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SYSTEMATIC REVIEW

Clinical outcomes of botulinum toxin type A injections in the management of primary bruxism in adults: A systematic review

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ABSTRACT

Statement of problem. Botulinum toxin has been used for various therapeutic and esthetic purposes for nearly 4 decades and has shown positive outcomes in patients with bruxism. However, the effectiveness of botulinum toxin injections as an alternative to traditional therapies in the management of primary bruxism is still unclear.

Purpose. The purpose of this systematic review was to analyze the clinical outcomes of the use of botulinum toxin type A injections in the management of primary bruxism in adults.

Material and methods. Databases such as PubMed, Web of Science, Scopus, LILIACS, Cochrane Library, and Open Grey Literature were searched without language or date restrictions until October 6, 2019. Using Mendeley Desktop software to organize the references, 2 independent researchers selected the published clinical studies (Study type) on the improvement of symptoms (Outcome) in human adults with primary bruxism (Participants/Population) who received botulinum toxin type A injections (Intervention), placebo injections, saline injections, no injections, or other treatments (Comparator(s)/Control) for the management of bruxism.

Results. A total of 601 references were initially obtained from the 6 databases. Six randomized clinical trials and 4 case series were selected and critically appraised according to the Fowkes and Fulton guidelines. Heterogeneity among the studies did not allow for a meta-analysis. All studies supported the efficacy and safety of botulinum toxin injections in reducing the symptoms of primary bruxism.

Conclusions. Botulinum toxin type A injections are effective in the treatment of the symptoms of primary bruxism in adults. Randomized clinical trials are still needed to establish a protocol for using botulinum toxin as an alternative to traditional therapies in the management of primary bruxism. (J Prosthet Dent 2020;■:■-■)

Approximately 85%-90% of the general population report bruxism to some degree.[1] The etiology of primary bruxism has not been associated with medical disorders or medication usage.[2] In addition, it is ill-defined and related to multiple risk factors.[3]

Muscle fatigue, pain, tooth wear, fractures, and implant loss are some of the signs and symptoms of bruxism.[4] Traditional therapies such as guidance, habit management, an occlusal device, medications, and electrical stimulation have been used to prevent and reduce the negative effects of primary bruxism. However, no single treatment has been reported to be completely effective.[5]

Botulinum toxin (BT) has been used for various therapeutic and esthetic purposes for nearly 4 decades,[6] and positive outcomes have been reported in patients with bruxism since 1990.[7] The few and recent findings associating BT with bone loss[8,9] and incomplete muscle recovery[10] appear to be questionable and may be clinically irrelevant compared with the benefit of controlling bruxism. BT type A injections have been reported to decrease bruxism-induced

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Clinical Implications

Studies involving patients with bruxism showed that botulinum toxin type A injections can safely reduce myofascial pain symptoms in patients with bruxism. Botulinum toxin injections are a promising alternative to traditional therapies in the management of primary bruxism.

pain,[11-20] with unusual, localized, and dose-dependent adverse reactions.[21] Considering the lack of effectiveness of the traditional therapeutic modalities to manage primary bruxism, BT may be a promising treatment alternative. This systematic review analyzed the clinical outcomes of the use of botulinum toxin type A injections in the management of primary bruxism in adults.

MATERIAL AND METHODS

This study was registered with PROSPERO 2019 reference number CRD42019135511. This systematic review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement-www.prismastatement.org).[22] The PRISMA checklist was used to ensure the quality and transparency of the study.[23] The PICOS strategy was used to construct a focused question[24]: "Are botulinum toxin injections effective in the management of primary bruxism?". Clinical outcomes of BT injections in the management of primary bruxism were evaluated with a systematic review. The published clinical studies (Study type) selected addressed the improvement of the occurrences of symptoms of bruxism (Outcome) in human adults with primary bruxism (Participants/Population) who received BT injections (Intervention), placebo injections, saline

Table 1. Search strategy

Database	Search Strategy
PubMed	#1 "Botulinum Toxins"[MeSH Terms]) OR "Botulinum Toxins"[Title/Abstract]) OR "Botulinum Toxin"[Title/Abstract]) OR "Clostridium botulinum Toxins"[Title/Abstract]) OR Botulin[Title/Abstract]) OR "Botulinum Toxins, Type A"[MeSH Terms]) OR "Botulinum Toxins, Type A"[Title/Abstract]) OR "Clostridium Botulinum Toxin Type A"[Title/Abstract]) OR "Botulinum Toxin Type A"[Title/Abstract]) OR "Clostridium botulinum A Toxin"[Title/Abstract]) OR "Botulinum Neurotoxin A"[Title/Abstract]) OR "Botulinum A Toxin"[Title/Abstract]) OR Neuronox[Title/Abstract]) OR Meditoxin[Title/Abstract]) OR Oculinum[Title/Abstract] #2 Bruxism[MeSH Terms]) OR Bruxism[Title/Abstract]) OR "Teeth Grinding Disorder"[Title/Abstract]) OR "Teeth Grinding Disorders"[Title/Abstract]) OR "Sleep Bruxism"[MeSH Terms]) OR "Sleep Bruxism"[Title/Abstract]) OR "Sleep Bruxisms"[Title/Abstract]) OR "Nocturnal Teeth Grinding Disorder"[Title/Abstract]) OR "Nocturnal Bruxism"[Title/Abstract]) OR "Nocturnal Bruxisms"[Title/Abstract]) OR "Sleep-Related Bruxism"[Title/Abstract]) OR "Sleep Related Bruxism"[Title/Abstract]) OR "Sleep-Related Bruxisms"[Title/Abstract]) OR "Adult Sleep Bruxism"[Title/Abstract]) OR "Adult Sleep Bruxisms"[Title/Abstract] #1 and #2
Web of Science	#1 TOPIC: ("Botulinum Toxins") OR TOPIC: ("Botulinum Toxin") OR TOPIC: ("Clostridium botulinum Toxins") OR TOPIC: (Botulin) OR TOPIC: ("Botulinum Toxins, Type A") OR TOPIC: ("Clostridium Botulinum Toxin Type A") OR TOPIC: ("Botulinum Toxin Type A") OR TOPIC: ("Clostridium botulinum A Toxin") OR TOPIC: ("Botulinum Neurotoxin A") OR TOPIC: ("Botulinum A Toxin") OR TOPIC: (Neuronox) OR TOPIC: (Meditoxin) OR TOPIC: (Oculinum) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI #2 TOPIC: (Bruxism) OR TOPIC: ("Teeth Grinding Disorder") OR TOPIC: ("Teeth Grinding Disorders") OR TOPIC: ("Sleep Bruxism") OR TOPIC: ("Sleep Bruxisms") OR TOPIC: ("Nocturnal Teeth Grinding Disorder") OR TOPIC: ("Nocturnal Bruxism") OR TOPIC: ("Nocturnal Bruxisms") OR TOPIC: ("Sleep-Related Bruxism") OR TOPIC: ("Sleep Related Bruxism") OR TOPIC: ("Sleep-Related Bruxisms") OR TOPIC: ("Adult Sleep Bruxism") OR TOPIC: ("Adult Sleep Bruxisms") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years #1 and #2
Scopus	(TITLE-ABS-KEY ("Botulinum Toxins") OR TITLE-ABS-KEY ("Botulinum Toxin") OR TITLE-ABS-KEY ("Clostridium botulinum Toxins") OR TITLE-ABS-KEY (botulin) OR TITLE-ABS-KEY ("Botulinum Toxins, Type A") OR TITLE-ABS-KEY ("Clostridium Botulinum Toxin Type A") OR TITLE-ABS-KEY ("Botulinum Toxin Type A") OR TITLE-ABS-KEY ("Clostridium botulinum A Toxin") OR TITLE-ABS-KEY ("Botulinum Neurotoxin A") OR TITLE-ABS-KEY ("Botulinum A Toxin") OR TITLE-ABS-KEY (neuronox) OR TITLE-ABS-KEY (meditoxin) OR TITLE-ABS-KEY (oculinum)) #2 (TITLE-ABS-KEY (bruxism) OR TITLE-ABS-KEY ("Teeth Grinding Disorder") OR TITLE-ABS-KEY ("Teeth Grinding Disorders") OR TITLE-ABS-KEY ("Sleep Bruxism") OR TITLE-ABS-KEY ("Sleep Bruxisms") OR TITLE-ABS-KEY ("Nocturnal Teeth Grinding Disorder") OR TITLE-ABS-KEY ("Nocturnal Bruxism") OR TITLE-ABS-KEY ("Nocturnal Bruxisms") OR TITLE-ABS-KEY ("Sleep-Related Bruxism") OR TITLE-ABS-KEY ("Sleep Related Bruxism") OR TITLE-ABS-KEY ("Sleep-Related Bruxisms") OR TITLE-ABS-KEY ("Adult Sleep Bruxism")) #1 and #2
Cochrane Library	"botulinum toxins" OR botulin OR "Botulinum Toxin" OR "Clostridium botulinum Toxins" OR "Botulinum Toxins, Type A" OR "Botulinum A Toxin" OR "Botulinum Neurotoxin A" OR "Botulinum Toxin Type A" OR "Clostridium Botulinum Toxin Type A" OR "Clostridium botulinum A Toxin" OR meditoxin OR neuronox OR oculinum in Title Abstract Keyword AND bruxism OR "Teeth Grinding Disorder" OR "Teeth Grinding Disorders" OR "Sleep Bruxism" OR "Adult Sleep Bruxism" OR "Adult Sleep Bruxisms" OR "Nocturnal Bruxism" OR "Nocturnal Bruxisms" OR "Nocturnal Teeth Grinding Disorder" OR "Sleep Bruxisms" OR "Sleep Related Bruxism" OR "Sleep-Related Bruxism" OR "Sleep-Related Bruxisms" in Title Abstract Keyword
Grey Literature	"botulinum toxins" OR botulin OR "Botulinum Toxin" OR "Clostridium botulinum Toxins" OR "Botulinum Toxins, Type A" OR "Botulinum A Toxin" OR "Botulinum Neurotoxin A" OR "Botulinum Toxin Type A" OR "Clostridium Botulinum Toxin Type A" OR "Clostridium botulinum A Toxin" OR meditoxin OR neuronox OR oculinum in Title Abstract Keyword AND bruxism OR "Teeth Grinding Disorder" OR "Teeth Grinding Disorders" OR "Sleep Bruxism" OR "Adult Sleep Bruxism" OR "Adult Sleep Bruxisms" OR "Nocturnal Bruxism" OR "Nocturnal Bruxisms" OR "Nocturnal Teeth Grinding Disorder" OR "Sleep Bruxisms" OR "Sleep Related Bruxism" OR "Sleep-Related Bruxism" OR "Sleep-Related Bruxisms"
BVS/ LILIACS	tw:((tw:("botulinum toxins" OR botulin OR "Botulinum Toxin" OR "Clostridium botulinum Toxins" OR "Botulinum Toxins, Type A" OR "Botulinum A Toxin" OR "Botulinum Neurotoxin A" OR "Botulinum Toxin Type A" OR "Clostridium Botulinum Toxin Type A" OR "Clostridium botulinum A Toxin" OR meditoxin OR neuronox OR oculinum)) AND (tw:(bruxism OR "Teeth Grinding Disorder" OR "Teeth Grinding Disorders" OR "Sleep Bruxism" OR "Adult Sleep Bruxism" OR "Adult Sleep Bruxisms" OR "Nocturnal Bruxism" OR "Nocturnal Bruxisms" OR "Nocturnal Teeth Grinding Disorder" OR "Sleep Bruxisms" OR "Sleep Related Bruxism" OR "Sleep-Related Bruxism" OR "Sleep-Related Bruxisms"))) AND (db:("LILACS"))

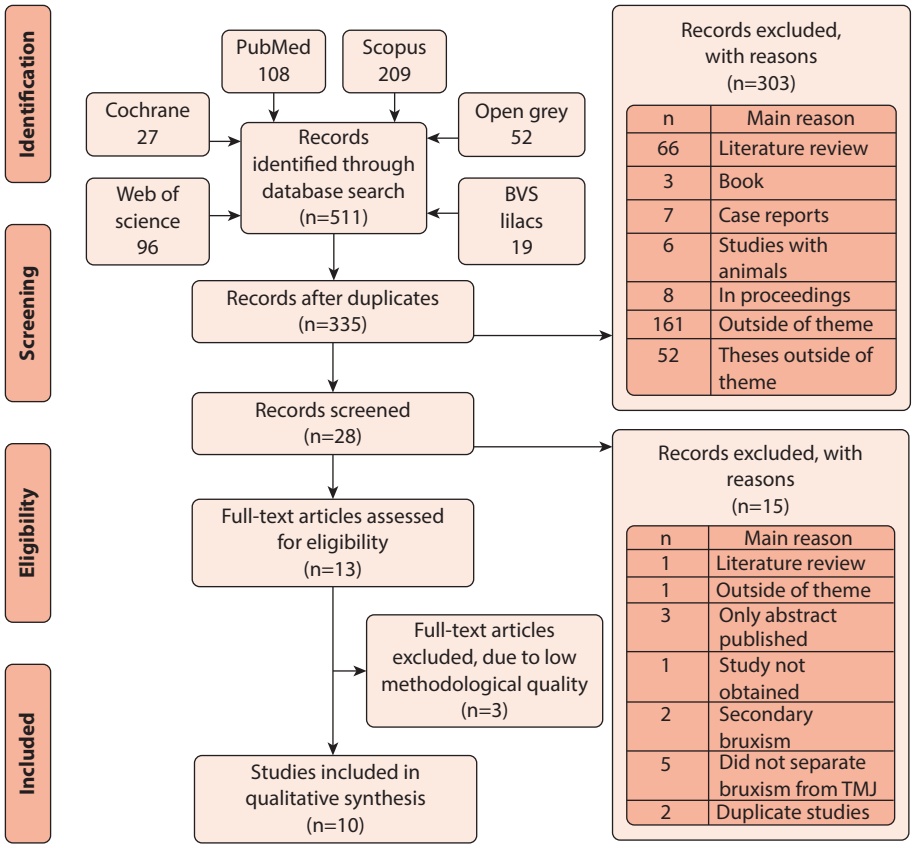

Figure 1. Flow diagram of screening and selection process according to PRISMA.[22]

injections, no injections, or other treatments (Comparator(s)/Control).

A systematic search without date or language restrictions was performed using the PubMed/MEDLINE, Web of Science, Scopus, Cochrane Library (CENTRAL), and BVS Lilacs electronic databases to include articles published through October 6, 2019. The nonpeer-reviewed literature was accessed by using the database system for Information on Grey Literature in Europe (SIGLE) (http://www.opengrey.eu).[25] The search strategy was composed of the following Medical Subject Headings (MeSH) terms: "Botulinum Toxins,""Botulinum Toxins, Type A,""Bruxism," and "Sleep Bruxism." Free text words and related terms were also included. The full electronic search strategy is presented in Table 1.

This review included published clinical studies reporting the effects of BT on the management of primary bruxism in humans. Animal studies, studies reported in proceedings, in vitro studies, case reports, books, dissertations, theses, monographs, and reviews were excluded. Studies not fully published, those conducted on children or teenagers, those with data associated with other health problems, and with nonprimary bruxism were also excluded. Figure 1 shows the flowchart of the systematic review selection process.

Two reviewers (L.S., C.M.) conducted the search and screening process independently. Duplicate studies were removed, and an analysis of the titles and the available abstracts was performed by using the Mendeley tool. Article selection was made according to the previously stated eligibility criteria. Any questions were resolved by consensus.

Data were extracted by 3 authors (K.V., L.S., C.M.), and a standardized form was used to register the primary author's name, year of publication, study design, number of participants, diagnosis, treatment methodology, investigation methods, follow-up period, clinical outcomes, and conclusions (Table 2).

Two authors (L.S., C.M.) independently evaluated the methodological quality and risk of bias of the included studies according to the Fowkes and Fulton checklist.[26] The analysis of each study was based on its design, sample, control group, quality of measurements and results, and completeness and distortion influences.

The checklist items were evaluated for the ability of the method to produce consistent information. A signal (++) was assigned when the analyzed item had a major problem and (+) in cases of minor problems. When no problems were found, the sign (0) was used, and (NA) was used when the analysis was not applicable to the type of study (Table 3).

Table 2. Characteristics of selected studies

Studies	Bolayir et al[11]	Guarda-Nardini et al[12]	Lee et al[13]	Redaelli[14]	Finiels and Batifol[15]
Year	2005	2008	2010	2011	2014
Study Design	CS	RCT	RCT	CS	CS
Participant number	N=12	N=20 TG: 10 CG: 10	N=12 TG: 6 CG: 6	N=120	N=8
Diagnosis	Sleep bruxism	Bruxism and myofascial pain	Sleep bruxism	Bruxism	Disabling posterior neck muscle contractures linked with bruxism
Treatment	BTX-A	TG: BTX-A CG: SPI	TG: BTX-A CG: SPI	BTX-A	BTX-A
Brand	Dysport	Botox	Dysport	Vistabex	Botox
Needle size	0, 8 mm hypodermic	Uninformed	Uninformed	Needle 30 G × 8 mm	Uninformed
Dose - Number of injection points - Muscles	Total: "An average of 50 U to the muscles" 3 points per masseter	Total: 100 U 30 U in 3 points per masseter and 20 U in 2 points per anterior temporalis	Total: "80 U in 0.8 ml of saline" "3 points per masseter"	Total: 28 U 14 U in 3 points per masseter	Total: "Varying from 10 to 100 U, according to the muscles chosen" Masseter, parietal, temporal and trapezium
Investigation methods	VAS	VAS Clinical measures Evaluation of subjective efficacy results and tolerance to treatment	Questionnaire Electromyography	Questionnaire	Questionnaire Radiography (Angle of cervical lordosis of the neck)
Data collection	Baseline 1 mo 3 mo	Baseline 1 wk 1 mo 6 mo	Baseline 4, 8, 12 wk	15 d	6 wk 3-mo follow-up for an average 15-mo period with injections every 3 mo
Principal final outcomes	No AE Pain: right masseter 1.80 ±1.31 (P<.050); left masseter 1.50 ±0.71 (P<.050)	No AE Maximum nonassisted opening: TG 48.40 ±7.63; CG 43.50 ±9.11 Mastication efficiency: TG 7.40 ±1.90; CG 7.50 ±1.96 Pain at chewing: TG 3.60 ±2.37; CG 4.70 ±2.79 Pain at rest: TG 3.60 ±2.88; CG 4.10 ±2.85	No AE Subjective symptoms of bruxism: TG 0.61 ±0.64; CT 1.39 ±1.00 (P=.006)	No AE Results according to participants: 3.3% scarce; 26.7% fairly good; 65.8% good; 4.2% excellent	No AE VAS: an improvement of 4.5 points Angle of lordosis: an improvement of +15°38′
Conclusion	BTX-A useful treatment method in patients with bruxism.	Supported efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger sample sizes.	Study supported use of BT injection as effective treatment for nocturnal bruxism.	Single method of treatment of bruxism, without side effects and appreciated by patients. Technique needs further studies to assess long-term outcome on target structure, especially on teeth.	In certain selected patients which associate bruxism and posterior cervical contractions, BT could offer interesting alternative in terms of cost, effectiveness, and relative innocuousness.

AE, adverse effect; BT, botulinum toxin; BTX-A, botulinum toxin type A injections; CG, control group; CS, case series; G, group; RCT, randomized clinical trial; RMMA, rhythmic masticatory muscle activity; SPI, saline placebo injections; TG, test group.VAS, Visual Analogue Scale.

To determine the value of the study, 3 summary questions were answered with "YES" or "NO": "Are the results erroneously biased in a certain direction?","Are there any serious confounding or other distorting influences?", and "Is it likely that the results occurred by chance?". If the answer was NO to all 3 questions, the article was considered to have a low risk of bias.

The positive effect of BT and the follow-up period of the included studies were calculated by estimating the intervention that was expressed in mean difference (MD) and α=.05. In this review, a meta-analysis was not possible because of considerable heterogeneity among the studies.

RESULTS

The systematic review process is shown in a flowchart (Fig. 1). After screening, 6 randomized clinical trials[12,13,16,18-20] and 4 case series[11,14,15,17] were included in the final analysis. All studies were published in English between 2005 and 2018. The studies consisted of sample sizes of 8[15]-120[14] participants. Four different brands of BT were used in doses of 14 units per masseter[14] to 200 units per participant.[20] The follow-up period ranged from 1 week[12,18] to 15 months [15] In addition, different clinical evaluation methods were used. Two articles[12,18] evaluated pain by using the

Table 2. *(Continued)* Characteristics of selected studies

Shim et al[16]	Asutay et al[17]	Jadhao et al[18]	Al-Wayli[19]	Ondo et al[20]
2014	2017	2017	2017	2018
RCT	CS	RCT	RCT	RCT
N=20 G A: 10 G B: 10	N=25	N=24 G I: 8 G II: 8 G III: 8	N=50 G I: 25 G II: 25	N=23 TG: 13 CG: 10
Sleep bruxism	Nocturnal bruxism	Bruxism and myofascial pain	Bruxism associated with chronic pain	Sleep bruxism
BTX-A	BTX-A	G I: BTX-A G II: SPI G III: control	G I: BTX-A G II: traditional methods	TG: BTX-A CG: placebo
Neuronox	Botox	Botox	Botox	Botox
29 gauge 0.5 inch	Uninformed	Uninformed	Uninformed	28 gauge 1/2-inch
Total: 50 or 100 U G A: 25 U in 3 points per masseter G B: 25 U in 3 points per masseter and 25 U in 3 points per temporalis	Total: 40 U 20 U in 4 points per masseter	Total: 100 U 30 U in 1 point per masseter and 20 U in 3 points per temporalis	Total: 40 U 20 U in 3 points per masseter	Total: 200 U 60 U in 2 points per masseter and 40 U in 3 points per temporalis
Questionnaire Electromyography	VAS Duration of effectiveness	VAS from 0 to 5 and another questionnaire Occlusal force analysis system I-Motion occlusal force analyzer.	Questionnaire	VAS and another questionnaire Polysomnography
Baseline 4 wk	Baseline 2 wk, 1, 3, 4, 6 mo	Baseline 1 wk 3, 6 mo	3 wk 2, 6 mo 1 y	Baseline 4, 8 wk
AE: 3 participants complained of masticatory difficulties In both groups, BT did not reduce the frequency, number of bursts or duration of RMMA episodes. BT decreased the peak amplitude of EMG burst of RMMA (P=1.000) Morning jaw stiffness (%): G A 47.50 ±15.86; G B 57.50 ±30.30 (P=.371) Decrement of subjective masticatory force: G A 30.00 ±17.64; G B 40.50 ±18.33 (P=.208)	No AE Pain score: 3.40 ±2.141	No AE Pain at chewing: G I 3 ±0.95; G II 3.8 ±0.98; G III 3.9 ±0.96 Maximum bite force (kg): G I 30.12 ±5.23; G II 24.34 ±2.81; G III 3.56 ±0.76 (P=.051)	No AE Pain score: G I 0.2 ±0.51; G II 2.1 ±0.74 (P=.000)	AE: 2 participants with cosmetic change in smile VAS: TG 65.0 ±19.6; CG 44.2 ±14.3 (P<.050)
Single BTX-A is effective strategy for controlling sleep bruxism for at least 1 month. It reduces intensity rather than generation of contraction in jaw-closing muscles. Future investigations on efficacy and safety in larger sample sizes over a longer follow-up period needed before establishing management strategies.	BTX-A effective in treatment of nocturnal bruxism	Results supported efficacy of BTX-A to reduce myofascial pain symptoms in bruxers and effective in reducing occlusal force.	Results suggested that botulinum toxin injection reduced mean pain score and number of bruxism events, most likely by decreasing muscle activity of masseter rather than affecting central nervous system.	BTX-A effectively and safely improved sleep bruxism in this placebo-controlled pilot trial. Large multicenter trial needed to confirm these encouraging data.

visual analog scale (VAS) 6 months after injections of 100 units of BT. However, 1 study[18] used a VAS of 0-5 and the other one[12] used a scale of 0-10. Heterogeneity among the studies did not allow a meta-analysis.

The assessments of the risks of bias for the selected articles according to the Fowkes and Fulton checklist[26] are shown in Table 3. Six studies[12,13,16,18-20] were rated as having a low risk of bias 3[11,15,17] and as having a moderate risk of bias, and 1[14] was evaluated as having a high risk of bias.

The kappa statistic for the 2 reviewers was 100% for the potential articles to be included (titles and abstracts) and for the articles selected. This indicated substantial agreement for the potential articles and "perfect" agreement, κ=1.[27]

All studies supported the efficacy and safety of BT injections in reducing the symptoms of primary bruxism. Of all 237 participants who underwent different BT treatments, only 5 had short-term adverse effects.

DISCUSSION

Systematic reviews are designed to provide a summary of current evidence in published studies, allowing evidence-based clinical practice. This systematic review analyzed

Table 3. Evaluation of methodological quality and risk of bias according to Fowkes and Fulton[26]

Questions	Items		Bolayir et al[11]	Guarda-Nardini et al[12]	Lee et al[13]	Redaelli[14]	Finiels and Batifol[15]	Shim et al[16]	Asutay et al[17]	Jadhao et al[18]	Al-Wayli H[19]	Ondo et al[20]
Study design appropriate to objectives?	Objective	Common design	-	-	-	-	-	-	-	-	-	-
	Prevalence	Cross sectional (CS)	-	-	-	-	-	-	-	-	-	-
	Prognosis	Cohort (C)	-	-	-	-	-	-	-	-	-	-
	Treatment	Controlled trial	X	x	x	x	x	x	x	x	x	x
	Cause	C, c-control, CS	-	-	-	-	-	-	-	-	-	-
Study sample representative?	Source of sample		0	0	0	+	+	0	+	0	+	0
	Sampling method		+	0	0	++	+	0	+	0	0	0
	Sample size		++	+	++	0	++	+	+	+	0	+
	Entry criteria/exclusions		0	0	0	+	+	0	0	0	0	0
	Nonrespondents		0	0	0	0	0	+	0	0	0	+
Control group acceptable?	Definition of controls		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Source of controls		NA	0	0	NA	NA	0	NA	0	0	0
	Matching/randomization		NA	+	+	NA	NA	+	NA	+	+	0
	Comparable characteristics		NA	0	0	NA	NA	0	NA	+	0	0
Quality of measurements and outcomes?	Validity		+	+	+	+	0	0	+	0	0	0
	Reproducibility		0	0	+	+	0	0	+	0	+	0
	Blindness		NA	0	0	NA	NA	0	NA	+	+	0
	Quality control		+	+	0	+	+	0	+	0	0	0
Completeness?	Compliance		0	0	0	0	0	+	0	0	0	+
	Drop-outs		0	0	0	0	0	+	0	0	0	+
	Deaths		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Missing data		0	0	0	0	0	0	0	0	0	0
Distortions influences?	Extraneous treatments		0	0	0	0	0	0	0	0	+	0
	Contamination		0	0	0	0	0	0	0	0	0	0
	Changes over time		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Confounding factors		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Distortion reduced by analysis		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Summary of Issues	Bias - Are the results erroneously biased in a certain direction?		Yes	No	No	Yes	Yes	No	Yes	No	No	No
	Confounding - Are there any serious confounding or other distorting influences?		No	No	No	No	No	No	No	No	No	No
	Chance - Is it likely that the results occurred by chance?		No	No	No	Yes	No	No	No	No	No	No

+, Minor problem; ++, Major problem; 0, no problem; NA, not applicable.

the clinical outcomes of BT type A injections in the management of primary bruxism in adults.

The sample size is important for the validation of scientific papers. In the present systematic review, only 2 of the 10 selected studies assessed more than 30 participants. The medication cost, the short-term nature of the effects, and the absence of label indication for BT injections into the masticatory muscles could explain the low number of participants in these studies. In addition, no study compared the different brands of BT. Each brand of BT has different manufacturing processes and different sets of interactions with the tissue. Results from 1 brand cannot be extrapolated to the others.[28] Therefore, randomized clinical trials comparing different brands are necessary.

The absence of an established protocol has led to a wide range of BT treatment methods. Most studies[11-15,17-20] evaluated the results of a single BT injection method, without varying the muscles or the injection points. Only 1 study[16] compared the use of this drug in the masseter muscles, concomitant or not with the temporalis muscle. More trials evaluating the outcome of different numbers and sites of injections are needed to establish the most effective and safe protocol.

Only 1[18] of the 10 selected papers used ultrasound guidance for the BT injections. The authors who selected injection points and depths by clinical estimation, in addition to palpation and measurements, obtained favorable results, with few or no reports of undesirable effects.[11-17,19,20] Most of the studies[12,13,15,17-19] did not provide information on needle size. None of the studies mentioned the depth of injection into the muscles; therefore, the relevance of injection depth needs to be determined.

A maximum dose of 100 units of BT is recommended per dental session.[21] In this systematic review, only 1 study[20] used a dose greater than 100 units. The included

studies used different doses and reported the findings without correlating the dose with the extent or duration of the paresis. Redaelli[14] adjusted the BT type A doses according to patient's satisfaction with the improvement of bruxism symptoms. The author suggested 14 units as the most effective dose for each masseter and 20 units for stronger muscles.

Most studies conducted more than one evaluation after the BT intervention and used different follow-up periods. According to Asutay et al,[17] participants began to feel the effects of BT at 12.24 ±2.02 days and lost them at 4.76 ±1.01 months. Only 1 study reported a follow-up period longer than 6 months, and that study found that the improvement obtained with BT injections was maintained for up to 1 year after treatment.[19]

All studies included in this systematic review used questionnaires to evaluate the effects of BT.[11-20] However, a questionnaire is a subjective form of evaluation, which makes it difficult to reach definitive conclusions. Five studies used the VAS[11,12,17,18,20]; however, the studies used different BT dosages and different follow-up periods. Two studies[12,18] evaluated the use of 100 units of BT per participant 6 months after application, but a quantitative study could not be performed because of the different VAS scores used. One study[18] used a VAS scale of 0-5 and the other one[12] used a scale of 0-10. The questionnaire of 1 study[13] was not validated because, although the authors stated that the symptoms of bruxism were evaluated, the questions were related to the frequency of episodes. Five studies used objective investigation methods such as polysomnography,[16] radiography of the neck,[15] electromyography,[13] digital occlusion analysis,[18] and clinical measurement of maximum mouth opening.[17]

Adverse reactions from BT injections have been reported to be uncommon, and, when they occurred, localized and dose-dependent.[21] Among the selected studies, only that by Ondo et al[20] found a change in the smile of 2 participants. Shim et al[16] reported 3 participants with masticatory difficulties. Asutay et al[17] reported no adverse effects; however, the authors classified 2 participants with no significant improvements as having adverse events. Recent studies[8,9] have reported an association between mandibular bone loss and the use of BT in the masticatory muscles. However, the difference in bone pattern in humans and animals hinders the extrapolation of these findings. Raphael et al,[9] who noted a decrease in bone density of 7 women exposed to BT, questioned the significance of these findings and indicated the need for further studies with a larger sample size and longer follow-up periods. Possible bone loss may be clinically irrelevant in comparison with the bruxism management achieved. Mathevon et al[10] reported incomplete muscle recovery, reduction in muscle thickness, and volumetric muscle atrophy 1 year after the use of BT in humans. However, in patients with bruxism, muscle weakening is a desired outcome. The authors are unaware of a clinical study exploring the undesirable formation of botulinum antitoxin antibodies that decrease the duration and therapeutic effect of the toxin on the masticatory muscles.

Limitations of this systematic review include that the 10 studies were heterogeneous, hindering comparison and quantitative analysis. This, therefore, underscores the need for further studies. A strength of this study was that all the different studies demonstrated a positive effect of BT on primary bruxism. After providing explanations about the study and obtaining consent from a patient without contraindication, BT injections seem to be an effective alternative for the management of primary bruxism, mainly in patients who have shown no improvement with conventional and more conservative treatments.

CONCLUSIONS

Based on the findings of this systematic review, the following conclusions were drawn:

1. Botulinum toxin type A injections are effective in the treatment of the symptoms of primary bruxism in adults.
2. Randomized clinical trials are still needed to establish a protocol for using botulinum toxin as an alternative to traditional therapies in the management of primary bruxism.

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