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Systematic Review

Application of Botulinum Toxin in Temporomandibular Disorders: A Systematic Review of Randomized Controlled Trials (RCTs)

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Abstract: Temporomandibular disorders (TMDs) are multi-factorial and polysymptomatic pathologies and their management must be customized for every patient. Numerous therapy techniques are available to treat temporomandibular disorders-related muscular discomfort and persistent orofacial pain. Botulinum toxin (BoNT) has emerged as a popular option for patients with myofascial TMD who do not completely recover from their condition after receiving conservative care and medication. A systematic search of the literature, from January 2000 until 1 April 2022, was performed in the MEDLINE (PubMed), Web of Science, and Lilacs databases. The following search terms combination: (temporomandibular disorders) OR (botulinum) OR (toxin) was employed. A total of 357 articles were initially found in the electronic search. After screening, 11 full-text articles satisfied the inclusion criteria. The Cochrane risk of bias tool (RoB 2) tool, which uses seven domains of bias to assess random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment of self-reported outcomes, blinding of outcome assessment of objective measures, incomplete outcome data, selective reporting, and other biases, was employed to analyze randomized controlled trials. The aim of this systematic review of randomized controlled trials is to provide an overview of the use of BoNT for TMDs by comparing the application of BoNT with other therapeutic approaches. BoNT-A could help patients that do not respond to conservative treatments. Low doses are recommended when BoNT-A is considered for persistent orofacial pain related to TMD. Future research should, however, conduct clinical trials with a stricter design. The results of BoNT-A could be confirmed by more randomized controlled trials with larger sample sizes, less bias, and longer follow-up times.

Keywords: botulinum toxin A; joint disorders; temporomandibular disorders; temporomandibular joint; temporomandibular diseases; toxin; botulinum A

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1. Introduction

The temporomandibular joint (TMJ) is structured by the mandibular condyle inserted into the mandibular fossa of the temporal bone [1,2]. Mastication muscles are primarily involved in the movement of this joint [3,4]. Temporomandibular disorders (TMDs) have been described by the American Association for Dental Research (AADR) as 'a cluster of musculoskeletal and neuromuscular conditions that involve the TMJ, the masticatory muscles, and all associated tissues [5–8]. In general, TMDs are divided into myofascial TMDs or arthrogenic TMDs. The myofascial temporomandibular disorder is associated with pain arising from hyperfunctioning muscles of mastication that leads to chronic

myositis [9,10]. In contrast, arthrogenic temporomandibular disorder is associated with intracapsular pathology and pain at the joint level [11–16].

Up to 25% of the population seeks professional care for TMD treatment, with the prevalence of TMDs ranging from 30 to 44 percent [17–19]. They are thought to be the third most prevalent cause of chronic pain overall, behind headache and backache [20–24], and the most frequent cause of chronic pain in the orofacial region. TMDs have a complex etiology that involves biological, environmental, social, emotional, and cognitive causes. Other pain-related illnesses, such as fibromyalgia, immunological disorders, sleep apnea, and psychiatric illness are also regularly linked to TMDs (e.g., chronic headaches) [21,25–27]. As a result, the degree of discomfort and dysfunction, as well as the course of symptoms, determines the necessity for treatment [28–31].

Clinically differentiating serious abnormalities that require treatment from incidental findings in individuals with facial pain from other sources is crucial for the clinician treating patients with TMDs [28]. Nonpharmacologic therapy, conservative pharmacotherapy, and open surgery are all forms of treatment for TMDs [32,33]. The main treatment is non-pharmacological and often entails avoiding triggers, modifying nutrition, managing pain, engaging in physical therapy, and applying warm compresses. Otherwise, [34] systemic medication for TMDs, including anti-inflammatory drugs, muscle relaxants, analgesics, and occasionally tricyclic antidepressants, may be used as an additional therapy [14]. Despite the use of a number of therapeutic modalities, including oral splints, medications, and behavioral techniques, none have been shown to be completely effective [15].

In this context, controlled clinical trials have demonstrated botulinum neurotoxin type A (BoNT-A)'s efficiency for the treatment of different pathologies such as bruxism, neuropathic pain, facial paralysis, sialorrhea, dystonia and TMDs [11,16]. BoNT is a biological toxin and a viable treatment option. For an increasing number of orofacial applications, neuromuscular conduction pathways can be used in order to study the effects of the BoNT-A process on muscle activity. Cholinergic neuromuscular connections exist between extrafusal muscle fibers and alpha motor neurons in skeletal muscles. The alpha motor neuron activity that innervates the skeletal muscles is controlled by information from the muscle spindle organs and the Golgi tendon organs. BoNT-a is injected intramuscularly and produces both intrafusal and extrafusal fiber atrophy. This atrophy prevents muscle action potentials from being induced by stimulation of both extrafusal and intrafusal fibers, and it gradually lowers spindle afferent discharges. BoNT can also inhibit the gamma motor neuron terminals in the masseter muscles. Additionally, BoNT relaxes striated muscle by preventing the release of acetylcholine from presynaptic neuron [17]. Therefore, BoNT injection has become an attractive choice as an adjuvant therapy in patients with myofascial TMD who do not achieve a complete resolution with conservative treatment and pharmacotherapy [11].

Anecdotal accounts of individuals treated for hyperfunctional facial lines who reported less frequent and less severe headaches were the first sign that BoNT might be helpful for managing pain [8,18]. The heterogeneity of published results about the management of persistent pain related to TMDs and the lack of randomized controlled trials lead to inconsistent results. Consequently, the progress of evidence-based and well-designed studies reporting on the efficacy and proper dose of BoNT became necessary to define it as a valid treatment for persistent pain associated with TMDs. Several recent systematic reviews showed the effects of BoNT-A on temporomandibular disorders with discordant results, highlighting the need for high-quality RCTs to increase confidence in effect estimates [8,19,20]. Therefore, the aim of this systematic review of randomized controlled trials is to provide an overview of the use of BoNT in TMDs by comparing the application of BoNT-A with other therapeutic approaches.

2. Materials and Methods

2.1. Protocol

All of the authors a priori approved the protocol for carrying out this systematic review, including the steps of selection, extraction, and risk of bias assessment. In addition, the PRISMA checklist was correctly followed for the reporting of this systematic review.

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2.2. Eligibility Criteria

In order to answer to the following focused PICO research question: "In patients with temporomandibular disorders (P) treated with botulinum toxin (I), is there a difference between the application of botulinum toxin and other treatments (C) in terms of post-operative clinical parameters such as orofacial pain and muscular diseases (O)?" the inclusion criteria were randomized controlled trials (RCTs) performed in humans with at least 1 month follow-up, including at least 10 patients treated for TMDs, evaluating at least one postoperative clinical outcome (e.g., orofacial pain and/or muscular diseases), published in English, Italian, or Spanish. As exclusion criteria, publication status or grey literature were not considered.

2.2.1. Literature Search

A systematic search of the literature was performed using the following databases: MEDLINE (PubMed), Web of Science, and Lilacs databases. The following search terms were used: (temporomandibular disorders) OR (botulinum) OR (toxin). All databases were searched from January 2000 until 1 April 2022. In addition, a complementary manual search was carried out. This research time frame was employed due to the absence of RCTs before January 2000.

2.2.2. Data Selection and Extraction

Two authors (F.D., G.M.), working independently and in duplicate, selected and extracted the data. Titles and abstracts were initially scrutinized for inclusion. The inclusion and exclusion criteria were then applied to full-text articles. The following information was gathered through data extraction: authors, publication year, study design, patient count, comparison of interventions, follow-up interval, and postoperative clinical outcomes.

2.2.3. Risk of Bias and Quality of the Studies Assessment

Two reviewers individually and independently examined the included studies' risk of bias (F.D, G.M). In order to analyze randomized controlled trials, the Cochrane risk of bias tool, also known as the RoB 2, was used. It uses seven domains of bias to look into random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment of self-reported outcomes, blinding of outcome assessment of objective measures, incomplete outcome data, selective reporting, and other biases [21].

3. Results

The flowchart of data selection is shown in Figure 1. A total of 357 articles were found in the electronic search. After all titles were checked, 87 duplicates were removed, and 270 articles were selected for abstract reading. Then, the analysis of the abstracts excluded articles that clearly did not satisfy the eligibility criteria. Therefore, 55 full-text articles were identified. Finally, 11 full-text articles satisfied the inclusion criteria. Features of the included studies are reported in Table 1.

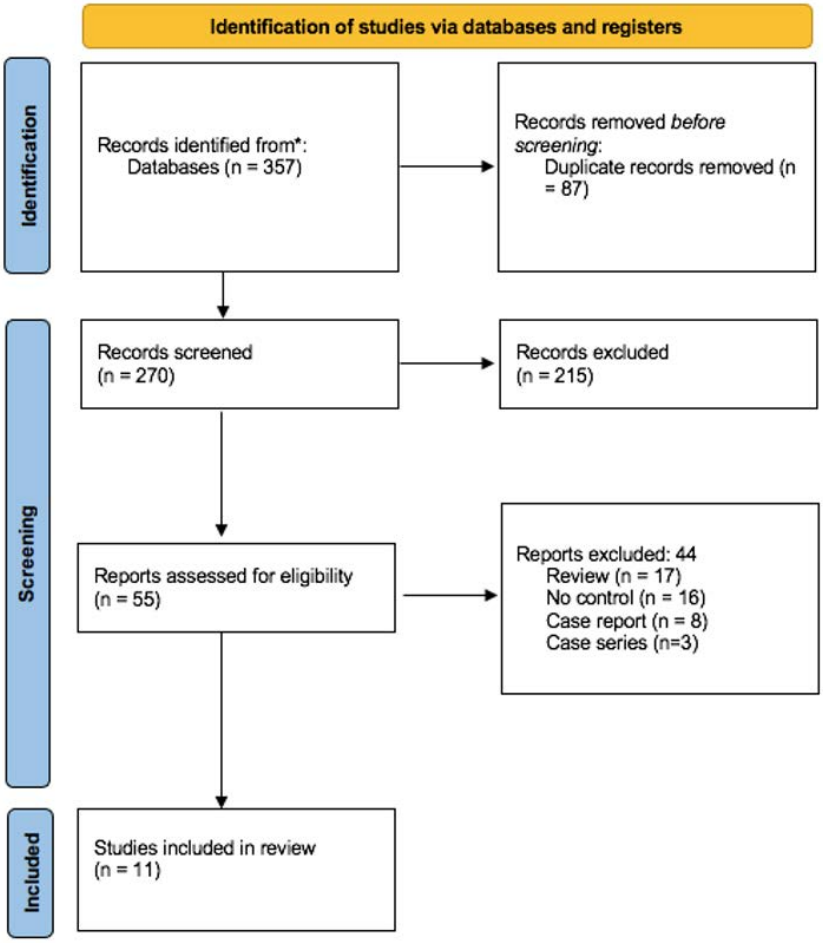

Figure 1. Flow diagram of the selection of the studies (performed according to the PRISMA guidelines).

Table 1. Features of included randomized controlled trials.

Authors	Publication Year	Study Design	No. Patients	Comparison of Interventions	Follow-Up
De la Torre Canales et al. [23]	2021	RCT	100	FID vs. SS vs. BoNT-A	6 months
Kaya et al. [22]	2021	RCT	40	Occlusal splint vs. BoNT-A	6 months
De la Torre Canales et al. [24]	2021	RCT	54	Acupuncture vs. SS vs. BoNT-A	1 month
De la Torre Canales et al. [31]	2020	RCT	100	FID vs. SS vs. BoNT-A	6 months
Montes-Carmona et al. [25]	2020	RCT	60	Lidocaine vs. SS vs. BoNT-A	6 months
Cahlin et al. [32]	2019	RCT	12	SS vs. BoNT-A	4 months
Zhang et al. [26]	2016	RCT	30	SS vs. no injection vs. BoNT-A	6 months
Guarda-Nardini et al. [27]	2012	RCT	30	Fascial manipulationvs BoNT-A	3 months
Ernberg et al. [29]	2011	RCT	21	SS vs. BoNT-A	3 months
Guarda-Nardini et al. [33]	2008	RCT	20	SS vs. BoNT-A	6 months
Von Lindern et al. [28]	2003	RCT	90	SS vs. BoNT-A	3 months

The included human studies had at least 1 month follow-up, included at least 10 patients treated for TMDs, and evaluated at least one postoperative clinical outcome, such as orofacial pain and/or muscular diseases.

Kaya et al. [22], comparing the use of BoNT-A and occlusal splints, showed that there was a statistically significant decrease in orofacial pain by visual analogue scale (VAS) during the control period (6 months) after the application of both treatments, though there were no significant differences between these methods. Similarly, De la Torre et al. [23], comparing BoNT-A and a maxillary flat intraoral device used during sleep, reported that, in contrast to treatment with a flat intraoral device, BoNT-A treatment enhanced psychosocial aspects in patients with masticatory myofascial pain. Similarly, De la Torre et al. found that acupuncture, saline solution, and BoNT-A all reduced the self-perceived pain in patients with orofacial pain over the course of a month. However, BoNT-A was not superior to acupuncture in terms of pain reduction, but both were superior to saline solution (P.001). In contrast to treatment with a flat intraoral device, BoNT-A treatment enhanced psychosocial aspects in patients with masticatory myofascial pain. Similarly, De la Torre et al. found that acupuncture, saline solution, and BoNT-A all reduced the self-perceived pain in patients with orofacial pain over the course of a month. However, BoNT-A was not superior to acupuncture in terms of pain reduction, but both were superior to saline solution (P.001) [24]. Conversely, Montes-Carmona et al. [25], reporting a comparative analysis between BoNT-A, saline solution, and lidocaine injections, showed significant differences favoring the BoNT-A group by means of pain intensity reduction on VAS scores, maximum interincisal opening, and right and left lateral and protrusion movements, in comparison to saline solution and lidocaine groups.

Apart from that, Zhang et al. [26] showed there was a significant variation in maximum occlusal force favoring the BoNT-A group in comparison with placebo and a negative control group. Guarda-Nardini et al. [27], comparing single-session BoNT injections or multiple-session fascial manipulation, showed that, although fascial massage was slightly superior to minimize subjective pain perception and BoNT injection was slightly superior to increase jaw range of motion, the two therapies appear to be almost equally effective. Furthermore, Von Lindern et al. [28], comparing BoNT-A and saline solution, showed a significant improvement of local facial pain symptoms in terms of VAS, favoring the use of BoNT-A. On the contrary, Ernberg et al. [29], comparing BoNT-A and saline solution, reported no statistical differences after treatment regarding most outcome measures with the exception of pain on palpation, which decreased 3 months after saline injection ($p < 0.05$). Thus, the authors [29] do not show a clinically relevant effect of BoNT-A in patients with persistent myofascial TMDs pain. Based on this systematic review of randomized controlled trials, no consensus could be reached on the therapeutic benefits of BoNT -A on TMDs.

Quality Assessment and Risk of Bias

Overall, the outcomes of the quality assessment of included RCT studies are reported in Figure 2. By applying the RoB 2, all the 11 RCTs studies revealed high, low, and unclear risk of bias in some key domains. No studies were shown in the overall rating to have a low risk of bias in accordance with the authors' definitions [21]. A low risk of bias was identified by the randomization technique for all studies. While 75% of studies disclosed all outcome data, and 100% of the included trials adequately left out bias in the selection of the reported outcomes, only 20% of studies adequately left out performance bias. Only 4 out of 11 RCT trials overall showed a minimal risk of bias.

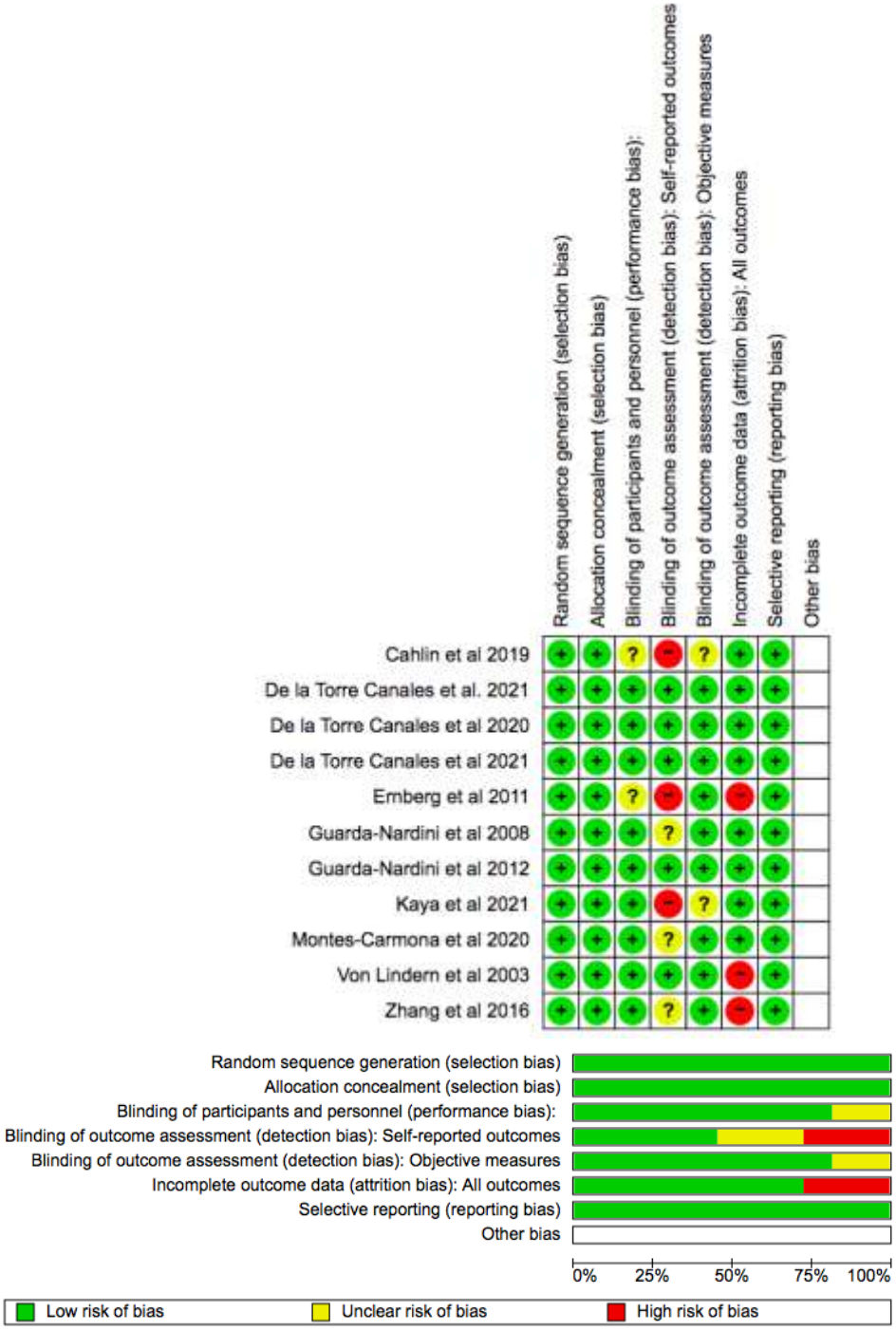

Figure 2. RoB 2 assessment of RCTs. The randomization process reported 100% of the studies with a low risk of bias. Of the studies, 80% excluded a performance bias [23–28,30,31,33] but 75% reported all outcome data [23–25,27,30–33] and 100% of included trials adequately left out bias in the selection of the reported results. [23–33] The overall ranking showed no studies with low risk of bias. Only 4 out of 11 RCT studies were shown to have a low risk of incurring bias. [23,24,27,31].

4. Discussion

TMDs are examined in two groups: temporomandibular joint disorders and muscle originated disorders. TMDs include internal structure irregularities or involve mismatch disorders. Muscle hyperactivity is occasionally thought to be the root of intra-articular dysfunction and other times it is seen to be a contributing factor. In this context, bruxism is a parafunctional activity that is typically observed when sleeping and is characterized by

involuntary spasmodic or rhythmic nonfunctional teeth grinding. Neck pain, headaches, a restriction in the mandibula's functional mobility, and pain and spasm in the masticatory muscles can all occur in bruxism sufferers. The most recent theory concerning the origins of bruxism affirms the contribution of the autonomic and central nervous systems to the development of oromandibular activity when we sleep. Particularly, sleep-related mechanisms influenced by brain chemical activity, airway patency maintenance during sleep, and rhythmic masticatory muscle action may heighten the motor activity that underlies the development of sleep bruxism.

TMDs impair quality of life and create chronic discomfort. About two-thirds of TMD patients reported no or very minor functional limitations, which is a measure of functional impairment that takes into account pain-related disability. This may come as a surprise, given that the patients' levels of somatization and depression were relatively high; both of which have been associated with varying degrees of functional impairment. Although TMDs begin as a functional muscular disorder, it ultimately can cause degenerative changes and internal derangement in the temporomandibular joint. Various therapeutic procedures are available for the management of chronic orofacial pain and muscular diseases related to TMDs, such as pharmacological treatment, physiotherapy, behavioral approaches, and occlusal splints or surgical treatment, although no specific treatment has proven to be consistently effective. The most effective course of treatment is currently a matter of debate. Presynaptic neurotoxic BoNT-A impairs the release of acetylcholine from motor nerve ends via Ca + 2, leading to dose-dependent weakening or paralysis in skeletal muscle. By doing this, the afflicted muscle regions are functionally denervated. The neuroparalytic impact of the toxin may impair the delicate control between bones and muscles in the musculoskeletal system. Both tissues retain a cross-talk mechanism in this system. In vivo investigations [18,19] showed bone alterations after a single BoNT-A injection in the masticatory muscles for 1 to 3 months. Similar to this, changes in mandibular structures following repeated injections of BoNT-A were observed in other clinical investigations [16,17]. In fact, according to De la Torre et al. [23], this negative effect persisted even after a single high-dose injection of BoNT-A. Therefore, it is possible to speculate that effects of BoNT-A on bone tissues may result in decreased bone loading, raising the mRNA expression of RANKL and block neurotransmitters. BoNT-A has been employed extensively in treatment of oromandibular dystonia, myofascial pain, and temporomandibular dislocation. Similarly, BoNT-A has been widely employed in the management of TMDs due to its analgesic and relaxing abilities; however, few scientific studies support its use on account of the heterogeneity of the populations studied so far. Mouth opening is frequently restricted in TMD patients, and botulinum toxin therapy helps relax the nearby masticatory muscles, reducing muscle inflammation and improving mouth opening. Nevertheless, approximately 10% of TMDs patients develop a disorder associated with chronic orofacial pain [30]. De la Torre et al. [31] reported that BoNT-A is at least as effective as occlusal splints for persistent orofacial pain, thus conservative treatments such as occlusal devices should be the first option for the management of orofacial pain related to TMDs. The authors [31] suggested employing low doses of BoNT-A in patients who do not obtain considerable pain relief from conservative treatments. These findings are in accordance with other two RCTs [22,23] included in this study. On the other hand, most of the included studies [25,26,28,31–33] comparing BoNT-A and saline solution showed significant differences favoring the BoNT-A group regarding pain intensity reduction and changes in maximum occlusal force. Differently, only one RCT by Ernberg et al. [29], comparing BoNT-A and saline solution, reported there were no significant changes after treatment in most of the evaluated outcome measures, with the exception of pain on palpation.

Bite forces and electromyographic activity are both significant factors in assessing the performance of the masticatory muscles. Sitnikova et al. supported previous findings concerning the significant decrease in electromyographic activity and bite force values after BoNT-A injections, showing a recovery of electromyographic activity occurring by 33 weeks and bite force by 25 weeks after a moderate dose of BoNT-A [30]. BoNT-A injections are

not recommended for patients who are growing because it is known that reduced muscular power and activity lead to bone loss, and that the biochemical and biomechanical interactions are particularly significant during the growth period of masticatory structures [30]. Despite this, low doses of BoNT-A, such as a total dose of 50U, are proposed not to be dangerous because the grade and duration of the adverse effects are dose-dependent [17]. Furthermore, according to some clinical trials, bigger doses are not likely to get more therapeutic benefits when treating pain conditions [11,17,34].

The available research on bruxism and botulinum toxin is inconclusive and there is no evidence that bruxism can be cured with injections of BoNT-A. The repetitive activity of the masticatory muscles known as bruxism, which can show in either sleep bruxism (SB) or awake bruxism (AB), is defined by the tightness or grinding of the teeth. In addition to tooth abrasions and mobility, dental restoration fractures, hypertrophy of the masseter muscle, and myalgia or arthralgia typical of temporomandibular disorders, it is a frequent condition with an adult prevalence. The cause and pathophysiology of bruxism are still unknown, despite the fact that etiological factors such emotional stress, neurological illnesses, certain medicines, and occlusal interferences have been hypothesized. Occlusal splints, medications such as benzodiazepines or L-dopa, and cognitive–behavioral therapy are just a few of the treatment modalities that have been researched for the management of bruxism. However, these methods have not been proven to be completely effective because they only appear to address the symptoms of patients rather than the underlying cause, limiting the damaging effects of bruxism on anatomical structures. At present, it has been shown that botulinum toxin is effective for treatment of bruxism associated with TMDs [19,34–36]. A systematic review of Fernandez-Nunez et al., analyzing 68 studies, reported that treatment with BoNT-A is a safe and effective clinical option in patients affected by bruxism, underlining that injections of BoNT-A give better outcomes than traditional treatment [36]. Furthermore, this systematic review showed that application of BoNT-A should be considered in daily clinical practice, especially for patients affected by severe bruxism [36]. However, another systematic review by Agren et al. analyzed 311 studies and reported that there is a lack of evidence concerning the treatment of bruxism employing BoNT-A [35]. Thus, more clinical trials with more participants comparing different dosages are needed in order to understand the efficacy of BoNT-A in the treatment of patients with bruxism [35,36].

Adverse effects of botulinum toxin are dose-dependent, and the complications can be classified into two categories such as systemic and local complications. Systemic complications occur mostly in the case of overdose of toxin and include nausea, malaise, diarrhea, abdominal pain, and anaphylaxis due to allergic reactions. Local complications, related to the injection site, are represented by headache, edema, ecchymosis, pain at the injection site, and sensory abnormality. Headache is the most common adverse effect developing within 24 h after the injection. Given the lack of high-quality evidence, the authors recommend further studies with established diagnostic criteria and refined clinical protocols. Furthermore, clinical trials analyzing the advantageous effect of a moderate dose of BoNT-A should be performed.

5. Conclusions

TMDs are a multi-factorial and polysymptomatic pathology and their management must be customized for each patient. BoNT-A is one of the proposed treatments for the management of TMDs due to its analgesic and relaxing abilities. Thus, it has become an attractive choice as an adjuvant therapy in patients with myofascial TMDs who do not achieve a complete response with conservative management and pharmacotherapy. This systematic review of RCTs showed BoNT-A was safe and efficacious for the management of patients with muscular temporomandibular disorders and its effect extends beyond its muscle-relaxing effects. However, due to its dose-dependent adverse events, its efficacy to development of adverse events ratio should be assessed. Low doses are recommended when BoNT-A is considered for persistent orofacial pain related to temporomandibular

disorders. Furthermore, BoNT-A has also been proposed for the treatment of bruxism associated with TMDs. Individual studies have shown promising results. However, the reported systematic reviews analyzing the effect of BoNT on bruxism reported different conclusions, suggesting that more clinical trials with more participants and comparisons of different dosages are needed. In conclusion, to further clarify the indications for BoNT-A, additional randomized controlled studies with larger sample sizes, lower levels of bias, and longer follow-up times must be conducted.

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Abbreviations

TMD	Temporomandibular disorder
TMJ	Temporomandibular joint
AADR	American Association for Dental Research
BoNT-A	Botulinum neurotoxin type A
SS	Saline solution
FID	Flat intraoral device

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