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Botulinum toxin type for the management of masticatory muscle pain in temporomandibular disorders: a systematic review

Abstract

Background: Botulinum toxin type A (BoT-A) has gained significant clinical interest in the management of masticatory muscle pain in temporomandibular disorders (TMD). This may be due to clinical success of BoT-an in treatment of other neuromuscular and refractory chronic pain disorders in the head and neck region, and the limited understanding of the underlying pathophysiology of masticatory muscle pain.

Methods: A systematic review was conducted to determine the effectiveness of botulinum toxin type A in the management of masticatory muscle pain in temporomandibular disorders, specifically myalgia, or myofascial pain. Three reviewers separately identified the pertinent literature by searching MEDLINE via PubMed, Web of science and Cochrane databases and reference lists of relevant articles under the inclusion criteria of all studies in English language.

Results: Thirteen manuscripts met the inclusion criteria. Among these six were randomized controlled trials (RCT) and seven were case-series investigations. Two out of 6 RCT and all of the 7 case-series investigations have suggested BoT-A therapy being significantly better in management of masticatory muscle pain in TMD.

Conclusion: The effectiveness of BoT-A treatment for the management of masticatory muscle pain in TMD has yet to be established. Results of both types of investigations are convoluted by the presence of multiple methodological limitations and heterogeneity in protocol. Botulinum toxin injection therapy appears to effective in certain patients with masticatory muscle pain disorders in TMD. However, there is limited evidence regarding the characterization of participants that would benefit from this therapeutic modality.

Keywords: temporomandibular disorders, botulinum toxin, myalgia, masticatory muscle pain, pain

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Introduction

Temporomandibular disorders (TMD) encompass a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joints (TMJs), the masticatory muscles, and associated tissues.[1] The prevalence of pain-related TMD, such as, masticatory myalgia, masticatory myofascial pain and TMJ arthralgia, has been reported to be between 2.5 % to 10 % in the general adult population, making it the second most common musculoskeletal condition, after chronic back pain, which results in pain and disability.[2,3] Common manifestations of pain-related TMD consist of pain, of a persistent, recurring, or chronic nature,[4,5] limitation in the range of mandibular motion, and joint noises.[4–6] Pain-related TMD can affect the individual's daily activities, psychosocial functioning, and quality of life.[7] It has been estimated that the annual pain-related TMD management cost in the United States, excluding diagnostic imaging, in the last decade was approximately $4 billion.[8] Furthermore, in the United States, it is estimated that for every 100 million working adults, pain-related TMD contributes to 17.8 million lost workdays annually.[9,10] Although the pathophysiology of pain-related TMD is poorly understood, multiple risk factors have been identified, such as, gender, pain provoked during jaw function and/or palpation, oral parafunctions, other chronic pain conditions, pain sensitivity and psychosocial characteristics.[11,12] Multiple treatment modalities have been suggested as a treatment for masticatory muscle pain disorders, including patient education, behavioral management, physical therapy, occlusal splints, and pharmacotherapy.[6–14] However, no specific therapy has been proven uniformly effective in providing symptomatic relief.[13] Because of this, the search for effective and safe therapies has been topic of interest among researchers. An example of such therapy is the emergence of botulinum toxin type A (BoT-A) as a potential therapeutic modality for management of masticatory muscle pain in TMD. Botulinum toxin type A is a subtype of a potent biologic toxin produced by Clostridium botulinum, a presynaptic neurotoxin. It blocks the calcium ion-mediated release of acetylcholine at the neuromuscular junction. The primary effect is on alpha-motor neuron function. However, it has been suggested that it may also alter the functioning of gamma-motor neurons in the muscle spindles.[15,16] Independent of the neuromuscular effects, BoT-A has been suggested to have analgesic properties.[16,17] However, the mechanism by which the analgesic effects are mediated is not fully understood. Animal-based investigations suggest BoT-A inhibits neurogenic inflammation by peripherally blocking the release of inflammatory neuropeptides, such as, substance P (SP) and glutamate.[17,18] In addition, BoT-A has

been found to inhibit the release of Calcitonin Gene-Related Peptide (CGRP),[18] and reduce the vascular response to algogenic substances, such as capsaicin, applied to human skin.[1] Botulinum toxin type–A may also act centrally, it has been suggested that it may undergo retrograde transportation by sensory neurons and inhibit the release of neurotransmitters at the central nerve terminals.[17–20] Intra-muscular administration of botulinum toxin has shown to be significantly useful in the management of muscle hyperactivity disorders, such as cervical dystonia, spasmodic dystonia, or blepharospasm.[21,22] In addition to the reduction in dystonia-associated muscle hyperactivity, it has been shown to reduce the associated pain.[15–21] Masticatory muscle hyperactivity in TMD and its associated pain have been suggested as self-perpetuating in nature.[23] However, based on multiple EMG-based investigations, current evidence suggests that TMD-associated pain is correlated with muscle hypoactivity.[23–25] Botulinum toxin has also been shown to be clinically beneficial in the management of refractory chronic pain disorders when injected into the soft-tissue (subcutaneously or intra-muscularly) as in case of chronic migraine headaches[26,27] and trigeminal neuralgia.[28,29] Likewise, it has been shown to be effective when injected intra-articularly for the management of refractory arthritis joint pain.[30,31] The proposed mechanism of relief has been attributed to the neuro-inhibitory and anti-nociceptive properties of the toxin along the peripheral and central nervous system.[17] The clinical success of BoT-A in treatment of neuromuscular and refractory chronic pain disorders in the head and neck region, and the limited understanding of the underlying pathophysiology of pain in TMD as well as the refractory nature of pain in some cases, may explain the clinical interest of physicians in the use of BoT-A in the management of masticatory muscle pain in TMD. The U.S. Food and Drug Administration (FDA) and the European Medicines Agencies (EMA) have not yet approved use of BoT-A to manage masticatory muscle pain in TMD. Nevertheless, it is being used and promoted as an off-label indication.[32] Several studies have been conducted on the effectiveness of BoT-A for the management of masticatory muscle pain in TMD. However, the results have been inconsistent. While some of the studies have reported evidence for its efficacy, others have reported inconclusive findings. Due to this difference in reporting, a systematic review was conducted to determine the effectiveness of BoT-A in the management of masticatory muscle pain in TMD, specifically masticatory myalgia, or masticatory myofascial pain.

Materials and methodology

The PRISMA guidelines were used as a template for the systematic review. The clinical question, "Is botulinum toxin A more efficacious than placebo treatment for management of pain associated with masticatory myalgia among patients of TMD, in an out-patient setting?" (PICOS) was utilized to guide the review. Observational investigations evaluating the effectiveness of BoT-A for treatment of masticatory muscle pain in TMD, specifically masticatory myalgia or masticatory myofascial pain were included. Publications were limited to English language, humans, and adults (≥16 years) only. Publication date limit for the selection of articles was from beginning to June 2016. Publications such as literature reviews and case-reports were excluded from this review. Three reviewers separately identified the pertinent literature by searching MEDLINE via PubMed, The web of science, and Cochrane databases and reference lists of relevant articles for manuscripts meeting the inclusion and exclusion criteria. The databases were searched using relevant keywords and MeSH terms. The search strategy was: ("botulinum toxin"[MeSH]) OR ("botulinum toxin type A"[MeSH]) OR (clostridium botulinum) OR (clostridium botulinum toxin) OR (onabotulinumtoxinA) OR (Abobotulinumtoxin) OR (botox) AND ("Myofascial Pain Syndromes"[MeSH]) OR ("myalgia"[MeSH]) OR ("masticatory muscle"[MeSH]) OR ("temporomandibular joint dysfunction syndrome"[MeSH]) OR ("facial pain"[MeSH]).Overview of the procedure is provided in figure 1. Three reviewers independently read the title and the abstract of all publications that were identified by the search strategy. The reviewers met and developed a final list of publications to be read by consensus. One reviewer read all the papers (SNK); the other two reviewers (HC, YG) equally divided the number of papers so that two reviewers evaluated each paper independently. Articles were reviewed based on the study design, aim of the study, demographics, clinical assessment methodology, botulinum toxin A type and protocol of administration, results, conclusions, adverse events, and limitations. In addition, the randomized controlled trials were assessed using Cochrane collaboration's tool for assessing risk of bias,[33] while rest of the investigations were assessed using Newcastle-Ottawa quality assessment scale for case-control studies.[34] Any disagreements between the reviewers were resolved through discussions and final decisions were reached through consensus.

Results

Three databases (MEDLINE via PubMed, The web of science, and Cochrane databases) and reference lists of relevant articles were systematically searched for articles. A total of 3.198 articles were identified with the search strategy. Three reviewers independently reviewed titles and abstracts of all of the identified manuscripts. The reviewers met and developed a final list of publications to be read by consensus. Three thousand one hundred and eighty five publications were excluded because of at least one of the following reasons: did not assess the effect of BoT-A on masticatory muscle pain associated with TMD, were case-reports or literature reviews, were not in the English language, or were based on animal-models. Thirteen met the inclusion criteria. Of these, 6 were randomized control trials (RCTs), and 7 were non-randomized case-series investigations. The randomized controlled trials included in the present systematic review were prospective human controlled trials, published between 2002 and 2012.[35–40] Of the six RCTs, two were crossover studies[35–39] and four were parallel design studies.[36–40] Each investigation evaluated participants using standardized examination protocol except one trial.[40] All of the participants were given diagnosis of either "masticatory myofascial pain" with or without "bruxism" and "functional disc displacement", or of "chronic facial pain associated with or caused by masticatory hyperactivity, parafunctional movements, and hypermobility disorders". Furthermore, included participants had chronic symptomatology (3>months) and were refractory to conservative therapy (such as, behavior modification, thermal therapy, physical therapy, and occlusal orthotic device therapy). In total, 200 individuals (mostly females) participated, of which 133 underwent botulinum toxin injection therapy. The location and technique of injections varied. Injections were primarily placed in masseter muscles. However, in few studies injections were also placed in temporalis and medial pterygoid muscles. Injections were placed in either a pre-determined area using a specified pattern, such as chessboard or reverse pyramid, or corresponding to the site of maximum pain, or at the "most active site" of the muscle, based on manual palpation or EMG guidance. The total dose of botulinum toxin injected ranged from of 30U-50U *per side* for masseter muscles, 20U–35U *per side* for temporalis muscles, and up to 35U *per side* for medial pterygoid muscles. In all of the trials, groups receiving BoT-A

therapy, has reduction in pain intensity and improvement in range of motion. However, these changes were statistically significant in only two of the six trials. Four of the six investigations reported minor adverse events, such as, discomfort/pain (4), transient facial paralysis (3), headache (7), fatigue (2), influenza like symptoms (2), dry mouth (1), difficulty with swallowing (1) and smiling (4) in association with BoT-A therapy. Overall, 3 of the 6 RCT investigations failed to reject the null hypothesis. However, 2 of these investigations were underpowered (<50%). The study characteristics are summarized in Table 1. The quality of the RCT was assessed using Cochrane risk of bias tool for randomized controlled trials. Three of the six RCT were classified as having unclear risk of selection bias because either limited evidence was provided regarding the randomization sequence generation or limited information was present regarding the allocation concealment. One of the included trials had high risk of performance bias.[37] In this particular investigation, the corresponding group underwent facial manipulation, which would have not made possible for blinding of the participants and researcher. Overall, majority of investigations had low risk of detection, attrition, and reporting bias. Table 2 presents the individual domain risk of bias for each of the included RCT. The non-randomized observational studies selected in this systematic review were case-series, published between 1999 and 2013. Participants were given the diagnosis of "masticatory myofascial pain", "muscle-centered TMD", "chronic facial pain", or "TMD" with or without "bruxism", "Chronic tension type headache", and "muscle hyperactivity". Similar to RCT, all of the participants had chronic symptomatology (3> months) and were refractory to conservative therapy. The location and protocol of injection therapy was variable. Injections were primarily placed in the masseter and the temporalis muscles. However, in some investigations medial pterygoid muscles were also injected. Injections were placed in either a pre-determined area using a specified pattern, such as chessboard or reverse pyramid, or corresponding to the site of maximum pain, or at the site of "maximum muscle thickness", using manual palpation or EMG guidance. The dosage of injection for each muscle varied from 7.5 U-200 U *per side*. All of the studies reported reduction in pain symptoms at follow-up. Transient adverse reactions were reported in four of the seven case-series. These consisted of facial muscle weakness and wasting (1), difficulty with speech and swallowing (2), muscle fatigue (35), headaches (3), bruising (1), and facial asymmetry (10). One study was found to be underpowered (< 50%). Six out of seven trials rejected the null hypothesis. However, reduction in pain after undergoing BoT-A injections was found to be statistically significant in all 7 investigations. The study characteristics are categorized and tabulated in Table 3. The quality of non-randomized case-series investigations was evaluated using Newcastle-Ottawa assessment scale for case-control studies. Based on the scale, all of the investigations scored 2 stars on the selection criteria, and 1 star on exposure criteria. No star was awarded to any investigation in comparability category. The results are summarized in Table 4.

Table 1 Assessment of randomized controlled trials using Cochrane collaboration's tool for assessing risk of bias tool

	Guarda-Nardini[36]	Ernberg[35]	Kortoglu [38]	Guarda-Nardini[36]	Von Lindern[40]	Nixdorff[39]
Random sequence generation	+	+	+	?	?	+
Allocation concealment	?	+	+	?	?	+
Blinding of participants and personnel	-	+	+	-	?	+
Blinding of outcome assessment	+	+	+	?	+	+
Incomplete outcome date	+	+	+	+	?	-
Selective reporting	+	+	+	+	?	?
Other bias	?	?	-	-	-	-

Low risk (+), High risk (-), Unclear risk (?)

Table 2 Summary of the randomized control trials included in the systematic review

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	statistics	Conclusions	Limitations
Guarda Nardini L et al.[37]	RCT (not blinded) Parallel design Aim: To determine the effectiveness of FM technique and BTA injections for the treatment of myofascial pain over 3 months.	N=30 22 ♀, 8 ♂ BTA Group Age: 47.7±14.3 yrs. FM Group Age: 43.2±13.9 yrs. All of the participants were given a diagnosis of bilateral "myofascial pain" for≥6 months. Participants with neurological, rheumatological, concurrent Arthralgia, or OA were excluded.	Participants underwent RDC/TMD examination. VAS for pain intensity. Assessments performed at baseline, post-injection and after 3 months.	Abobotulinum toxin A BTA group (15): - One time injection of BTA 150 U/side - Masseter muscle BTA 50 U/side (minimum 5 sites). - Temporalis muscle BTA 25 U/side (minimum 5 sites). Injection placed in pre-determined injection sites FM technique group (15)	ANOVA Repeated ANOVA Fisher's exact test	Failed to reject the null hypothesis. No statistically significant difference in outcome of VAS and all ROM except RL movement. Adverse event: Minor transient discomfort reported by participants in BTA group.	Reliability of clinical examiners not described. No information on preparation of BTA injections. Not blinded study design.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	statistics	Conclusions	Limitations
Ernberg M et al.[35]	RCT (double-blind) Cross-over design Aim: To test the hypothesis that BTA is more effective than isotonic saline for the treatment of persistent myofascial pain in TMD.	N=21 19 ♀, 2 ♂ Age: 38.0±12.0 yrs. Pain duration: 6.3±4.7 yrs. All of the participants were given a diagnosis of "myofascial pain". All of the participants undergone conservative therapy≥6 months. All of the participants had an average pain intensity of ≥30 mm on a 0-100 VAS. Participants with systemic inflammatory connective tissue diseases, whiplash-associated disorders, fibromyalgia, neuropathic pain or neurological disorders, pain of dental origin, use of muscle relaxants, or aminoglycoside antibiotics were excluded.	Participants underwent RDC/TMD examination. VAS for pain intensity. MPQ for pain assessment. PPT and PPTol. Participants were assessed during, after 1 month and 3 months.	Onabotulinum toxin A BTA group (21): One time injection of BTA 50 U/side (Diluted in saline) Masseter muscle BTA 50 U/side (10 U/0.1 mL, 3 sites). Control group (20): One time injection f saline Masseter muscle .5 mL of saline/side (3 sites) Injection placed in accordance with anatomy with EMG guidance.	2-way repeated measure ANOVA Holm-Sidak post Hoc test Dunn's method McNemar's test	Failed to reject the null hypothesis. After 1 month in BTA group change in pain intensity was 30 compared to 11 for control group. After 3 month in BTA group change in pain intensity was 23 compared to 4 for control group. 9 participants in BTA group compared to 7 in control group had 30 % pain reduction after 1 month. 7 participants in BTA group compared to 4 participants in control group had 30 % pain reduction after 3 months. Adverse events: Headache (7), fatigue (2), jaw pain (3), influenza like symptoms (2) and dry mouth (1) reported in BTA group.	Study was underpowered (<50%). Small sample size. Reliability of clinical examiners was not described. Both sides injected regardless of the site of pain.
Kurtoglu C et al.[38]	RCT (double-blind) Parallel design Aim: To evaluate: • Effect of BTA on pain and psychological status of myofascial pain pts. with and without DD. • Effectiveness of BTA compared to placebo	N=24 BTA group: 12 10 ♀, 2 ♂ Age: 29.6±12.7 yrs. (16-53 yrs.) Placebo group: 12 10 ♀, 2 ♂ Age: 23.4±4.7 yrs. (20-34 yrs.) All of the participants were given a diagnosis of "myofascial pain". In addition, 3 in BTA and 8 in placebo group were given a diagnosis of "Functional DD". All of the participants had undergone conservative TMD therapy without relief of symptoms. Participants with age < 14 years, allergy to botulinum toxin type A, pregnant or lactating were excluded.	Participants underwent RDC/TMD examination. Participants were assessed at baseline, day 14, and day 28. EMG was used for assessment of muscle activity.	Onabotulinum toxin A BTA group (12): • One time injection of BTA 100 U/participant. • (Diluted in saline) • Masseter muscle 30 U/side (10U/0.2 cc, 3 sites) • Temporalis muscle 20 U/side (10U/0.2 cc, 2 sites). Saline group [12]: • One time injection of 2cc of saline/participant. • Masseter muscle injected .3 cc (3 sites) • Temporalis muscle injected .2 cc (sites) Injected into the "most active" site of muscle as determined by palpation.	Friedman test Wilcoxon test Mann-Whitney U test Fisher's exact test	Null hypothesis was rejected. No significant difference found in pain, disability, and psychosocial status between two groups. Statistical difference between placebo and BTA group was observed in EMG at day 14. Adverse events: NR	Small sample size RDC-TMD does not have a diagnosis of "Functional DD". Participants were followed up for a short duration of time. Both sides injected regardless of site of pain. No clinical success criteria defined. Reliability of clinical examiners was not described. Inappropriate criteria to determine the "most active" part of the muscle.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	statistics	Conclusions	Limitations
Guarda Nardini L et al.[36]	RCT (double - blind) Parallel design Aim: To investigate the efficacy of BTA for treatment of myofascial pain symptoms in bruxers.	N=20 10 ♀, 10 ♂ All of the participants were given diagnoses of "myofascial pain" and "bruxism". Participants, who underwent treatment for myofascial pain or bruxism in ≤ 6 months, had neuromuscular pathologies or allergy to botulinum toxin type A were excluded.	Participants underwent RDC/ TMD examination and a validated set of screening criteria for bruxism. Assessment performed at baseline, 1 week, 1 month, and 6 months.	Onabotulinum toxin A. BTA group (10): • One time injection of 100 U/ participant Injected. • Masseter muscle 30 U/side (4 sites).- Temporalis muscle 20 U/ side (3 sites). Control group (10): • One time injection of saline. • Masseter muscle injected (4 sites) • Temporalis muscle injected (3 sites) • Injection placed in pre-determined injection sites.	2 sample permutation test Anderson-Darling permutation test	Null hypothesis was rejected. ROM improved in BTA group but remained constant in placebo group. Pain reduced in BTA group but remained unchanged in placebo group. Statistically significant difference observed in pain during chewing, perception of treatment efficacy at 6 month f/u.	Study was underpowered (<50%). No information on age of participants. Small sample size. BTA injection protocol not adequately described. Placebo injection protocol not adequately described. No information on adverse effects. Success criteria not defined. P-values are not adjusted for multiple comparisons. Effect of DD on the outcome of study not determined.
Von Lindern JJ et al.[40]	RCT (single- blind) Parallel design Aim: To investigate the therapeutic potential of BTA in the treatment of painful hyperactivity of the masticatory ms.	N=90 BTA group=60 Placebo group=30 All of the participants were given a diagnosis of "Chronic facial pain caused by masticatory muscle hyperactivity, parafunctional movements, and hypermobility disorders". All of the participants had failed to respond to ≥ 3 months of conservative therapy. Participants with non-muscular causes or unclear patterns of radiation of pain were excluded.	Participants underwent clinical examination and function analysis. VAS used for assessment of pain intensity. Assessment performed at baseline and at 4 weeks.	Abobotulinum toxin A BTA group (60): • 19/60 participants were injected ≥ 2 times (Diluted in saline). • Masticatory muscle BTA 35 U/muscle (5U/0.1 mL) Placebo group (30): Saline injected Injection placed in pre-determined injection sites	Chi-Square test	Null hypothesis was rejected. 91 % participants had improvement in symptoms. Statistically significant improvement of 3.2/10 in the BTA group compared to 0.4/10 in the placebo group. Adverse events: Difficulty in swallowing and temporary facial muscle paralysis (n=1)	No information on demographics. Clinical examination was not adequately described. Incomplete outcome data provided. BTA injection protocol not adequately described. Placebo injection protocol not adequately described. Participants were followed up for short duration of time. Success criteria not defined.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	statistics	Conclusions	Limitations
Nixdorf DR et al.[39]	RCT (double-blind) Cross-over design Aim: To determine whether the application of BTA to the masseter and temporalis ms. of patients with chronic myogenous orofacial pain reduces pain and increases function.	N=15 ♀ only Age: 33 yrs. (18-45 yrs.) All participants were given a diagnosis of "myofascial pain". Participants reported presence of symptoms for ≥ 6 months duration and average pain intensity of ≥ 50 mm on a 100 mm VAS. Participants who were lactating or pregnant, or diagnosed with inflammatory TMJ pathology, dental decay or intraoral soft tissue lesions, history of TMJ surgery or trauma, neurological or bleeding disorders, or actively on opioids, aminoglycoside antibiotics, anticholinesterases, muscle relaxants were excluded.	Participants underwent RDC/TMD examination. VAS used for assessment of pain intensity. Success criteria defined as reduction in VAS score of 20 mm or increase of 6 mm in MO. Assessments performed at baseline and 8 weeks.	Onabotulinum toxin A BTA group (13): - One time injection of BTA 150 U/side (Diluted in saline) - Masseter muscle BTA 50 U / side (8.3 U/0.1 cm3, 3 sites). - Temporalis muscle BTA 25 U / side (4.2 U/0.1 cm3, 3 sites). 4 weeks washout period Placebo group (12): • One time injection of saline. • Masseter muscle injected with 0.6cm^3 saline (3 sites). • Temporalis muscle injected with 0.6 cm3 saline (3 sites). Injection placed in accordance with anatomy with EMG guidance.	Paired t-test Logistic regression	Failed to reject the null hypothesis. No statistically significant difference in pain intensity. Change in pain intensity for BTA group was 19 mm. Change in pain intensity for placebo group was 1 mm. PFO and MUO improved statistically in placebo group. 5 participants did not complete study due to use of prohibited medicine (3) and paralysis of muscle (2). Adverse events: Transient paralysis of zygomaticus major ms. (2) and difficulty in smiling (4)	Study was underpowered (<50%). Only females. Participants were followed up for short duration of time. Small sample size. Only single point measurement in time. Data of successful outcome not provided separately for two groups.

Table 3 Assessment of non-randomized studies using Newcastle-Ottawa quality assessment scale

Study	Selection	Comparability	Exposure
Sidebottom et al.[48]	★★		★
Freund et al.[51]	★★		★
Boradic et al.[41]	★★		★
Freund & Schwartz M[47]	★★		★
Von Lindern[50]	★★		★
Freund[51]	★★		★
Freund[46]	★★		★

Table 4 Summary of non-randomized controlled articles included in the systematic review

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	Statistics	Conclusions	Limitations
Sidebottom AJ et al.[48]	Case-series Aim: To evaluate the effectiveness of the BTA in participants with masticatory myofascial pain who have failed to respond to conservative therapy.	N=62 49 ♀, 13 ♂ Age: 41.0±14.4 yrs. All of the participants had previously received 3 months of conservative therapy. All of the participants were given a diagnosis of "masticatory myofascial pain".	Participants underwent clinical examination. VAS for pain intensity. Assessment performed at baseline and 6 weeks.	Abobotulinum toxin A BTA group (62): -22/62 participants were injected≥2 times. - ≤3 sites per muscle. Injection placed corresponding to trigger points. 76 % injections were placed into masseter ms., 20 % injections were placed into temporalis ms., and 4 % injection were placed into medial pterygoid ms.	Spearman's correlation Wilcoxon's test Mann-Whitney U test	Null hypothesis was rejected. Statistically significant reduction in pain score. 53 % reported reduction in pain at all sites. 57 % reported reduction in overall pain. 43 % participants had pain reduced by 75 % or more. No correlation was observed between maximum dose injected and pain reduction. Mouth opening improved by 0.9 mm. Adverse events: Participants reported transient muscle weakness and wasting (1) and difficulty in speech and smiling (1).	Study was underpowered (<50%). No control group. Clinical examination was not adequately described. Reliability of examiners not described. Exclusion criteria not provided. Number and site of injections were dissimilar among participants. Participants were followed up for short period.
Freund B & Schwartz M[45]	Case-series Aim: To examine the time course of muscle relaxation and pain relief.	N=35 26 ♀, 9 ♂ Age: 29 yrs. (17-64 yrs.) All of the participants were given the diagnoses of "muscle-centered TMD" and bruxism. All of the participants had previously found pain relief with centrally acting oral muscle relaxants, were healthy and free from coexisting chronic pain conditions.	Participants underwent clinical examination. VAS used for assessment of pain intensity. Bite fork apparatus used for measurement of bite force. Assessments performed at baseline and then biweekly until 8 weeks.	Onabotulinum toxin A. BTA group (35): 1. One time injection of 150 U/ participant 2. (Diluted in saline). 3. Masseter muscle BTA 50 U/side (5U/.1 mL, 5 sites). 4. Temporalis muscle BTA 25 U/side (5U/.1 mL, 5 sites). Injection placed in pre-determined injection sites	Pearson correlations Paired t-test	Failed to reject the null hypothesis. Statistically significant difference in pain at 2 weeks and between 2 and 4 weeks. Bite force reduced significantly between baseline and 2 weeks and between 6 and 8 weeks. No statistical difference between bite force at baseline and 8 weeks. Adverse events: Muscle fatigue (35), transient headaches (3), and bruising (1).	No control group Bite fork apparatus was not calibrated. Clinical examination was not adequately described. Participants were followed up for short duration of time.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	Statistics	Conclusions	Limitations
Borodic GE & Acquadro, MA[44]	Case-series Aim: To evaluate efficacy of BTA injections for the treatment of patients with chronic facial pain seeking tertiary care at a pain clinic.	N=44 32 ♀, 12 ♂ Age: 54.2 yrs. (34-89 yrs.) Participants were given diagnosis of "chronic facial pain". All of the participants had undergone failure of at least 3 medicinal therapies, had high severity and intensity of pain in a distinct anatomical area, and had presence of pain symptoms for ≥ 2 years. Participants with neuromuscular disease were excluded.	Participants underwent assessment based on history and examination. At least 2 physicians confirmed diagnosis. TMJS: 8 EH: 12 Neuralgia: 11 PSP: 13 Assessment performed at baseline, 2 weeks, 6 weeks, and 4-20 months (: 7.65 months).	Onabotulinum toxin A BTA group (44): **1.** One-four cycles of injections (: 2.12) of 25-75 U (: 48.3 U)/ patient **2.** Masticatory muscle (≤7.5 U/site) Injection placed at site of maximum pain. *1 cycle was defined as injections given within 2-week period (≤100 U).	Chi-square	6/8 TMJS, 8/12 EH, 8/11 Neuralgia, and 11/13 PSP patients had 50 % or more improvement in pain. Adverse events: Transient facial asymmetry (29), asymmetry during dynamic movements (5), and bothersome (5).	No control group Clinical examination was not adequately described. Small sample size. Incomplete outcome data provided.
Freund BJ & Schwartz M[47]	Case-series Aim: To determine the utility of treatment with BTA for patients with coexisting TMD and CTTH.	N=60 50 ♀, 10 ♂ Age: 36.2 yrs. (17-65 yrs.) All of the participants were given a diagnosis of "chronic TMD". Participants reported presence of facial pain symptoms for duration of ≥ 1 year. In addition, 46 participants were given the diagnosis of "CTTH".	Participants underwent RDC/TMD examination. HIS criteria used to assess for CTTH. VAS used for assessment of pain intensity. Assessments performed at baseline and monthly until 3 months.	Onabotulinum toxin A BTA group (60): One time injection of 150 U/participant (Diluted in saline). Masseter muscle BTA 50 U/side (10 U/ 0.1 mL, 5 sites). - Temporalis muscle BTA 25 U/side (5 U/ 0.1mL, 5 sites). Injection placed in accordance with anatomy with EMG guidance.	None	Null hypothesis was rejected. 63 % reported 50 % or more improvement in pain during f/u. All CTTH patients reported 50 % or more improvement in HA pain. Number of HA free days increased. Adverse events: none	No control group. No statistical analysis performed. Reliability of clinical examiners was not described. Both sides injected regardless of the site of pain.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	Statistics	Conclusions	Limitations
Von Lindern JJ[50]	Case-series Aim: A prospective study to assess the therapeutic potential of BTA in the treatment of painful hyperactivity of the masticatory muscles.	N=41 All of the participants had "painful masticatory muscle hyperactivity, parafunctions, and hypermobility disorders". All of the participants had previously received conservative treatment for ≥ 3 months. Participants with non-muscular causes or unclear patterns of radiation of pain were excluded.	Participants underwent clinical examination and function analysis. VAS was used for assessment of pain intensity. Assessments performed at baseline, 3 weeks, 6 weeks, and 3-12 months.	Abobotulinum toxin A BTA group (41): - 12 patients underwent 2 or more cycles of therapy. - Masseter muscle BTA 200 U/side (40 U/0.1mL) Injection placed in accordance with anatomy (41), or with EMG guidance (8).	None	Null hypothesis was rejected. 80 % participants had improvement (45%) in symptoms. 13 participants had complete remission. pain change was from 6.4 to 3.5. Symptoms reoccurred within 3 months in 7 and in 6.7±2.7 months in 34 participants. Adverse events: Speech and swallowing difficulty (1).	No control group. Participant demographics not provided. Clinical examination was not adequately described. BTA protocol was not adequately described. Reliability of clinical examiners was not described. Time-period between injections cycle not described. Incomplete outcome data provided. No statistical analysis performed.
Freund BJ. et al.[51]	Case-series Aim: To evaluate the response of patients with TMD to BTA.	N=46 39 ♀, 7 ♂ Age: 40.5 yrs. (16-75 yrs.) All of the participants were given a diagnosis of "TMD". Participants who were never given, or failed to respond to conservative therapy, had history of allergic reactions, pregnancy, or lactation were excluded.	Participants underwent RDC/TMD examination. VAS used for assessment of: **1.** Pain **2.** Function Bite fork apparatus used for measurement of bite force. Assessments made at baseline and then biweekly until 8 weeks.	Onabotulinum toxin A BTA group (46): - One time injection of 150 U / participant (Diluted in saline) Masseter muscle BTA 50 U/side (10 U/0.1 mL). - Temporalis muscle BTA 25 U/side (5 U/ 0.1 mL). Injection placed in accordance with anatomy with EMG guidance.	Duncan's multiple range test.	Null hypothesis was rejected. Statistically significant improvement in VAS pain, VAS function, opening of jaw, and tenderness to palpation. No statistically significant difference in bite force. Adverse events: none reported	No control group Reliability of clinical examiners was not described. Reliability of bite fork apparatus not described. Participants were followed up for short duration of time. Both sides injected regardless of the site of pain. Incomplete outcome data provided.

Table continued...

Author and year	Study design and aim	Demographics	Clinical assessment methodology	Botulinum Toxin a type and protocol	Statistics	Conclusions	Limitations
Freund BJ et al.[46]	Case-series Aim: To evaluate the response of patients with TMD to BTA.	N=15 13 ♀, 2 ♂ Age: 39 yrs. (16-75 yrs.) All of the participants were given a diagnosis of "TMD". Participants who were never given, or failed to respond to conservative therapy, had history of allergic reactions, pregnancy, or lactation were excluded.	Participants underwent RDC/TMD examination. VAS used for assessment of: Pain Functional Bite fork apparatus used measurement of bite force.	Onabotulinum toxin A BTA group (15): - One time injection of 150 U / participant (Diluted in saline) Masseter muscle BTA 50 U/side (10 U/0.1 mL). - Temporalis muscle BTA 25 U/side (5 U/ 0.1 mL). Injection placed in accordance with anatomy with EMG guidance.	Duncan's multiple range test	Null hypothesis rejected. Statistically significant improvement in VAS pain, VAS function, opening of jaw, and tenderness to palpation. No statistically significant difference in bite force. Adverse events: none reported	No control group Small sample size Both sides injected regardless of the site of pain. Reliability of clinical examiners was not described. Reliability of bite fork apparatus not described. Participants were followed up for short duration of time. Authors recorded psychosocial characteristics at baseline but did not report any f/u.

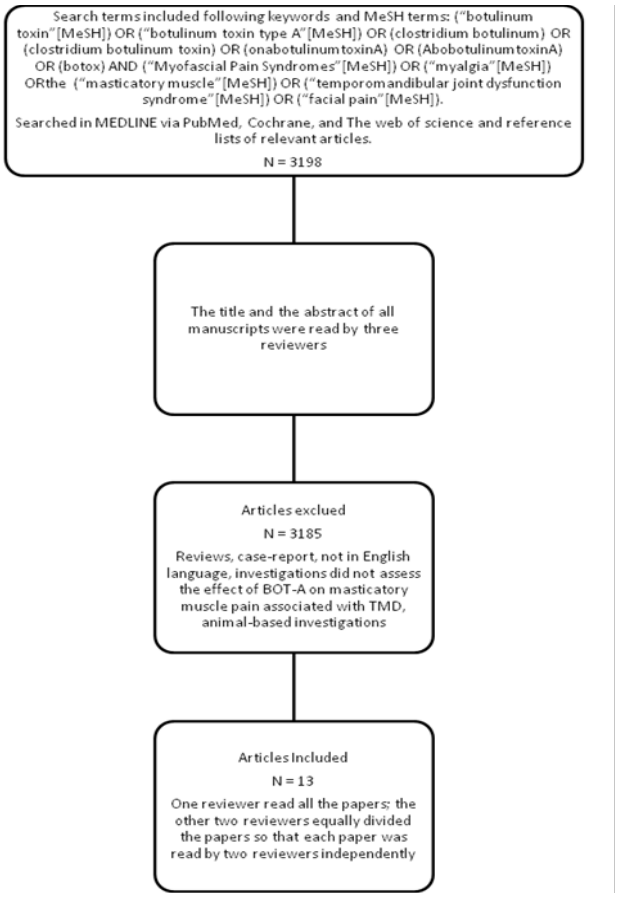

Figure 1 Overview of the search strategy.

Discussion

A systematic review was conducted to determine the effectiveness of BoT-A in the management of masticatory muscle pain in TMD. Total of 13 articles published on this topic were reviewed. Two out of 6 RCT suggested BoT-A therapy was significantly better in management of masticatory muscle pain in TMD. In contrary, all of the 7 case-series investigations suggested that BoT-A resulted in significant improvement in pain scores and range of motion in patients with masticatory muscle pain. Based on the review of RCT the therapeutic efficacy of the BoT-A therapy in management of masticatory muscle pain in TMD appears to be equivocal. This inconsistency in the literature may be attributed to multiple methodological variations, such as in the assessment of the subjects and injection protocol, risk of bias, and limitation in the research designs, such as, small sample sizes,[35–38] short duration of the follow-up period,[38,39] inadequate (low) statistical power,[35–39] injecting into the muscle regardless of the site of pain,[35–38] or as a one-time intervention.[38,39] These limitations potentially convolute the results. Small sample sizes with short duration follow-up periods, inadequate time of collection of data (<1 hour after injections), or under powered investigations may not allow adequate appreciation of clinically beneficial effects, which may take 5 weeks or even more to be clinically noticeable and last for up to 4-6 months.[41] It has been shown that clinically beneficial effects of BoT-A therapy tend to potentiate with the number of injection cycles,[26] however it is not clear if such effects will take place in masticatory muscle pain patients with TMD. In addition, all of the investigations have relied on general sample of masticatory muscle pain patients. Musculoskeletal disorders associated with TMD and other conditions, have multiple underlying pathophysiological mechanisms. Though, they may present clinically with similar characteristics. It may be possible that botulinum toxin may help in disorders associated with specific etiologies (for e.g. muscle pain associated with hypertrophy or hyperactivity) and in general sample of TMD patients these effects may get clouded. Similarly, it has been reported that BoT-A may induce, or in some instances, patients may have pre-existing neutralizing antibodies against BoT-A. Although rare, it may result in clinical ineffectiveness of BoT-A therapy.[42,43] Together, presence of such limitations may have influenced the results in favor of false negative findings. All seven of the case-series investigations found BoT-A therapy to be effective in management of masticatory muscle pain in TMD. However, these results need to be interpreted with caution. Case-series are considered low quality trials in the hierarchy of evidence because of the lack of randomization and blindness, and absence of a control arm. These methodological limitations in research design increase the risk of examiner and subject-associated bias. These risks were also highlighted in the current review by the outcome of Newcastle-Ottawa quality assessment tool. However, it can be argued that due to the acknowledged neuromuscular effects of BoT-A, both subjects and examiners are able to determine the group assignment. Therefore, case-series investigations may be given a consideration when compiling the results. Similarly, among articles reporting effectiveness of BoT-A treatment, some of the investigators failed to apply a standardized clinical examination, or report reliability of examiners to assess the masticatory pain associated with TMD.[44–48] Together, these limitations may have influenced the results in favor of false positive findings. Among the studies investigated, multiple discrepancies in the protocol for BoT-A injection therapy for the management of masticatory muscle pain in TMD were found. The dosage of BoT-A injected varied from 25 units per muscle (one side) to up to 200 units per muscle (one side). Similar differences were observed for the volume and concentration of BoT-A injections. The volume of injected solution varied from .25 milliliters (mL) per muscle to up to 1 mL per muscle, while the concentration of BoT-A also varied from 5 units per 0.1 mL to 40 units per 0.1 mL. The optimal dosage of BoT-A depends on the anatomical characteristics of the individual muscle, such as mass and location, and on the severity of the symptomatology. However, there is no consensus on the therapeutic dosage.[49] Based on our review, BoT-A therapy demonstrated acceptable safety levels. However, these results should be interpreted with caution. The sample sizes of investigations are relatively small and participants were followed for a short period of time. Adverse events associated with BoT-A therapy were transient (hours to weeks) and localized to the areas of injection. Participants reported discomfort at the site of injection, muscle weakness and wasting, difficulty in speech, smiling, and mastication, bruising, and facial asymmetry. Botulinum toxin type A has demonstrated similar safety levels for a variety of other indications.[21,22] Recently, use of BoT-A in the orofacial region has been associated with changes in trabecular bone density.[32] However, the magnitude of risk, genralizability of findings in male gender, and long-term clinical consequence has yet to be determined. Although rare, BoT-A may cause systemic adverse events. There have been reports of influenza-like symptoms, such as nausea, fatigue, upset stomach, and pruritus, as well as respiratory depression. In the present systematic review, a meta-analysis of the published literature was not conducted. This may be considered as a potential limitation. However, in order for the meta-analysis to be conducted, data has to be homogenous and free of any methodological limitations. Unfortunately, the included manuscripts do not fulfill these requirements.[50,51]

Conclusion

The effectiveness of BoT-A treatment for the management of masticatory muscle pain in TMD has yet to be established. Based on the assessment of randomized controlled trials, the body of literature is equivocal. In contrast, review of case-series investigations suggests therapeutic beneficence of BoT-A therapy in the management of masticatory muscle pain in TMD. Furthermore, results of both randomized controlled trials and case-series investigations are convoluted by the presence of multiple methodological limitations, and heterogeneity in BoT-A injection protocol. Botulinum toxin injection therapy appears to effective in certain patients with masticatory muscle pain disorders. However, there is limited evidence regarding the characterization of participants that would benefit from this therapeutic modality in terms of duration, frequency, quality, and intensity of pain, associated signs and symptoms, with detailed medical history and valid diagnosis. This advocates the need for multi-center investigations with larger sample size and longer follow up periods, with adequate characterization of the participants in terms of diagnostic and therapeutic variables.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to the authorship and/ or publication of this article.

Acknowledgments

None.

Clinical implications

Thirteen articles have been published regarding effectiveness

of BoT-A in management of muscle pain in TMD. Two out of 6 randomized controlled trials (RCT) and all of the 7 case-series investigations have suggested BoT-A therapy being significantly better in management of masticatory muscle pain in TMD. Results of both RCT and case-series investigations are convoluted by the presence of multiple methodological limitations, and heterogeneity in BoT-A injection protocol. Botulinum toxin injection therapy appears to effective in certain patients with masticatory muscle pain disorders in TMD. However, there is limited evidence regarding the characterization of participants that would benefit from this therapeutic modality.

Search strategy on PubMed

("clostridium botulinum"[MeSH Terms] OR ("clostridium"[All Fields] AND "botulinum"[All Fields]) OR "clostridium botulinum"[All Fields]) OR Abobotulinumtoxin[All Fields] OR ("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR "botulinum toxins"[All Fields] OR ("clostridium"[All Fields] AND "botulinum"[All Fields] AND "toxin"[All Fields]) OR "clostridium botulinum toxin"[All Fields]) OR ("onabotulinumtoxinA"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR "onabotulinumtoxina"[All Fields]) OR ("onabotulinumtoxinA"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR "botox"[All Fields]) AND "Myofascial Pain Syndromes"[MeSH] OR "myalgia"[MeSH] OR "temporomandibular joint dysfunction syndrome"[MeSH] OR "facial pain"[MeSH] AND ((Clinical Trial[ptyp] OR Clinical Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang])

Search strategy on the web of science

TOPIC: (botulinum toxin) OR TOPIC: ((onabotulinumtoxinA) OR (Abobotulinumtoxin)) OR TOPIC: (clostridium botulinum toxin A) OR TOPIC: (Botulinum Neurotoxin A) OR TOPIC: (Clostridium Botulinum Toxin Type A) OR TOPIC: (botulinum toxin type a) AND TOPIC: (myofascial pain syndrome) OR TOPIC: (myalgia) OR TOPIC: (temporomandibular joint dysfunction syndrome) OR TOPIC: (facial pain) OR TOPIC: (masticatory muscle)

Search strategy on cochrane database

((clostridium botulinum) OR (Abobotulinumtoxin) OR (botulinum toxins) OR (botulinum toxin A) OR (onabotulinumtoxinA) OR (botox))AND ((Myofascial pain) OR (Myofascial pain syndrome) OR (Myalgia) OR (Masticatory muscle) OR (Temporomandibular joint dysfunction) OR (Facial pain)) (Figures 2&3).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5,
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7, 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

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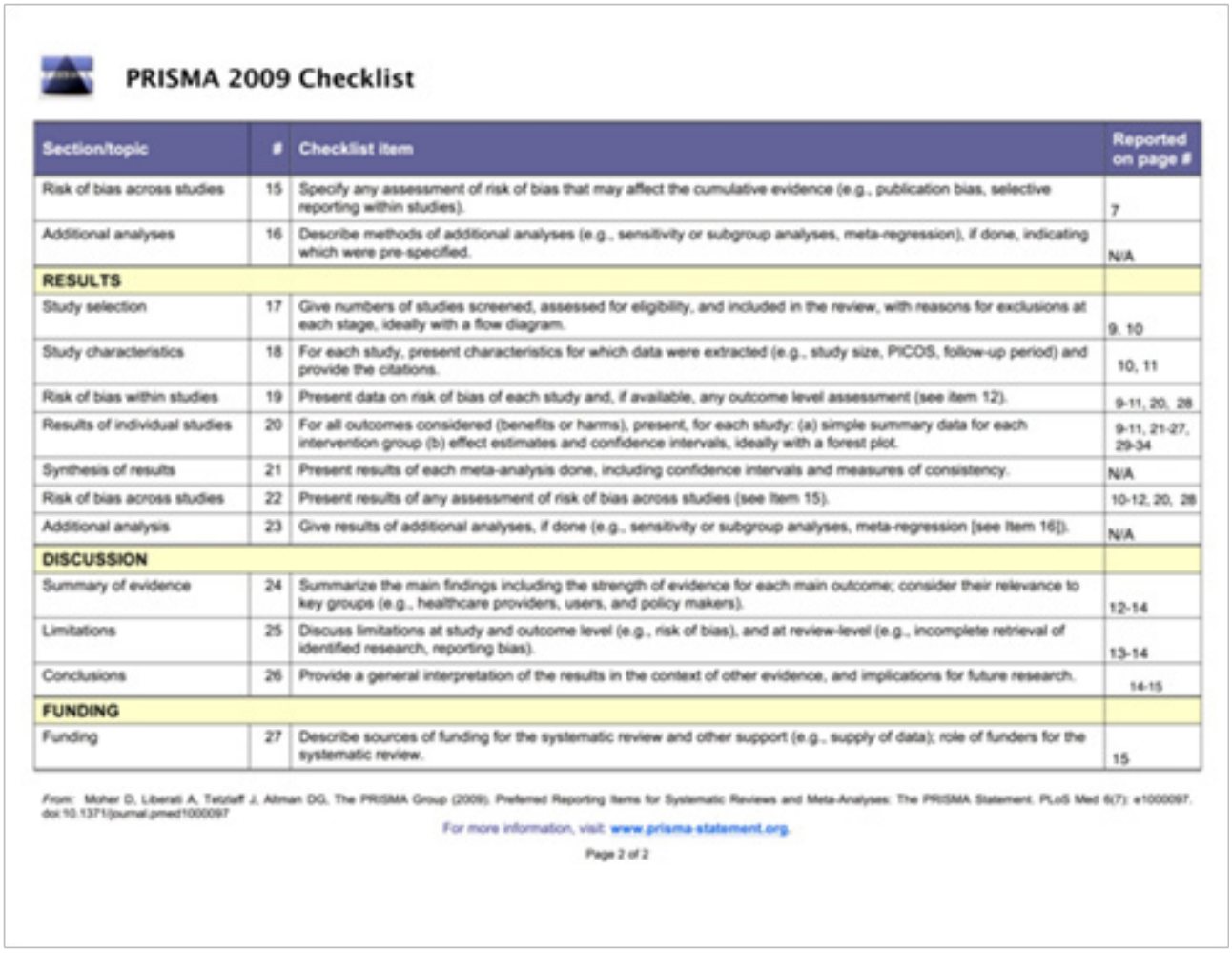
Figure 2



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9. 10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, 11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-11, 20, 28
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11, 21-27, 29-34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	10-12, 20, 28
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

Figure 3

Funding

None.

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None.

Conflicts of interest

Author declares that there is no conflict of interest.

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