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Is Botulinum Toxin More Effective than Occlusal Device for the Treatment of Temporomandibular Dysfunction? A Systematic Review

A Toxina Botulínica é Mais Eficaz do que o Dispositivo Oclusal para o Tratamento da Disfunção Temporomandibular? Uma Revisão Sistemática

João Marcos Carvalho-Silva[a]; Vitor de Paula Lopez[a]; André Luís Botelho[a]; Ana Beatriz Vilela Teixeira[a]; Andréa Cândido dos Reis[a]

Universidade de São Paulo, Faculdade de Odontologia. Departamento de Materiais Dentários e Prótese. SP, Brazil.
E-mail: andreare73@yahoo.com.br

Abstract

Temporomandibular disorders (TMDs) can cause muscular, skeletal, or mixed changes, and their treatment includes the use of occlusal devices (ODs). However, the literature shows that the use of botulinum toxin (BTX) can be effective for this purpose. Therefore, the aim of this study was to perform a systematic review to answer the following question: "Is botulinum toxin (BTX) more effective than occlusal devices (OD) for the treatment of temporomandibular disorders (TMD)?". The methodology was started following the PRISMA guidelines, and this project was registered with PROSPERO (CRD42022330701). A search of the Embase, PubMed, Scopus, Science Direct, and Lilacs databases was conducted on April 28th, 2022. Eligibility criteria included randomized and non-randomized in vivo experimental clinical trials comparing the effects of BTX and DO on TMD patients. Of the 447 results found, 10 studies were selected for full-text reading, and 6 were included in this review. Both treatments were effective in relieving the painful symptoms of TMD and orofacial pain. BTX had advantages such as increased mouth opening and range of motion; however, it had time-dependent efficacy and could cause side effects. In conclusion, BTX has advantages and is an effective therapy for TMD; however, due to its short-term effects and side effects, both treatments are considered to have similar efficacy.

Keywords: Temporomandibular Disorders. Occlusal Devices. Botox. Botulinum Toxin. Myofascial Pain.

Resumo

As disfunções temporomandibulares (DTM) podem ocasionar alterações musculatórias, esqueléticas ou mistas e seu tratamento inclui o uso de dispositivos oclusais (DO). No entanto, a literatura aponta que o uso da toxina botulínica (BTX) pode ser eficaz para esta finalidade. Assim, o objetivo desse estudo foi realizar uma revisão sistemática para responder a seguinte pergunta: "A toxina botulínica (BTX) é mais eficaz do que dispositivo oclusal (DO) para o tratamento das DTMs?". Iniciou-se a metodologia, seguindo-se as diretrizes PRISMA e registrou-se este projeto no PROSPERO (CRD42022330701). Foi realizada uma busca nas bases de dados Embase, PubMed, Scopus, Science Direct e Lilacs em 28 de abril de 2022. Os critérios de elegibilidade incluíram ensaios clínicos experimentais in vivo randomizados e não randomizados que compararam os efeitos da BTX e dos DO em pacientes com DTM. Dos 447 resultados encontrados, 10 estudos foram selecionados para leitura do texto completo e 6 foram incluídos nesta revisão. Ambos os tratamentos foram eficazes no alívio dos sintomas dolorosos da DTM e da dor orofacial. A BTX apresentou vantagens como o aumento da abertura bucal e da amplitude de movimento, entretanto, apresentou eficáciatempo-dose-dependente e pode causar efeitos colaterais. Em conclusão, a BTX apresenta vantagens e é uma terapia eficiente para a DTM, entretanto, devido ao seu efeito de curto prazo e aos efeitos colaterais, considera-se que ambos os tratamentos apresentam eficácia semelhante.

Palavras-chave: Desordens Temporomandibulares. Dispositivos Oclusais. Botox. Toxina Botulínica. Dor Miofascial.

1 Introduction

Temporomandibular dysfunction (TMD) is characterized by signs and symptoms of myofascial and neck pain, temporomandibular joint (TMJ) crepitation, mouth opening difficulty, and the development of parafunctional conditions such as bruxism[1-6]. The TMJ degeneration, parafunctional habits, and trauma cause painful symptoms of muscle and joint origin or both[1,2,7]. The etiology of TMD is multifactorial, related to anatomical, pathophysiological, psychosocial, and traumatic factors that cause changes in proprioceptors and muscle motor nerves, leading to muscle hyperactivity and painful symptoms[3,4,7].

The treatment of TMD involves the removal of etiological factors, control of parafunctional habits, and protection of the stomatognathic system with the use of occlusal devices (OD), which protect the dental cuspids from excessive force and help to maintain the mandibular condyle in centric relation, the most comfortable position among the maxillomandibular relations, and promotes greater muscular comfort for the patient due to the decrease in centrally mediated neuromuscular activity[1,7,8].

Among the treatments for TMD such as physiotherapy, phonoaudiological therapy, laser therapy and the use of OD, botulinum toxin type A (BTX-A) is an alternative to conventional treatments, because its application to the masseter, temporal and lateral pterygoid muscles promotes the blockage of neuromuscular function with decreased

stimulation of muscle action[1,2,7,9,10]. In addition, it promotes analgesic and anti-inflammatory activity[2,7,8,11,12].

Not all patients show improvement with OD treatment only, therefore, other BTX treatments have been gaining space, and the question of which treatment is more effective for the TMD remains[3,9]. Therefore, the aim of this study was to perform a systematic review to answer the following question: "Is botulinum toxin (BTX) more effective than occlusal devices (OD) for the treatment of temporomandibular disorders (TMD)?".

2 Material and Methods

2.1 Protocol and registration

This systematic review was registered in the PROSPERO (CRD42022330701) and prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Checklist (PRISMA)[13] to answer the question: "Is botulinum toxin more effective than the occlusal device for temporomandibular disorder treatment?"

The study design (PICOS) framework applied was P= patients with TMD; I= botox and occlusal device application; C= Botox, occlusal device, occlusal device, and botox, placebo, received no treatment; O= TMD assessment before and after treatment (symptom improvement, visual pain scale, electromyography, Research Diagnostic Criteria for Temporomandibular Disorders (RDC), Diagnostic Criteria for Temporomandibular Disorders (DC), other questionnaires); and S= randomized and non-randomized clinical trials.

2.2 Search strategy and studies selection

Search strategy: ((“Temporomandibular disorder” OR TMD OR “Temporomandibular dysfunction” OR bruxism) AND (“Botulinum toxin” OR Botox) AND (“occlusal splint” OR “occlusal device”)) was applied to the SCOPUS, PubMed/Medline, Science Direct, EMBASE and Lilacs databases on April 28th, 2022 without a period and language restriction.

The selection of studies was performed in two steps after removing duplicates in EndNote, which were exported to the Rayyan application[14], re-searching for duplicate references, and removing the remaining. The initial selection was performed by three authors (Researcher 1, Researcher 2, and Researcher 3) and the studies were evaluated by title and abstract. In the second phase, the selected studies were read in full and inclusion and exclusion criteria were applied. In a consensus meeting, a fourth reviewer (Researcher 4) resolved disagreements. Data extracted from included studies were tabulated in a docx table (Author, year; Type of study; Study evaluation; Population; TMD classification; Intervention; Results; Conclusion).

2.3 Inclusion and exclusion criteria

As eligibility criteria, experimental in vivo randomized and not randomized clinical trials that compared the effects of BTX and ODs in patients with TMD, through TMD assessments before and after the intervention were included, in peer-reviewed journals. The exclusion criteria involved: 1) animal studies, observational and retrospective studies, review articles, case reports, letters to the editor, short communication, patent, conferences, book chapters, and editorials; 2) it did not compare BTX with ODs or who underwent treatment with only some of the interventions.

2.4 Analysis of risk of bias

ROB2 tools were used for randomized studies and ROBIS-I for quasi-experimental studies (non-randomized experimental studies) to assess the risk of bias [15]. To classify the methodological quality of the studies, each question was scored with risk of bias “low”, “high” and “some concerns’’ for ROB2 and “low”, “serious” and “critical” for ROBIS-I [16]. ROB2 and robvis software were used to obtain the figures. A meta-analysis and assessment of the strength of evidence using GRADE was not performed due to the data heterogeneity, thus, a descriptive analysis of the effectiveness of BTX or OD for the treatment of patients with TMD was performed.

2.5 Data extraction

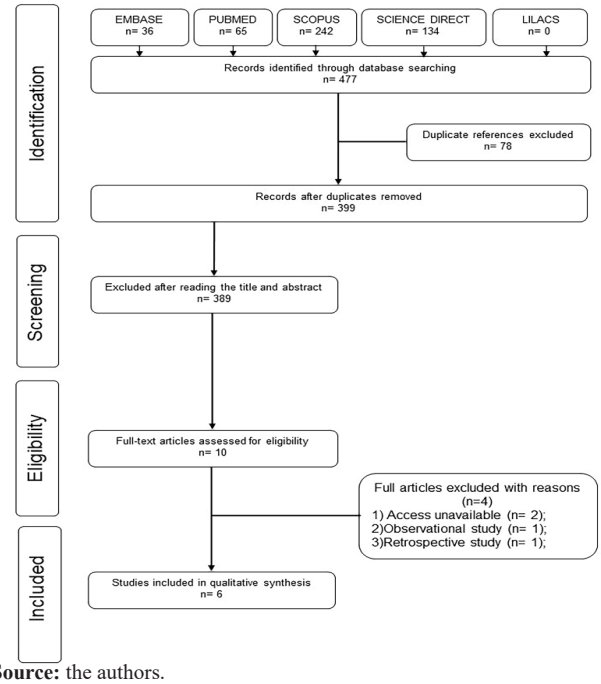
Data extraction was carried out using a table containing author, year, type of study, study evaluation, population, TMD classification, intervention, results, and conclusion. Three investigators independently assessed this process. A meta-analysis was not performed because of the data heterogeneity, and the results were descriptively analyzed.

3 Results and Discussion

3.1 Study selection

Of the 447 results found, 78 were duplicates. After the initial selection, 389 articles were excluded, 10 were selected for full-text reading and 6 were included. Figure 1 shows the process of analyses and inclusion of the articles in this review. Information on the included studies is presented in Table 1, and on the excluded in Table 2.

Figure 1 - Flow diagram of literature search and selection criteria



Source: the authors.

Table 1 - Characteristics of the included studies

Author, year	Type of study	Study evaluation	Population	TMD classification	Intervention	Results	Conclusion
Ali et al. 2021	Randomized experimental study.	Effectiveness of OA and BTX, through TMD/NS and PSQI.	42 participants with one of the arches restored by OD for at least one year, without previous treatment.	Sleep bruxism.	Group 1: control group, OD removal at night; Group 2: use of OA at night; Group 3: injection of BTX type A (Neuronox by 2.5 mL of 0.9% - 25 units) in the masseter and temporal muscles.	Groups 2 and 3 showed favorable results regarding TMD/NS and PSQI. Group 3 demonstrated the best results after follow-up at 3, 6, 9 and 12 months.	BTX has demonstrated favorable long-term results.
Canales et al. 2020	Randomized experimental study.	The safety and efficacy of 3 different doses of BTX. VAS, PPT, EMG, MP, UI and CBCT were evaluated 8 times during 6 months.	100 women aged 18 to 45 years with complete dentition and who underwent previous treatment for myofascial pain.	Persistent myofascial pain.	Group 1: OA overnight for 6 months; Group 2: 5 applications of SS (control group) (sterile saline solution 0.9%); Group 3: 5 applications of low dose of BTX (Temporal - 10U / Masseter - 30U); Group 4: 5 applications of medium dose of BTX (Temporal - 20U / Masseter - 50U); Group 5: 5 high-dose BTX applications (Temporal - 25U / Masseter - 75U).	BTX provided a greater decrease in masticatory performance, muscle contraction, muscle thickness and bone levels of the coronoid and condylar processes than OA. The effect was dose-dependent.	OA should be the first treatment option because it is conservative, using low doses of BTX in patients who did not get relief from OA.
Kaya et al. 2021	Randomized experimental study.	Efficacy between BTX and OA for pain reduction (VAS), functional movement and maximum bite force (prepared bite force measuring device). Assessments were made at 2 and 6 weeks and 3 and 6 months.	40 participants (33 women and 7 men) between 18 and 45 years old, without systemic diseases.	Bruxism and pain in TDM.	Group 1: OA for at least 8 hours a day; Group 2: injection of BTX (24 units) in one side of the masseter muscle.	Both treatments were effective, but the BTX injection was less effective in decreasing pain. Clinically, the treatments were equivalent.	OA is an effective non-invasive treatment and low-dose BTX may be complementary in patients unable to use the splint.

Sipahi Calis et al. 2019	Nonrandomized Clinical trial.	Efficacy of BTX in the treatment of TMD, through VAS, bite force (using a specially-designed force meter) and mouth opening (millimeter calculation).	25 participants diagnosed with TMD, without systemic diseases, with dentition in the mandible, non-pregnant and with failure in previous treatment due to OA, drugs and physical therapy.	Muscular dysfunction of origin.	Group 1: drugs (analgesics, anti-inflammatory drugs, muscle relaxants and antidepressants), diathermy for 15 days and OA for 6 months; Group 2: drugs and diathermy for 15 days, OA for 6 months and 100 U of BTX type A on both sides of the face, 30 U in the masseter muscle and 20 U in the temporal.	In 64% of the patients, drug, diathermy, and OA treatment was effective. The application of BTX was effective in 36% of patients, who did not respond to previous treatment.	BTX was a viable treatment in patients who did not respond to conventional therapies.
Taema et al. 2021	Randomized experimental study.	Efficacy of OA in conjunction with BTX on pain (NRS) and TMJ clicks. After 4 months, MRI evaluation. They were followed up at 2 weeks and 1, 2, 3, and 4 months.	20 joints of patients between 18 and 35 years old, excluding pregnant women, patients with parafunctional habits, pacemakers and arthritic/ osteophytic signs.	Anterior disc displacement with reduction.	Group 1: BTX (35 IU) in the pterygoid; Group 2: BTX (35 IU) in the pterygoid and anterior positioning plate (during sleep).	There was clinical improvement in both groups. Group 1 showed better results. In group 2 there was greater discomfort (stress and pain) due to the use of OA.	Consideration should be given to the cost of applying BTX and the complications caused by the anterior positioning plate.
Yurttutan et al. 2019	Randomized experimental study.	Efficacy of OA and BTX in reducing pain (VAS), TMD-related pain (TMD Pain Screener), pain intensity (Graded Chronic Pain Scale), jaw limitations (Jaw Function Limitation Scale) and parafunctional habits (Oral Behaviors Checklist). They were followed up at 7 days and 3 and 6 months.	73 participants aged over 18 years and who had myofascial pain for at least 6 months, excluding patients with disc displacement, with previous treatment, pregnant or lactating women, with neurological problems or in TMJ, use of specific drugs, with previous surgery in TMJ, with allergy or previous use of BTX.	Myofascial pain due to bruxism.	Group 1: OA (12 hours a day for 6 months); Group 2: BTX at 5 points on the masseter muscle (30 U) and 3 points on the temporal (15 U), bilaterally; Group 3: OA and BTX (similar to group 2).	All groups showed clinical improvement.	OA may not be necessary in patients treated with BTX.

TMD, temporomandibular disorder; OA, oral appliance; OD, overdenture; BTX, botulinum toxin; SS, saline solution; TMJ, temporomandibular joint;

Temporomandibular disorders/numeric scales, TMD/NS; Pittsburgh Sleep Quality Index, PSQI; Visual Analog Scale, VAS; Pressure Pain Threshold, PPT; Electromyography, EMG; Masticatory Performance, MP; Ultrasound Imaging, UI; Cone Beam Computed Tomography, CBCT; Magnetic resonance imaging, MRI; Numerical rating scale, NRS.
Source: research data.

Table 2 - Excluded articles and reasons for exclusion

Author, year	Reason for exclusion
Canales et al, 2021	Access unavailable
Miotto et al, 2021	Access unavailable
Pihut et al, 2017	Observational study
Yilmaz et al, 2021	Retrospective study

Source: research data.

Table 1 shows the results of the articles individually for comparison, and Table 2 shows the motive that caused the inclusion of the articles.

3.2 Risk of bias in studies

Figures 2, 3, and 4 show the risk of bias assessed according to the ROB2 and ROBIS-I tools[15,16].

Figure 2 - Risk of bias summary according to ROBINS-I

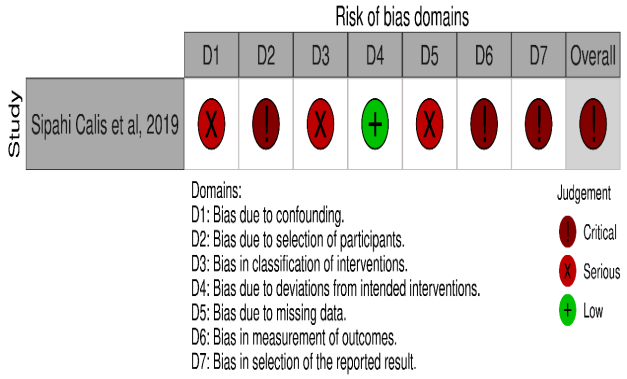


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Figure 3 - Risk of bias summary according to ROB2

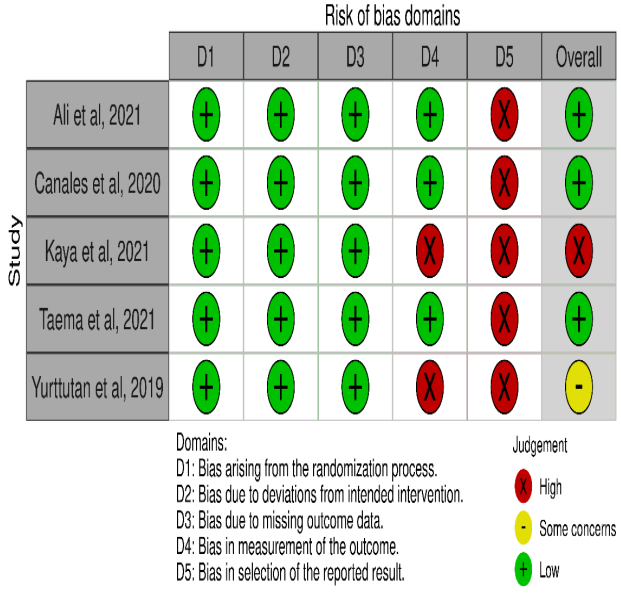

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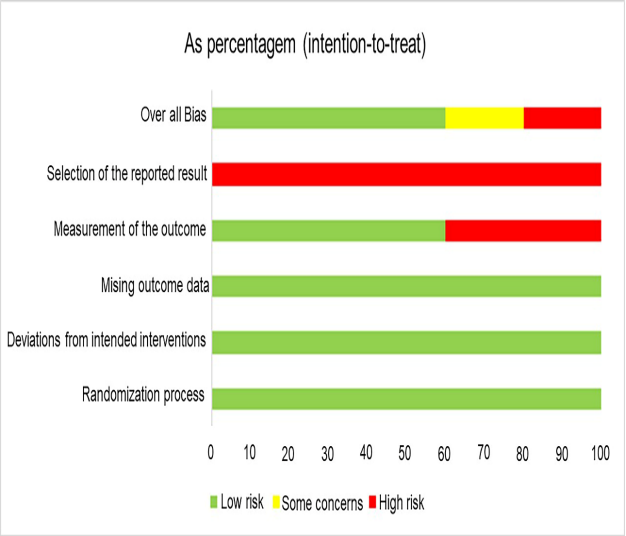
Figure 4 - Risk of bias graph



Source: research data.

Figures 1, 2, and 3 show the overall percentage of risk of bias and the individual sources of high risk of bias in the included studies.

For the randomized studies, only one had a high risk of bias[1] and another had "some concerns"[7], as there was no blinding in the outcome analysis (domain 4). All studies had a high risk of bias in domain 5, due to the use of multiple measurements to assess the outcome[1-3,7,9,11]. Although in domain 2 the studies were classified as having a low risk of bias, the participants and researchers were aware of the intervention applied due to the use of OD[1-3,7,9,11]. Sipahi Calis et al.[2] presented bias high risk because they did not discuss the confounding factors in their study, they did not report the randomization, blinding of participants and researchers method, they did not delimit the experimental and control groups and lack of data regarding the results of the interventions. Sipahi Calis et al.[2] apresentaram alto risco de viés devido não discutirem os fatores de confusão de seu estudo, não reportaram os métodos de randomização, cegamento dos participantes e pesquisadores, não delimitaram os grupos experimental e controle, e não foram reportados claramente resultados das intervenções.

3.3 Synthesis of findings

The studies were effective in relieving symptoms of TMD, orofacial pain, and sleep bruxism when doses of BTX-A were used in the masseter and/or temporal muscles[1-3,7,9,11]. Due to the invasiveness of this therapy, Canales et al.[11] and Kaya et al.[1] report that the first treatment option should be OD, as they do not pose a risk to the patient's systemic health.

Ali et al.[9] observed that patients who used OD or BTX showed improvement in sleep quality, with better results for BTX at 12 months of follow-up.

Patients treated with different doses of BTX or OD had a significant reduction in pain. BTX had side effects, dose-dependent results, and reduced muscle activity in the first 28 days. However, after 90 days, it was equivalent to the use of OD[11].

Kaya et al.[1] showed that the use of BTX or OD reduced pain. Regarding bite force, BTX significantly reduced, while for OD, after the 6th month of use, there was an increase.

In 64% of the patients evaluated by Sipahi Calis et al.[2], there was remission of TMD symptoms with the use of anti-inflammatory drugs, analgesics, muscle relaxants, antidepressants, diathermy, and ODs. However, for 36% of the cases, the proposed treatment was not efficient and additional treatment with BTX was necessary.

Treatment with BTX provided a greater increase in mouth opening and mandibular lateral range of motion than OD, and in terms of pain reduction, both were effective[3].

Yurttutan et al.[7] observed that patients treated with OD and/or BTX had a significant reduction in pain and reported that in patients treated with BTX there is no need to use OD.

The included studies showed that treatments with BTX-A and OD were effective in TMD treatment and improving myofascial pain symptomatology, sleep and awake bruxism, and anterior disk displacement with reduction[1-3,7,9,11]. Both treatments have advantages and disadvantages that should be considered by dentists for the correct indication to treat pain symptomatology, and joint disorder, and promote health and well-being[1-3,7,9,11].

In general, the studies presented some confounding factors in the diagnoses, with heterogeneous groups and subjective evaluation indexes, which can be considered limiting factors and promotes the absence of the RDC questionnaire and its most current DC version, which is a reference for the biopsychosocial diagnosis of TMD[9,11]. Few objective analyses such as electromyography and imaging exams were evaluated, which can be the subject of future studies[9,11].

The treatment with OD showed a reduction in pain index, better sleep quality, and mouth opening in patients who used it during the night, while the BTX showed better results for sleep quality, bite force reduction, mouth opening, and lateral mandibular movement, it has a fast application and is a minimally invasive alternative[1,3,5,8,9]. It also acted to control bruxism by reducing muscle hyperactivity and thus reducing pain [7]. These results are inconsistent with the study by Nixdorf et al.[10], which reported that BTX-A is not effective in treating severe mandibular pain. A possible cause for this difference may be that the analysis was performed using a visual pain scale and not electromyography or the RDC questionnaire, and also the small number of patients[5].

OD prevents the patient from remaining in the maximum intercuspation relationship and maintains an inter-arch opening of approximately 3mm[7]. It acts on muscle reprogramming and physiological positioning of the centric relationship between the condyle and glenoid cavity[2,7,9]. This method is effective in the control of parafunctional habits such as bruxism and tooth clenching, protecting occlusion and the teeth integrity, and reducing painful symptoms[7]. However, this method requires patient compliance, and even with continuous use, the therapeutic effects may appear after about the 6th month[7].

BTX-A is a toxin produced by *Clostridium botulinum* that acts on the neural branches present in the skeletal muscles and prevents the propagation of nervous impulses by interrupting acetylcholine with a reduction in muscle contraction and a decrease in TMD symptoms[3,4,7-9,11]. Its use presents increased mouth opening, improved sleep quality, reduced bite force, and lateral mandibular movement for cases of bruxism, myofascial pain, and TMJ pain, with sustained effect for up to 4 months[1,3,7,9,11]. They have advantages over OD, such as rapid remission of symptoms, clinical safety, and certainty of continuous use by the patient[1,11,12]. However, there are disadvantages because they are more invasive, require reapplications, are expensive, and have dose-dependent side effects, such as muscle atrophy, reduced mandibular bone volume, and bite force, which can influence TMD and lead to treatment failure[3,7-9,11].

The etiology of TMD-related pain is not completely elucidated, but alterations in nociceptors caused by inflammatory changes with a consequent action on the peripheral and central nervous system have been reported[5]. Psychological factors have a great influence on the symptomatology and treatment of TMD, thus multidisciplinary treatments should be proposed[6,8]. The inflammation present in the TMJ can be controlled with the use of anti-inflammatory medication, OD, and the application of BTX-A, which, in addition to controlling neuromuscular excitation, has analgesic and anti-inflammatory effects[5].

In clinical practice, the use of OD is preferentially indicated because it is a non-invasive treatment, easy to prepare, low cost, low risk of side effects, easy to replace, and to discontinue treatment[1,11]. However, in cases of failure or need for combined treatment, BTX should be applied in low doses bilaterally in the masticatory muscles, mostly in the temporal and masseter[1,2,7,9,11].

4 Conclusion

According to the limitations of this review, due to the small number and heterogeneity of the evaluated and included studies, we can conclude that:

BTX has similar efficacy to OD for the treatment of TMD, with OD being preferred because they are non-invasive treatments.

The use of BTX is an excellent therapeutic alternative to be used together with these devices and as an alternative in cases of failure with OD.

More studies are needed to perform the analysis of the strength of evidence for a better interpretation of the results.

Data Availability Statement: The data that support the findings of this study are available from the corresponding

author upon reasonable request.

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