided • Conflict of interest was stated	• Did not differentiate between distinct formulations of BoNTA • Alternative drugs were not specified

BoNTA=Botulinum Toxin A; US=the United States of America

Table A3.2: Summary of Critical Appraisal of the included Randomized-controlled trial

First Author, Publication Year, Country	Strengths	Limitations
Nicol et al. 2014,[13] US	• The study was double blinded, however it is not describe how patients and study personal were blinded • Objectives and inclusion/ exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • P-values provided	• Randomization method and allocation concealment were not described. • The article did not precise if the analysis was based on the intention to treat or per-protocol dataset • The sample size was based on convenience rather than power analysis • Only patients who were responders to BoNTA in the first phase of the study were enrolled in the second phase, hence only patients who are most likely will respond to BoNTA were included • Industry-sponsored study • Adverse events were not reported
Guarda-Nardini et al. 2011,[14] Italy	• Objectives and inclusion/ exclusion criteria were stated. • Randomized but open label study • Choice of sample size was justified.	• Randomization method was not described. • patients and investigators were not masked to treatment allocation • Allocation was not described • small sample size • number of patients randomized to treatment groups was not reported • Adverse events were not reported
Benecke et al. 2011,[15] Germany	• The study was double blinded • Appropriate method of randomization described. • Allocation was concealed • Objectives and inclusion/ exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • Choice of sample size was justified. • P-values provided • intent-to-treat analysis was used	• Industry-sponsored study
Ernberg et al. 2011,[16] Sweden and Denmark	• The study was double blinded • Appropriate method of randomization described. • Allocation was concealed	• Small sample size • Blinding might not have been maintained because of the cross over study design

First Author, Publication Year, Country	Strengths	Limitations
	• Objectives and inclusion/ exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • Choice of sample size was justified. • P-values provided • intent-to-treat analysis was used	• Adverse events were not reported
BoNTA=Botulinum Toxin A; US=the United States of America		

APPENDIX 4: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS

First Author, Publication Year, Country	Main Findings	Authors' Conclusion
Systematic review/Meta-analysis		
Zhang et al. 2011,[12] Canada Systematic review and meta-analysis	• Pooled SMD of pain relief from eight studies was -0.16 (95% CI: -0.39 to 0.06) • Out of the 12 trials included in this review, only 3 studies reported positive result with respect to relieving pain intensity • None or transient side effects that were resolved spontaneously were reported in most studies.	There is convincing evidence that BoNTA injection do not result in any significant pain relief for patients with MPS
Zhou et al. 2014,[11] US Systematic review	• Of the seven trials comparing BoNTA versus placebo, only three showed significant improvement in pain score, while in the other four studies no statistical difference between BoNTA and placebo was reported. • No significant difference between BoNTA and Bupivacaine in reducing pain	Results of BoNTA injection of trigger points for MPS are mixed, with some studies showed statistically significant pain relief from BoNTA injection, other studies showed no pain relief when compared to placebo saline injections.
Soares et al. 2014,[10] Brazil Systematic review	• Four studies with a total of 233 participants were included in this review • one study with 145 participants reported significant improvement rates of pain intensity scores and duration of daily pain in favor of BoNTA when compared with placebo • No statistically significant difference between BoNTA and placebo in pain intensity was reported in the other three studies • Significantly more adverse events were reported in BoNTA group when compared with placebo group in one of the studies, with the most common adverse event was sore muscle. Adverse event rates were similar in both groups in the other three	There is inconclusive evidence to support the use of BoNTA in the treatment of MPS.

First Author, Publication Year, Country	Main Findings	Authors' Conclusion
	studies.	
Randomized Controlled Trials		
Nicol et al. 2014,[13] US	• Injection of BoNTA into painful muscle groups improved average visual numerical pain scores compared to placebo (*P* = 0.019, 95% CI: [0.26, 2.78]). • No significant difference between BoNTA and placebo in quality of life measure using SF-36 • Subjects who received BoNTA had a statistically significant improvement in the interference scores for general activity (P = 0.046, 95% CI: [0.038, 3.700]) and sleep (P = 0.02, 95% CI: [0.37, 4.33]) when compared to placebo	Average pain scores and certain facets of quality of life were improved in patients experiencing severe cervical and shoulder girdle myofascial pain after having BoNTA injected directly into painful muscle groups
Guarda-Nardini et al. 2011,[14] Italy	• Both BoNTA treatment and Fascial manipulation technique provided significant improvement in pain symptoms. • Difference between the two treatment protocols as to change in pain symptoms assessed using VAS was not significantly different.	BoNTA treatment and Fascial manipulation technique seems to be almost equally effective with Fascial manipulation technique being slightly superior in reducing subjective pain perception.
Benecke et al. 2011,[15] Germany	• The proportion of patients with mild or no pain at week 5 was 37/76 (49%) in the BoNTA group compared with 27/72 (38%) of patients in the placebo group (*P* = 0.1873) • Compared with patients in the placebo group, patients in the BoNTA group had a their duration of daily pain reduced from week 5, however results were statistically significant differences at weeks 9 and 10 (*P* = 0.04) • Pain intensity for all trigger points was significantly lower in the BoNTA group compared with placebo group from week 4 to week 12 (*P* ≤ 0.001)	Improvements in pain control for at least 8 weeks following treatment was produced in patients with upper back myofascial pain syndrome after receiving BoNTA in 10 fixed location injections of 40 units however significance difference was only found in week 8 after treatment for the proportion of patients with mild or no pain

First Author, Publication Year, Country	Main Findings	Authors' Conclusion
	• No statistical differences in the number of adverse events experienced by the two group was reported • No patients withdrew from the study due to adverse events, and no serious adverse events occurred during the study.	
Ernberg et al. 2011,[16] Sweden and Denmark	• No difference in average weekly pain intensity was found between BoNTA and Saline. • The proportion of patients with 30% pain reduction was 43% after 1 month and and 33% after 3 month in the BoNTA group compared to 33% and 19% in the Saline group. The between group difference was not significantly larger for BoNTA than saline at any follow-up visit. • No significant changes after treatment in physical functioning	BoNTA is not efficacious in patients with persistent myofascial TMD pain when used as an adjunct to conservative treatment
BoNTA=Botulinum Toxin A; CI=confidence interval; MPS=Myofascial pain syndrome; SMD=standardized mean difference; TMD=Temporomandibular disorders; US=the United States of America		