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# Botulinum Toxin Type A for Painful Temporomandibular Disorders: Systematic Review and Meta-Analysis


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**Abstract:** **This systematic review investigated the effectiveness and safety of botulinum toxin type A (BTX-A) for painful temporomandibular disorders. We searched for randomized controlled trials (RCTs) in 10 databases, from inception to February 12, 2019 (MEDLINE, EMBASE, CENTRAL, LILACS, BBO, Web of Science, Scopus, ClinicalTrials.gov, WHO and OpenGrey). We included 12 RCTs that compared BTX-A versus inactive or active interventions. BTX-A was slightly more effective than placebo for pain reduction at 1 month: mean difference −1.74 points (0–10 scale), 95% confidence interval −2.94 to −.54, 3 RCTs, 60 participants, I-square ($I^2$) = 0%. However, there were no significant differences at 3 and 6 months. BTX-A was similar to no treatment for pain reduction at 3 and 6 months. BTX-A was more effective than conventional treatment and low-level laser therapy for pain reduction at 1, 6, and 12 months, but less effective than facial manipulation for pain reduction at 3 months. BTX-A was not associated with a significant increase in the risk of adverse events. The quality of the evidence was low, and results are insufficient to support the use of BTX-A for painful temporomandibular disorders. High-quality RCTs are needed to increase confidence in effect estimates.**

***Perspective:*** ***BTX-A for painful temporomandibular disorders appears to be well tolerated. For pain reduction, BTX-A is slightly more effective than placebo only at 1 month; conventional treatment and low-level laser at 1, 6, and 12 months. Low-quality evidence limits the applicability of these findings and precludes recommendations for practice.***



***Key Words:*** *Temporomandibular joint disorders, myofascial pain syndromes, botulinum toxins, type A, systematic review, evidence-based medicine.*

Painful temporomandibular disorders are chronic conditions that can have a negative impact on the quality of life and well-being of affected individuals. It is frequently associated with dysfunction of the masticatory muscles due to specific or nonspecific temporomandibular disorders. Potential risk factors for painful temporomandibular disorders include trauma, dental malocclusion, excessive masticatory system loading, hypermobility, parafunctional habits and anatomical, psychosocial and/or systemic disorders.[4,5,39]

The pain usually involves the masticatory muscles, the preauricular and/or temporomandibular joints and can lead to restriction of mandibular movement and temporomandibular joint blockage. Headaches and cervical pain are also common, depending on the degree of

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involvement of adjacent muscles.[14,20,39] There is a direct relation between progressive pain, the risk of increased symptoms, and deterioration of temporomandibular function. Relaxation of the involved muscles is one of the treatment options for this disorder.[5]

A British study reported that 10% of 2,504 participants complained of pain in the temporal region, 6% in the preauricular region and 6% in temporomandibular region, and that symptoms were more frequent in young women (18–25 years).[31] A population-based study in Sweden involving 137,718 individuals reported that 5.5% of the women and 1.8% of the men had recurring temporomandibular pain when they moved their jaws.[30]

Botulinum toxin type A (BTX-A) has been widely used for treat muscle spasms and myofascial pain in patients with temporomandibular muscle disorders. This potent neurotoxin extracted from Clostridium Botulinum bacteria bonds irreversibly to the presynaptic cholinergic junctions and leads to decreased muscular action. BTX-A can also have an effect on pain neurotransmitters and inflammatory mediators.[2,8,34,46] BTX-A can provide prolonged pain relief that can last 3 to 6 months. Since most cases of temporomandibular disorders are associated with dental clenching, bruxism, or parafunctional mandibular movements, it is logical to infer that inhibition of muscular activity could lead to pain reduction.[2,46] However, there are controversial findings on the effects (benefits and risks) of BTX-A for the treatment of painful temporomandibular disorders. A Cochrane systematic review did not find conclusive evidence to support or refute the use of BTX-A for patients with cervical, shoulder, or lumbar myofascial pain.[47] Another review concluded that despite the increasing use of BTX-A in dentistry, there is no consensus on the effects of this intervention applied to masticatory muscles in patients with bruxism.[8] The objective of this systematic review was to assess the effectiveness and safety of BTX-A for the treatment of temporomandibular joint pain.

# Methods

## *Study Design*

We followed the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[22] and the reporting guidelines of the PRISMA Statement.[27] We registered a protocol of this review in PROSPERO (CRD42018094154).

## *Eligibility Criteria*

We formulated our research question according to patient, intervention, comparison and outcomes framework.

### Types of Studies

We included randomized clinical trials (RCTs) with parallel designs. We also included the first period of crossover RCTs.

### Types of Participants

We included adults (≥18 years) with a diagnosis of painful temporomandibular disorders based on clinical examination and/or the recommendations of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), the American Association of Orofacial Pain,[9,29,45] the International Classification of Sleep Disorders (for defines sleep bruxism),[44] among other validated classification systems. The DC/TMD define temporomandibular pain as pain of muscular origin, pain in the jaw, temples, face, preauricular area, or inside the ear at rest or during function, as well as pain associated with localized areas of tenderness to palpation in the muscle.

### Types of Interventions

We included studies that compared the use of BTX-A at any dosage and treatment schedule versus placebo, or no treatment, or any other active intervention, including pharmacological and nonpharmacological treatments. We also included RCTs that tested BTX-A associated with other co-interventions if both groups received the same co-intervention. We excluded studies that included patients with central or neuropathic disorders affecting masticatory muscles, myofascial pain of cervical origin, and/or fibromyalgia. We also excluded studies that recruited a mixed population with individuals <18 years of age, unless they presented results separately for different age groups.

### Outcomes

*Primary Outcomes.*

- Pain relief assessed by any validated scale, such as the visual analogue scale (VAS).[43] We extract the numerical data for this assessment as reported by the RCT author;
- Health-related quality of life assessed by any validated tool, such as the Short Form 36 Health Survey;[52]
- Major adverse event: proportion of participants with any major adverse events such as life-threatening events, hospitalization, or that resulted in serious disability and/or incapacity (eg, infection, dysphagia);
- Any adverse events: proportion of participants with at least 1 adverse event (eg, fatigue when chewing, tenderness after the injection, muscle paralysis, esthetic modifications, and headache).

*Secondary Outcomes.*

- Maximum mouth opening in millimeters (mm);
- Function assessed by any validated questionnaire, such as the Mandibular Function Impairment Questionnaire,[49] the Jaw Functional Limitation Scale,[36] the Craniomandibular Clinical Dysfunction Index or Helkimo's dysfunction index;[21]
- Use of pain medication assessed by dose used per day.

We included all time-points reported by the RCTs, but we pooled in meta-analyses only those that were similar. We defined short-term assessment as up to 1 month after treatment, intermediate-term as between 1 and 3 months, and long-term as more than 3 months after treatment.

## Search for Studies

We conducted a sensitive literature search without language, date, or publication status restrictions (see Supplementary file 1 for complete search strategies). We conducted the last search on February 12, 2019, in the following electronic databases:

- MEDLINE (via Pubmed);
- EMBASE (via Elsevier);
- Cochrane Central Register of Controlled Trials—CENTRAL (via Wiley);
- Literatura Latino Americana em Ciências da Saúde e do Caribe - LILACS (via Biblioteca Virtual em Saúde);
- Web of Science (via Clarivate Analytics);
- BBO - Bibliografia Brasileira de Odontologia (via Bireme);
- Scopus (via Elsevier);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch);
- OpenGrey (http://www.opengrey.eu/).

We also screened the reference lists of all included studies. We contacted experts in the field to inquire about potentially relevant ongoing or unpublished RCTs.

## Process of Study Selection and Data Extraction

We downloaded all citations retrieved into a reference manager software (Endnote web) and excluded duplicates. We conducted study selection in a 2 stages, using the Rayyan software[38] (https://rayyan.qcri.org/). In the first stage, we screened the titles and abstracts of all unique references and coded them as "potentially eligible" or "excluded," according to our selection criteria. In the second stage, we read the full texts of all potentially eligible references and included those that fulfilled the aforementioned criteria. We reported the reasons for excluding studies at this stage. The process of study selection was performed in duplicate by 2 independent investigators (D.M. and A.L.C.M.); a third investigator (E.M.S.) solved any disagreements. Data extraction was also performed in duplicate by 2 independent investigators (A.L.C.M. and S.K.B.) using a data extraction form especially created for this review. A third investigator (E.M.S.) solved discrepancies in extraction.

## Assessment of the Risk of Bias of Included Studies

We used the Cochrane Risk of Bias table to assess the quality of the included RCTs.[22] This tool assesses the following domains in each of the trials: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcomes assessors, 5) incomplete outcome data, 6) selective reporting of outcomes, and 7) other potential sources of bias (eg, baseline imbalances). We performed study-level assessment for domains 1, 2, 6, and 7. We planned to conduct outcome-level assessment for domains 3, 4, 5, and 6, if needed (eg, in case of different rates of losses between outcomes, we would assess item 5 at the outcome level). Two independent investigators (R.L.P. and A.L.C.M.) assessed the risk of bias of each trial; a third investigator (R.R.) was consulted in case of disagreements. We present the reasons for each judgment.

## Unit of Analysis Issues, Measures of Treatment Effect, Analyses and Assessment of Heterogeneity

We considered the individual participant as the main unit of analysis. For the treatment effects estimate, we calculated mean differences (MDs) for continuous outcomes and risk ratio (RR) for dichotomous outcomes, with their respective 95% confidence intervals (CIs). When possible (depending on the availability and homogeneity of data) we pooled data into meta-analyses using the random effects model (inverse variance method for continuous outcomes and the Mantel-Haenszel method for the dichotomous outcomes). We used the software Review Manager 5.3 for all meta-analyses.[42] We assessed statistical heterogeneity of the trials by visual inspection of forest plots and chi-square tests ($P > .10$ was considered indicative of statistical heterogeneity). We used $I^2$ tests to measure inconsistency across studies ($I^2 > 50\%$ was considered indicative of significant inconsistency).[6] We planned to explore reasons for heterogeneity by performing sensitivity and subgroup analyses. When needed, we contacted trial authors to obtain missing data and more details to assess risk of bias. When numerical data were not available, we tried to impute data and report all imputation procedures.

## Additional Analyses

We planned the following subgroup analyses for all primary outcomes: 1) different doses of botulinum toxin (up to 200 units (U) per side vs more than 200 U per side) and 2) different durations of symptoms (acute vs chronic symptoms, defined as lasting more than 3 months). The following prespecified sensitivity analyses were planned for all primary outcomes: 1) risk of bias (selection, detection, and attrition bias) of included trials and 2) fixed-effect model meta-analysis. We planned to investigate publication bias using funnel plots, if 10 or more studies were included in the same meta-analysis. This was not possible due to lack of data.

### Assessment of the Quality of the Evidence

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to assess the quality (certainty) of the overall body of evidence.[19] The GRADE approach assesses 5 domains to downgrade the quality of the evidence (risk of bias, inconsistency, imprecision, indirectness, and publication bias). We created a summary of findings table using the GRADEpro GDT software[15] for all primary outcomes of the main comparison (BTX-A vs placebo). Reasons to downgrade the quality of the evidence were justified.

## Results

### Search Results

The electronic database search retrieved 539 references: 230 in MEDLINE (via Pubmed), 83 in EMBASE (via Elsevier), 25 in LILACS (via Bireme), 18 in the Cochrane Central Register of Controlled Trials (via Wiley), 160 in Scopus, 17 in the Web of Science, 1 in ClinicalTrials.gov, and 5 in ISRCTN. We did not find any additional studies from other sources. After the exclusion of 74 duplicate references, we screened 351 unique titles and abstracts, excluded 330, and selected 21 records as potentially eligible. After full text reading, we excluded 9 studies. Four studies did not include patients with temporomandibular pain of muscular origin, and 1 was a nonrandomized trial.[4,18,28,50] We categorized 1 study[25] as awaiting classification due to lack of information on diagnostic criteria; we contacted the authors by email and did not obtain a response so far. We found 4 ongoing trials[12,23,33,40] that compared BTX-A versus placebo; these may contribute data in a future update of this review. We included 12 studies[1,7,10,16,17,24,26,35,37,39,51,54] in the review; 9 of these contributed data to meta-analyses (Fig 1).

### Characteristics of Included Studies

Ten[1,7,16,17,24,26,37,39,51,53] of the 12 studies were parallel design RCTs and 2[10,34] were crossover trials. The 12 studies included 362 participants in total, mostly women (87.2%), between 26 and 69 years of age. Sample sizes

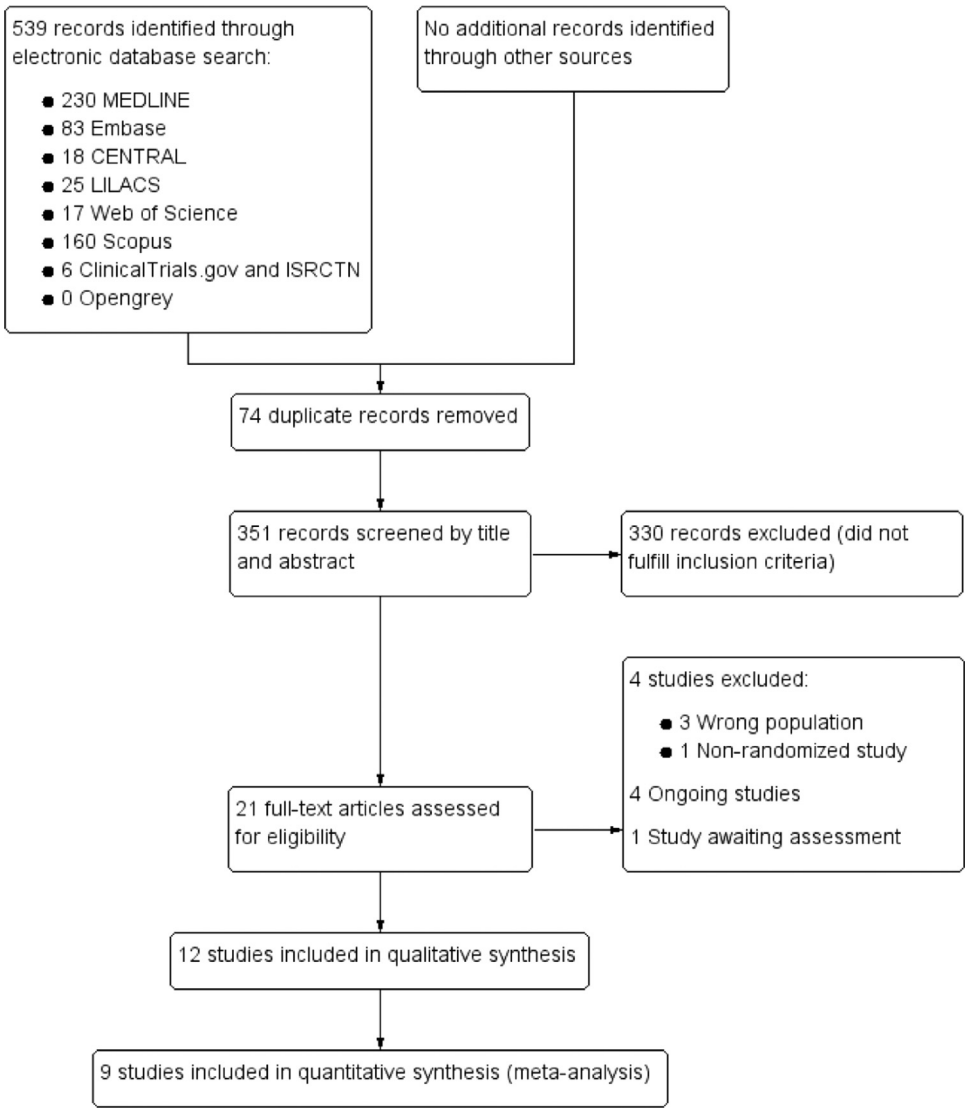


**Figure 1.** Flow diagram of the process of study identification and selection.

ranged from 15 to 90 participants per study. All studies were published in English, between 2002 and 2018. Most of the studies included participants with a clinical diagnosis of TMD and bruxism, with previous treatment failure. One study included patients with or without functional joint disk displacement.[26] The most frequently reported symptom was muscle pain in the temporomandibular region, with a duration of 1 to 6 months. Most participants had a history of a previous conservative treatment that had been unsuccessful. Exclusion criteria were predominantly systemic and inflammatory diseases, fibromyalgia, neuropathic pain or neurological disorders, pain of dental origin, cervical lesions, pregnant women, temporomandibular joint surgery up to 6 months before starting the study and/or being on any treatment for TMD. All participants in the intervention group received BTX-A. Doses ranged from 20 to 100 U. Most studies used a total dose of 100 U, injected in 2 to 3 points of each of the masseter, temporalis, and pterygoideus muscles, bilaterally. We contacted the authors of all trials by e-mail for additional information; 2 replied and provided the data requested.[7,10] Table 1 presents the main characteristics of the 12 included trials.

## Risk of Bias of Included Studies

Fig 2 presents the summary of the risk of bias of the included trials (see Supplementary file 2 for details). All studies had a high risk of bias for blinding of participants, personnel, and outcome assessors, due to the nature of the intervention. BTX-A may produce esthetic changes in the region applied, and it is unlikely that the patient will not know which intervention was performed. Two studies were judged to have a high risk of attrition bias because they had a high rate of losses (16% and 32%) and the authors did not explain the reasons.[7,35] Only one trial[37] published a study protocol (NTC00908050, in Clinicaltrials.gov). However, we judged this study as having a high risk of reporting bias because the outcomes reported in the article were not planned in the protocol.

## Effects of the Intervention

### Comparison 1: BTX-A Versus Placebo

*Pain intensity.* Nine[10,16,24,26,34,37,39,51,53] of the 12 RCTs (267 participants) compared BTX-A versus placebo. Eight trials[10,16,24,34,37,39,51,53] (237 participants) assessed temporomandibular pain reduction using a VAS (0−10 scale, higher values indicate more pain), while one trial[26] asked participants to fill out the RDC/TMD Axis II Biobehavioral Questionnaire to evaluate pain intensity. We pooled the results of 4 RCTs[10,16,24,39] in meta-analyses at 3 time points: 1, 3, and 6 months post-treatment. At 1 month post-treatment, there was an improvement in pain favoring the BTX-A group (100−170 U, each side): MD −1.74 points (VAS), 95% CI −2.94 to −.54 points, 3 RCTs, 60 participants, $I^2 = 0\%$, low-quality evidence. However, the CI did not include the minimal clinically important difference of 2.0 points for VASs.[13] At 3 and 6 months, there were no significant differences between groups, with a mean reduction of −.89 and −1.33 points, respectively (3 months 95% CI −2.04 to .26 points, 2 RCTs, 37 participants, $I^2 = 0\%$; 6 months 95% CI −2.74 to .07 points, 36 participants, 2 RCTs, $I^2 = 51\%$, low-quality evidence; Fig 3).

The other 4 trials did not provide data that could be pooled into our meta-analyses; we therefore present their results narratively. Two trials[37,51] reported pain reduction in favor of the BTX-A group (mean 70 U on each side) 1 month post-treatment ($P < .01$; 90 participants, and $P < .05$; 23 participants, respectively). The other 2 studies[26,35] reported nonsignificant differences between the BTX-A (70−100 U, each side) and placebo groups 4 weeks ($P = .45$, 24 participants) and 4 months ($P = .10$; 10 participants) post-treatment.

*Any Adverse Events.* Seven RCTs[10,26,34,37,39,51,53] assessed the proportion of participants with at least 1 adverse event. We pooled their findings and found a nonsignificant difference between BTX-A and placebo 1 month (RR 1.34, 95% CI .72−2.50, 7 RCTs, 207 participants, $I^2 = 0\%$, low-quality evidence) and 3 months (RR 1.17, 95% CI .32−4.28; 4 RCTs; 141 participants; $I^2 = 44\%$, low-quality evidence) post-treatment (Fig 4).

*Maximum Mouth Opening.* Three RCTs[10,16,35] assessed this outcome but only 2[10,16] provided data that could be included in the meta-analysis. We found nonsignificant differences between groups for this outcome at all time points assessed. The MD at 1 month was 2.05 mm (95% CI −2.80 to 6.89 mm, 2 RCTs, 41 participants, $I^2 = 0\%$). At 3 months, there was a nonsignificant reduction of less than 1 mm (MD −.90 mm, 95% CI −8.26 to 6.46 mm, 1 RCT, 21 participants) and at 6 months there was a nonsignificant increase of 4.90 mm (CI 95% −2.47 to 12.27 mm, 1 RCT, 20 participants; Fig 5). The other trial[34] (10 participants) reported a significant improvement favoring the placebo group ($P = .02$).

*Use of Pain Medication.* Two RCTs[10,37] assessed the amount of analgesics consumed but used different ways of measuring this outcome. One trial[10] (21 participants) measured medication consumption using an ordinal scale (0−5, where 0 indicates no analgesics and 5 indicates daily analgesic consumption) and reported no significant differences between the BTX-A and placebo groups after 1 month (MD −.40, 95% CI −1.52 to .72) and after 3 months (MD −.10, 95% CI −1.21 to 1.01) of treatment. The other trial[37] (20 participants) evaluated daily consumption and also found nonsignificant differences between the groups 1 month post-treatment (MD −8.50, 95% CI −18.96 to 1.96).

### Comparison 2: BTX-A Versus No Treatment

Two[24,53] RCTs compared BTX-A versus no treatment (46 participants) but each study assessed a different outcome. One trial[24] (16 participants) assessed only

**Table 1. Main Characteristics of 12 Randomized Clinical Trials on BTX-A for Temporomandibular Muscle Pain**

| *Study/Country* | *Study Design* | *Participants* | *Intervention* | *Comparators* | *Included Outcomes* | *Follow-Up* | *Funding* |
|---|---|---|---|---|---|---|---|
| Ondo, 2018[36]<br>USA | Parallel RCT | N = 23<br>Bruxism<br>Diagnostic criteria: ICSD-3; EMG of masseter and temporalis muscles<br>82,6% women<br>Mean age 47.4 ± 16.9 y<br>Symptoms duration: NR | BTX-A (N = 13)<br>100 U (each side):<br>−30 U masseter (2 points)<br>−20 U temporalis (3 points) | Placebo (N = 10)<br>Saline injections | Pain (VAS)<br>Adverse events | 1 mo post-treatment | Allergan Pharmaceutics |
| Patel, 2017[38]<br>USA | Parallel RCT | N = 20<br>TMD<br>Diagnostic criteria: pain >3 on a 0-10 ordinal scale; at least 10 d per mo<br>Age and gender: NR<br>Symptoms duration: >3 mo | BTX-A (N = 10)<br>85 U (each side):<br>−50 U masseter<br>−25 U temporalis<br>−10 U external pterygoid | Placebo (N = 9)<br>Saline injections | Pain (VAS)<br>Adverse events<br>Use of pain medication | 1 mo post-treatment | Unrestricted research Grant from Merz North America |
| Al-Wayli, 2017[1]<br>Saudi Arabia | Parallel RCT | N = 50<br>Masseter muscle pain and in TMJ area related to bruxism<br>Diagnostic criteria: ICSD-2<br>Only women<br>Mean age 45.5 ± 10.8 y<br>Symptoms duration: >2 mo | BTX-A (N = 25)<br>20 U (each side):<br>- Masseter (3 points) | Conventional treatment (N = 25)<br>Behavioral strategies, occlusal splints and pharmacologic measures | Pain (VAS)<br>Adverse events | 2, 6 and 12 mo post-treatment | NR |
| Jadhao, 2017[24]<br>India | Parallel RCT | N = 24<br>Bruxism and myofascial pain of masticatory muscles.<br>Diagnostic criteria: >5 episodes/wk, grinding sounds during morning masticatory muscle fatigue or pain.<br>Age and gender: NR<br>Symptoms duration: 6 mo | BTX (N = 8)<br>100 U (each side):<br>- Masseter (2 points of 30 U)<br>- Temporalis (2 points of 20 U) | Placebo (N = 8)<br>Saline injections<br><br>Control (N = 8)<br>No treatment | Pain (VAS) | 3 and 6 mo post-treatment | NR |
| De Carli, 2016[6]<br>Brazil | Parallel RCT | N = 15<br>Myofascial pain (> 1 mo), complaint of pain on mouth opening; bruxism, clenching or tooth wear.<br>Diagnostic criteria: clinical examination<br>86.6% women<br>Mean age: 30 y<br>Symptoms duration: 1 mo | BTX (N = 7)<br>100 U (each side):<br>—Masseter (2 points of 30 U)<br>—Temporalis (1 point of 20 U)<br>After 15 d:<br>—Masseter (2 points of 30 U)<br>—Temporalis (1 point of 15 U) | LLLT (N = 8)<br>GaAlAs, 100 mW, 830 nm, 80 J/cm$^2$<br>—masseter muscles (2 points)<br>—temporalis muscles (1 point)<br>Each side. | Pain (VAS)<br>Mouth opening (in mm) | 1 mo post-treatment | NR |

(*continued on next page*)

**Table 1. Continued**

| Study/Country | Study Design | Participants | Intervention | Comparators | Included Outcomes | Follow-Up | Funding |
|---|---|---|---|---|---|---|---|
| Zhang, 2016[52]<br>China | Parallel RCT | N = 30<br>TMD and bruxism<br>Diagnostic criteria: clinical examination<br>13% women<br>Age range: 25–37 y<br>Symptoms duration: >2 mo | BTX (N = 10)<br>100 U each side:<br>—Masseter (3 points) | Placebo (N = 10)<br>Saline injections<br><br>Control (N = 10)<br>No treatment | Adverse events | 6 mo post-treatment | NR |
| Guarda-Nardini, 2012[16]<br>Italy | Parallel RCT | N = 30<br>TMD<br>Diagnostic criteria: DC/TMD<br>73.3% women<br>Age range: 26–69 y<br>Symptoms duration: >6 mo | BTX (N = 15)<br>150 U each side:<br>—Masseter and temporalis (mean of 5 points) | Facial manipulation (N = 15)<br>Deep digital pressure:<br>3 sessions wk (50 min), 2–4 wk | Pain (VAS)<br>Mouth opening (in mm)<br>Adverse events | 3 mo post-treatment | NR |
| Ernberg, 2011[9]<br>Sweden and Denmark | Cross-over RCT | N = 21<br>TMD<br>Diagnostic criteria: DC/TMD<br>90.4% women<br>Mean age: 38 ± 12 y<br>Symptoms duration: >6 mo | BTX (N = 12)<br>100 U each side:<br>—Masseter (2 points of 50) | Placebo (N = 9)<br>Saline injections | Pain (VAS)<br>Adverse events<br>Use of pain medication | 1 and 3 mo post-treatment | NR |
| Kurtoglu, 2008[26]<br>Turkey | Parallel RCT | N = 24<br>TMD<br>Diagnostic criteria: DC/TMD<br>79.1% women<br>Mean age BTX: 29.6 ± 12.7, Placebo: 23.4 ± 4.7<br>Symptoms duration: >6 mo | BTX (N = 12)<br>100 U each side:<br>—Masseter (3 points of 10 U)<br>—Temporalis (2 points of 10 U) | Placebo (N = 12)<br>Saline injections | Pain (RDC/TMD Axis II)<br>Adverse events | 28 d post-treatment | NR |
| Guarda Nardini, 2008[15]<br>Italy | Parallel RCT | N = 20<br>Bruxism and myofascial pain of masticatory muscles.<br>Diagnostic criteria: DC/TMD<br>50% women<br>Mean age: 38 ± 12 y<br>Symptoms duration: 6 mo | BTX = A (N = 10)<br>100U (each side):<br>—Masseter (2 points of 30 U)<br>—Temporalis (3 points of 20 U) | Placebo (N = 10)<br>Saline injections | Pain (VAS)<br>Mouth opening (in mm)<br>Adverse events | 1 and 3 mo post-treatment | NR |
| von Lindern, 2003[49]<br>Germany | Parallel RCT | N = 90<br>Chronic facial pain caused by masticatory muscles hyperactivity, parafunctional movement and hypermobility disorders<br>Diagnostic criteria: clinical examination<br>Age and gender: NR<br>Symptoms duration: >3 mo | BTX=A (N = 60)<br>35 U (each side):<br>—Masseter, temporalis and pterygoideus medialis muscles. | Placebo (N = 30)<br>Saline injections | Pain (VAS)<br>Adverse events | 1 and 3 mo post-treatment | NR |

(*continued on next page*)

**Table 1. Continued**

| Study/Country | Study Design | Participants | Intervention | Comparators | Included Outcomes | Follow-Up | Funding |
|---|---|---|---|---|---|---|---|
| Nixdorf, 2002[34]<br>Canada | Cross-over RCT | N = 15<br>TMD<br>Diagnostic criteria: DC/TMD<br>All women<br>Mean age: 33 y<br>Symptoms duration: >6 mo | BTX (N = 60)<br>75 U each side:<br>−50 U masseter (3 points)<br>−25 U temporal (3 points) | Placebo (N = 30)<br>Saline injections | Pain (VAS)<br>Mouth opening (in mm)<br>Adverse events | 2 and 4 mo post-treatment | University of Alberta Fund for Dentistry, Allergan and McNeil Pharmaceutics |

Abbreviations: RCT, randomized clinical trial; N, number of participants; TMD, temporomandibular disorders; ICSD, International Classification of Sleep Disorder; EMG, electromyography; NR, not reported; BTX-A, botulinum toxin type A; VAS, visual analogue scale; U, units, LLLT, low-level laser therapy; AsGaAl, gallium arsenide and aluminum; mW, milliwatts; nm, nanometer; J/cm$^2$, Joules per square centimeter; mm, millimeters; DC/TMD, Diagnostic Criteria for Temporomandibular Disorders.




**Figure 2.** Summary of the risk of bias of included trials. (+) = low risk of bias; (?) = unclear risk of bias; (−) = high risk of bias.

temporomandibular pain reduction using a 0 to 10 VAS (higher values indicate more pain) and reported nonsignificant differences between groups 3 months (MD −1.60 points, 95% CI −4.30 to 1.10) and 6 months (MD −1.80 points, 95% CI −3.67 to .07) post-treatment. The other trial[51] (30 participants) assessed any adverse events and reported no events in either group up to 6 months post-treatment.

## Comparison 3: BTX-A Versus Facial Manipulation

One RCT[17] (30 participants) compared BTX-A versus manipulation. Pain intensity (VAS) 3 months post-treatment was significantly higher in participants treated with BTX-A than with facial manipulation (MD 2.30 points, 95% CI .80−3.80). This CI included the minimal clinically important difference of 2.0 points for a VAS.[13] There were no significant differences between groups

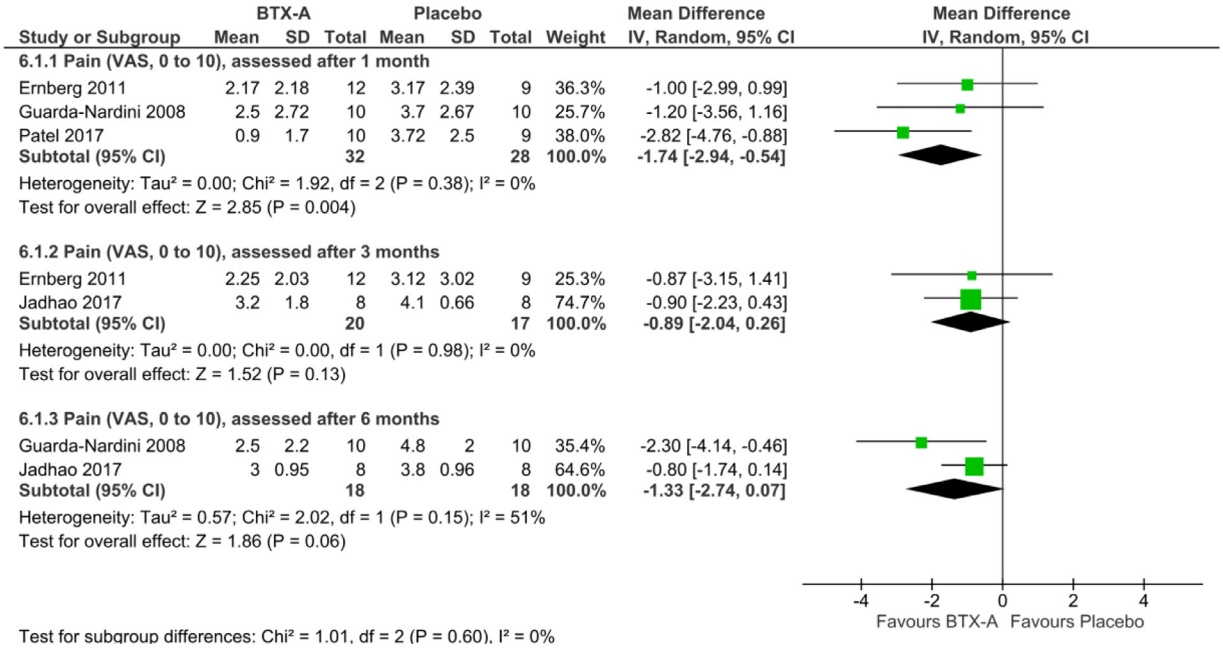


**Figure 3.** Forest plot BTX-A versus placebo for pain intensity.

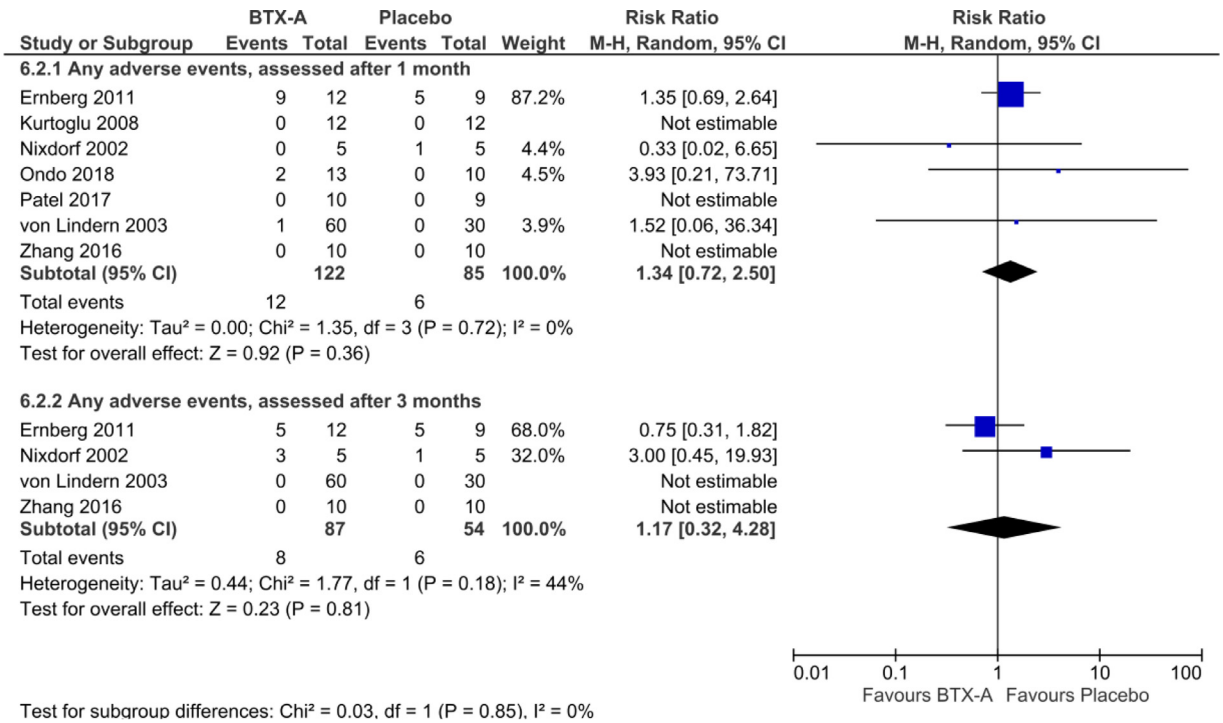


**Figure 4.** Forest plot of BTX-A versus placebo for any adverse events.

for maximum mouth opening (51.4 mm in BTX-A group and 52.4 mm in manipulation group). There were no adverse events in either group at all time points assessed.

## Comparison 4: BTX-A Versus Low-Level Laser Therapy

One RCT[7] (15 participants) compared these interventions and reported nonsignificant differences between groups in pain reduction (VAS MD −.40 points, 95% CI −2.53 to 1.73) and maximum mouth opening (MD .30 mm, 95% CI −10.10 to 10.79) 1 month after treatment.

## Comparison 5: BTX-A Versus Conventional Treatment

One RCT[1] (50 participants) compared BTX-A versus conventional treatment involving behavioral strategies (reassurance and detailed explanation of the nature of the disease, occlusal plates, and pharmacologic treatments).

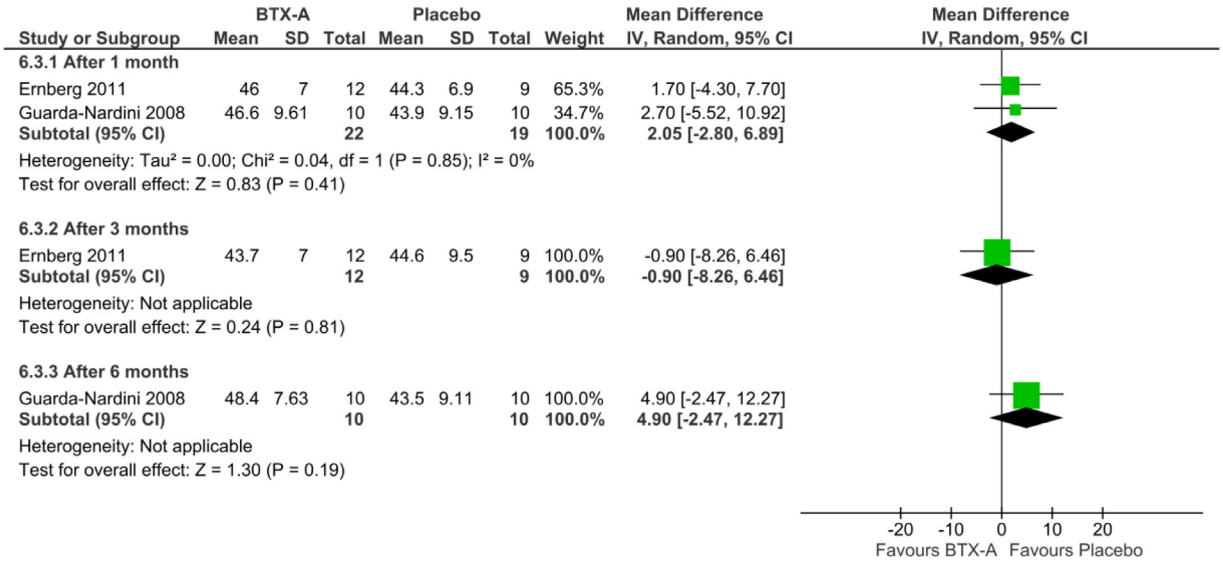


**Figure 5.** Forest plot of BTX-A versus placebo for maximum mouth opening.

Outcomes were assessed 2, 3, and 12 months post-treatment. Pain intensity (VAS) was significantly lower in the BTX-A group after 1 month (MD −1.80 points, 95% CI −2.10 to −1.50 points), 6 months (MD −1.90, 95% CI −2.25 to −1.55 points), and 12 months (MD −1.90, 95% CI −2.25 to −1.55 points). There were no adverse events in either group at all the time points assessed.

None of the included studies assessed health-related quality of life and function.

We did not perform subgroup and sensitivity analyses as planned because the population and methodological characteristics of the trials included were similar.

### *Quality of the Evidence*

We assessed the quality of the evidence using the GRADE approach for the main comparison (BTX-A vs placebo) for all primary outcomes and time points (1, 3, and 6 months post-treatment). The reasons to downgrade the evidence were methodological limitations of the trials (mainly related to performance bias) and imprecision (small sample size and wide CI). See Supplementary file 3 for the summary of findings table and detailed assessments of the quality of the evidence (GRADE).

## Discussion

This systematic review assessed the effectiveness and safety of BTX-A in the treatment of muscular temporomandibular pain, based on the hypothesis that the muscle relaxing effects of the toxin on masticatory muscles could help to reduce this type of pain.[4] We conducted a broad and sensitive search, without language or date restrictions, and identified 12 RCTs, involving only 362 participants in total, that fulfilled our selection criteria. There is low-quality evidence that BTX-A is statistically, but not clinically, better than placebo for temporomandibular muscle pain reduction 1 month post-treatment, but not 3 or 6 months post-treatment. There were no differences between BTX-A versus placebo on adverse events, maximum mouth opening, or use of pain medication, at any of the time points assessed. We found no significant differences in pain reduction or adverse events, 3 and 6 months post-treatment, between BTX-A versus no treatment. BTX-A was more effective in reducing pain than conventional treatment (behavioral intervention, occlusal plates, or medication) after 1, 6, and 12 months, and more effective than low-level laser therapy (at 1 month). On the other hand, BTX-A was statistically and clinically less effective than facial manipulation for pain reduction 3 months post-treatment. There were no significant differences between BTX-A versus other treatments for amplitude of mouth opening and adverse events.

Most trials injected BTX-A in 2 or 3 points of the masseter, temporal and pterygoideus muscles, bilaterally (total dose of 100 U). Only one trial[1] used a lower dose (20 U in 3 points of the masseter muscle), considered subclinical.[3,48] One of the trials[7] injected a second dose of the toxin 15 days after the first, despite the lack of evidence to support this short time interval. Most investigators recommend an interval of 2 to 6 months to optimize the effect of the first dose.[3,11] However, since there are no guidelines on the doses and treatment schedules, and because BTX-A is commercially available in different dilutions, it is difficult to determine the effectiveness and safety of different doses of the toxin for painful temporomandibular disorders.[33,41]

The quality of the evidence was low for the primary outcomes of the comparison BTX-A versus placebo. This means that we have limited confidence in the effect estimates. We downgraded the quality of the evidence because of the methodological limitations of the trials (mainly due to lack of blinding caused by the nature of the intervention), the small sample sizes, the wide CIs and the magnitude of the effect.

This review has several strong points. It followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[6] The 12 trials included in this review make it the largest systematic review to date

on BTX-A for the treatment of temporomandibular muscle pain due to muscular hyperactivity. We attribute the identification of these trials to our broad and sensitive search strategy. However, the systematic review is not without limitations. Despite our efforts, we had difficulties in obtaining additional information for most of our included RCTs. For instance, one of the trials was available only as an abstract[25] and we did not succeed in getting additional information from the authors. We cannot estimate the effect of this lack of information on the findings of the review. Moreover, we cannot dismiss the possible effect of publication bias. This means that it is possible that there are RCTs with nonsignificant findings that were not included in this review because they were not published. It is also important to note that 10 of 12 RCTs included in the review were funded by companies that produce BTX-A, which is also a potential bias. Another limitation of the review is that we did not find any studies that assessed important outcomes such as quality of life and functional capacity of the patients.

Another systematic review published in 2015 included 5 trials (117 participants in total) and reported similar findings on BTX-A for painful temporomandibular disorders. However, because of the diversity among the studies, the authors of that review did not conduct any meta-analyses.[3]

We found that BTX-A was more effective than placebo for pain reduction only 1 month after the treatment, and more effective than conventional treatment 1, 3, and 12 months post-treatment; however, these differences were not clinically relevant. These findings should be discussed with the patients and balanced against the costs associated with this intervention. We also found that BTX-A for painful temporomandibular disorders a safe intervention, since none of the studies reported any adverse effects (such as facial paralysis, muscular fatigue, or esthetic modifications).

## Conclusions

The use of BTX-A is well tolerated and produces a slight improvement in painful temporomandibular disorders, compared to placebo, at 1 month but, not at 3 or 6 months, and other active treatments (occlusal plates, behavioral interventions, and medication) and low-level laser, at 1, 6, and 12 months. However, the quality of the evidence is low. Therefore, the findings of this review are insufficient to support or refute the use of this intervention. More high-quality trials are needed to increase our quality regarding the effectiveness of this intervention, and to make recommendations for clinical practice. These RCTs should have larger sample sizes, assess outcomes that are relevant for the patients, and follow the CONSORT reporting recommendations.[32]

## Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.08.011.

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