Effects of Botulinum Toxin Type A on the Psychosocial Features of Myofascial Pain TMD Subjects: A Randomized Controlled Trial

Giancarlo De la Torre Canales, DDS, MSc, PhD
Department of Prosthodontics and Periodontology
Piracicaba Dental School, University of Campinas;
Department of Prosthodontics
Bauru School of Dentistry, University of São Paulo
São Paulo, Brazil

Rodrigo Lorenzi Poluha, DDS, MSc
Department of Prosthodontics
Bauru School of Dentistry, University of São Paulo
São Paulo, Brazil

Yeidi Natalia Alvarez Pinzón, DDS, MSc
Department of Prosthodontics and Periodontology
Piracicaba Dental School, University of Campinas
São Paulo, Brazil

Paulo César Rodrigues Conti, DDS, MSc, PhD
Department of Prosthodontics
Bauru School of Dentistry, University of São Paulo
São Paulo, Brazil

Daniele Manfredini, DDS, MSc, PhD
Department of Dentistry
University of Siena
Siena, Italy

Alfonso Sánchez-Ayala, DDS, MSc, PhD
Department of Dentistry
State University of Ponta Grossa
Paraná, Brazil

Célia Marisa Rizzatti-Barbosa, DDS, MSc, PhD
Department of Prosthodontics and Periodontology
Piracicaba Dental School, University of Campinas
São Paulo, Brazil;
Department of Dentistry, Inga University Center
Maringa, Brazil

Correspondence to:
Dr Giancarlo De la Torres Canales
Department of Prosthodontics, Bauru School of Dentistry
University of São Paulo
Al. Octávio Pinheiro Brisola, 9-75.
CEP 17012-901 Bauru, SP, Brazil
Email: giank_28@hotmail.com

Submitted January 25, 2021;
accepted July 5, 2021.

Aims: To determine the effects of botulinum toxin type A (BoNT-A) on the psychosocial features of patients with masticatory myofascial pain (MFP). **Methods:** A total of 100 female subjects diagnosed with MFP were randomly assigned into five groups (n = 20 each): oral appliance (OA); saline solution (SS); and three groups with different doses of BoNT-A. Chronic pain-related disability and depressive and somatic symptoms were evaluated with the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis II instruments at baseline and after 6 months of treatment. Differences in treatment effects within and between groups were compared using chi-square test, and Characteristic Pain Intensity (CPI) was compared using two-way ANOVA. A 5% probability level was considered significant in all tests. **Results:** Most patients presented low pain-related disability (58%), and 6% presented severely limiting, high pain-related disability. Severe depressive and somatic symptoms were found in 61% and 65% of patients, respectively. In the within-group comparison, BoNT-A and OA significantly improved ($P < .001$) scores of pain-related disability and depressive and somatic symptoms after 6 months. Only the scores for pain-related disability changed significantly over time in the SS group. In the between-group comparison, BoNT-A and OA significantly improved ($P < .05$) scores of all variables at the final follow-up when compared to the SS group. No significant difference was found between the BoNT-A and OA groups ($P > .05$) for all assessed variables over time. **Conclusion:** BoNT-A was at least as effective as OA in improving pain-related disability and depressive and somatic symptoms in patients with masticatory MFP. *J Oral Facial Pain Headache 2021;35:288–296. doi: 10.11607/ofph.2917*

Keywords: *botulinum toxin, depression, myofascial pain, psychosocial impairment, temporomandibular disorders*

Temporomandibular disorders (TMDs) are a group of musculoskeletal disorders that affect the stomatognathic system,[1] with pain being one of the most common complaints in TMD patients.[2] Currently, pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[3] This definition is based on the biopsychosocial model of pain and shows the importance of considering the interactions of biologic, social, environmental, and psychologic factors for a better understanding of pain.[4] Such factors are especially important for TMD patients who are commonly under psychosocial distress and have a high prevalence of psychologic disorders[5–7]; in fact, a psychologic evaluation can even predict the first onset of a TMD.[8]

The main instruments used for TMD diagnosis, such as the Research Diagnostic Criteria for TMD (RDC/TMD) and the updated Diagnostic Criteria for TMD (DC/TMD), are based on a dual-axis system: Axis I, which focuses on clinical conditions, and Axis II, which focuses on psychosocial status and pain-related disability.[1,9,10] The Axis II instruments include measures for depressive and somatic symptoms, pain-related disability, and pain intensity.[10] Although Axis I diagnoses and Axis II findings are not correlated,[11] the psychosocial profile obtained by Axis II is emerging as a fundamental factor for understanding and predicting treatment outcomes.[12]

Pain-related disorders, such as arthralgia and myofascial pain (MFP), are the most common subtypes of TMDs.[12] MFP accounts for about 45% of TMD diagnoses and is defined as a regional muscle pain associated with tenderness on palpation.[1,2] Due to its multifactorial etiology, a wide range of conservative and multidisciplinary therapies, such as behavioral approaches, oral appliances (OAs), and needling techniques, are used to control symptoms.[13] In addition, a systematic review demonstrated the clinical effectiveness of OAs for pain, making it the most popular treatment for MFP due to its cost-effectiveness and noninvasive and reversible characteristics.[14] However, OA effects on psychosocial symptoms, despite being positive (lowering anxiety, catastrophizing thoughts, and depressive and somatic symptoms), have been less explored.[15,16] However, MFP treatment is usually challenging, especially in cases refractory to conservative treatment and in patients with psychosocial distress.[17,18]

The US Food and Drug Administration (FDA) approved botulinum toxin type A (BoNT-A) for the treatment of several muscle disorders based on its ability to inhibit synaptic exocytosis of neurotransmitters, disabling neural transmission.[19] A recent study showed that low doses of BoNT-A are an effective treatment option for cases of masticatory MFP.[20] In addition, several studies have suggested that BoNT-A injection can significantly improve anxiety, depression, and psychosocial distress symptoms, resulting in increased quality of life in patients with varied painful conditions.[21–24] However, no study has evaluated the impact of BoNT-A on the psychosocial aspects of patients with masticatory MFP, which could allow for a deeper understanding of the clinical role of BoNT-A.

Therefore, the present randomized controlled clinical trial assessed the effects of BoNT-A on the psychosocial aspects of patients with masticatory MFP and compared them to an OA and saline solution (SS) treatments. The null hypothesis tested was that BoNT-A is as effective as OA and SS for improving the psychosocial aspects of patients with masticatory MFP over time.

Materials and Methods

The present study was approved by the Research Ethics Committee of Piracicaba Dental School (CAAE #22953113.8.0000.5418-Date: 04/02/2014) and the Brazilian Registry of Clinical Trials (ReBEC RBR-2d4vvv). All subjects provided a written informed consent before being included in the trial. This manuscript was based on secondary data analysis of a previous publication by De la Torre Canales et al.[20]

The sample size was based on the average treatment effect on pain scores from a previous study, considering mean = 1.0 and SD = 1.7 for the BoNT-A group, and mean = 3.8 and SD = 2.0 for the placebo group (effect size: 1.5).[25] A sample of 8 subjects per group was found to provide 80% power when α = .05. This study included 100 consecutive female subjects who were diagnosed with MFP according to the Brazilian Portuguese version of the RDC/TMD[26] at the TMD Clinic of Piracicaba Dental School, University of Campinas, São Paulo, Brazil, from June 2014 up to May 2017. The subjects were assessed by two calibrated researchers not involved in any other process of the study (kappa coefficient = 0.80 for RDC/TMD interexaminer assessment). As inclusion criteria, subjects must have undergone MFP treatment with no significant pain relief for at least 3 months and have a score of at least 50 on a 0–100 visual analog scale (VAS) for pain intensity at baseline. Subjects with concomitant TMD diagnoses besides MFP were also included. Exclusion criteria were a history of trauma in the face and neck area and dental pain in the last 6 months, systemic diseases (arthritis and arthrosis), major psychiatric disorders, current use of drugs acting on neuromuscular junctions, contraindication or hypersensitivity to BoNT-A, and having had an anti-tetanus vaccine in the 3 months before the start of the clinical trial.

Subjects (n = 100) were randomly assigned into one of five treatment groups (n = 20 each):

- Oral appliance (OA group)
- Saline solution 0.9% (SS; placebo control group): 0.4 mL in the temporalis and 0.6 mL in the masseter
- BoNT-A low (BoNTA-L): 10 U in the temporalis and 30 U in the masseter
- BoNT-A medium (BoNTA-M): 20 U in the temporalis and 50 U in the masseter
- BoNT-A high (BoNTA-H): 25 U in the temporalis and 75 U in the masseter

For this allocation, a computer software (https://random-allocation-software.software.informer.com/2.0/) was used by a technician not involved in any other procedures in the study.

Treatments

All participants attended a counseling session by a single trained clinician (Y.N.A.P.) at the first appointment in which they were informed about the structural characteristics of the stomatognathic system, the causes and prognosis of MFP, and self-care strategies to control pain and parafunctional habits.

The OA was a flat intraoral device made of transparent heat-cured acrylic resin that covered all maxillary teeth. Subjects were instructed to use the OA

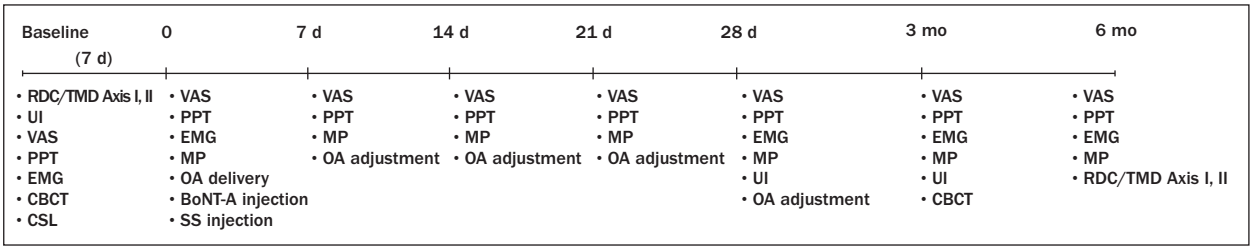

Fig 1 Flowchart showing time points and variables assessed in the study. VAS = visual analog scale (0 to 100); PPT = pressure pain threshold; EMG = electromyography; MP = masticatory performance; OA = oral appliance; BoNT-A = botulinum toxin type A; SS = saline solution; UI = ultrasound imaging; CBCT = cone beam computed tomography; CSL = counseling.

during sleep throughout the study. Adjustments for canine and anterior guidance were performed when required.

BoNT-A (100 U; Botox, Allergan) was reconstituted using nonpreserved 0.9% sterile SS. Doses of BoNT-A were based on a previous report.[20] Bilateral intramuscular injections were performed on the masseter and anterior temporalis muscles using a 1-mL syringe with a 30-gauge needle. Subjects were asked to clench their teeth to delimit the muscles, and a total of five injections per muscle, 5 mm apart, were applied. Injections of BoNT-A or SS were done during a single appointment and performed by the same trained clinician. Participants and the clinician were masked to BoNT-A and SS assignments, while the investigators assessing the outcomes were masked to all treatment assignments.

The psychosocial aspects of the patients were evaluated using the RDC/TMD Axis II instruments before and after 6 months of treatment.

Axis II Outcome Measures

The Graded Chronic Pain Scale (GCPS) assesses pain-related disability through 7 items rated on a 10-point scale, with the exception of 1 item regarding the number of days kept from usual activities due to facial pain. The GCPS provides hierarchical criteria to grade pain dysfunction into ordinal categories based on degrees of severity, as follows: 0 = no TMD pain in the prior 6 months; 1 = low disability, low intensity; 2 = low disability, high intensity; 3 = high disability, moderately limiting; and 4 = high disability, severely limiting.[1]

Characteristic Pain Intensity (CPI) was assessed by using numeric rating scales included in the following questions of the GCPS: "How would you rate your facial pain on a 0 to 10 scale at the present time, that is, right now?"; "In the past 6 months, how intense was your worst facial pain?"; and "In the past 6 months, on average, how intense was your facial pain (that is, your usual pain)?" The scales comprise a horizontal line numbered from 0 (left) to 10 (right), anchored by the words "no pain" and "worst pain imaginable," respectively. Participants were instructed to mark the number that best represented the average pain. The mean value of the three questions was used for data analysis.

The Symptoms Checklist-90R (SCL-90R) was used to measure the severity of depression (SCL-DEP) and somatic (SCL-SOM) symptoms. The SCL-DEP includes 20 items that classify levels of depressive symptoms into three categories: normal (< 0.535), moderate (0.535 to 1.105), and severe (> 1.105). The SCL-SOM evaluates the presence of nonspecific physical symptoms, including 12 items regarding pain and 7 items that are not pain related. Scores lower than 0.5 are considered normal, between 0.5 and 1.0 indicate moderate somatic symptoms, and above 1.0 indicate severe somatic symptoms.[1]

Subjects were evaluated more than twice during the 6-month study period (Fig 1), but for this study, only the data of Axis II tools applied at baseline and 6 mo after treatments are reported.

Statistical Analysis

SPSS Statistics software (version 25, IBM) was used, and all statistical comparisons were performed with two-tailed operations assuming a significance level of 5%. Normality assumption was verified using Shapiro-Wilk test and skewness and kurtosis values. The sphericity criterion was not assumed, considering Greenhouse-Geisser epsilon correction. Chi-square test was conducted to test the association of the GCPS data with experimental groups at baseline and after 180 days. To compare groups, chi-square test was adjusted for all pairwise comparisons using Bonferroni correction. Two-way repeated measures analysis of variance (ANOVA) was conducted to compare the SCL-DEP and SCL-SOM scores of experimental groups at baseline and after 180 days. Pairwise comparisons of estimated marginal means were performed using Bonferroni adjustment of 95% CI to determine the differences among factors. The difference between

groups regarding CPI before and after treatments was compared using ANOVA on ranks and multiple pairwise comparisons.

Results

A total of 540 volunteers were screened, and after the inclusion and exclusion criteria assessment, 100 participants were included in the study. Study sample characteristics are presented in Table 1.

Table 1 RDC/TMD Diagnoses, Pain Duration, and Age of the Included Subjects

Mean ± SD age, y	36.8 ± 5.6
Pain duration	n
6 to 12 mo	41
12 < 36 mo	37
≥ 36 mo	22
FL RDC/TMD diagnosis	
Myofascial pain alone	53
Myofascial pain/arthralgia	12
Myofascial pain/disc displacement with reduction	27
Myofascial pain/disc displacement without reduction	8

Table 2 RDC/TMD Axis II Graded Chronic Pain Scale (GCPS) Scores in Each Group for Different Treatment Phases

Chi-square = 12.175 *P* = .432	Group											
	OA		SS		BoNTA-L		BoNTA-M		BoNTA-H		Total	
GCPS at baseline	n	%	n	%	n	%	n	%	n	%	n	%
0	–	–	–	–	–	–	–	–	–	–	–	–
I	1	5.0	1	5.0	3	15.0	2	10.0	1	5.0	8	8.0
II	14	70.0	12	60.0	10	50.0	13	65.0	9	45.0	58	58.0
III	3	15.0	5	25.0	7	35.0	5	25.0	6	30.0	26	26.0
IV	2	10.0	2	10.0	0[#]	0.0	0[#]	0.0	4	20.0	8	8.0
Total	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**100**	**100.0**

Chi-square = 59.944 *P* < .0001												
	OA		SS		BoNTA-L		BoNTA-M		BoNTA-H		Total	
GCPS at 6 mo	n	%	n	%	n	%	n	%	n	%	n	%
0	14[a]	70.0	2[b]	10.0	4[b]	20.0	15[a]	75.0	10[ab]	50.0	45	45.0
I	2[a]	10.0	4[a]	20.0	15[b]	75.0	3[a]	15.0	6[a]	30.0	30	30.0
II	4[ab]	20.0	12[a]	60.0	1[b]	5.0	1[bc]	5.0	2[bd]	10.0	20	20.0
III	0[#]	0.0	1[a]	5.0	0[#]	0.0	1[a]	5.0	1[a]	5.0	3	3.0
IV	0[#]	0.0	1[a]	5.0	0[#]	0.0	0[#]	0.0	1[a]	5.0	2	2.0
Total	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**20**	**100.0**	**100**	**100.0**

GCPS = Graded Chronic Pain Scale; OA = oral appliance; SS = saline solution; BoNT-A = botulinum toxin type A; L = low (dose); M = medium (dose); H = high (dose).
Values in the same row with different superscript letters are significantly different at $P < .05$ according to two-sided test of equality for column proportions.
[#]This category was not used in the comparisons because its column proportion was equal to 0 or 1.

Considering the GCPS categories of the total population, most participants (58%) were grade II (low disability, high intensity) and grade III (26%; high disability, moderately limiting). Conversely, only 8% showed severely limiting, high disability (grade IV; Table 2). In the within-group comparisons, levels of chronic pain-related disability improved over time in all groups ($P < .0001$). In the between-group comparisons, no differences were found at the baseline assessment. The BoNT-A and OA groups had a higher proportion of subjects presenting with lower GCPS categories ($P < .0001$) when compared to the SS group after 6 months of follow-up. No differences were found between the BoNT-A groups or between the BoNT-A and OA groups at the final assessment ($P > .05$; Table 2).

Interactions between group and time factors for CPI are shown in Table 3. In the within-group comparisons, a significant decrease in CPI scores was found in all groups at the final follow-up ($P < .05$). In the between-group comparisons, no significant differences were found at baseline ($P > .217$); however, the scores of the BoNT-A and OA groups were significantly lower at the 6-month follow-up ($P < .05$) compared to the SS group (Table 4). No differences were found between the BoNT-A groups or between

Table 3 Two-way Analysis of Variance Results for the Comparison of Characteristic Pain Intensity According to Group and Time Factors

Source	Type III sum of squares	df	Mean square	F	*P*	Observed power
Within-group effects						
Time	90,312.500	1	90,312.500	306.719	.000	1.000
Time*Group	4,098.333	4	1,024.583	3.480	.011	0.845
Error (time)	27,972.500	95	294.447	–	–	–
Between-group effects						
Intercept	519,180.500	1	519,180.500	1,133.517	.000	1.000
Group	3,868.111	4	967.028	2.111	.085	0.607
Error	43,512.500	95	458.026	–	–	–

Table 4 Descriptive Statistics for Characteristic Pain Intensity in Each Group at Baseline and Final Time Point

	Group				
Time	OA	SS	BoNTA-L	BoNTA-M	BoNTA-H
Baseline	73.50^{a} (14.73)	71.33^{a} (15.91)	71.67^{a} (16.56)	69.17^{a} (14.34)	75.33^{a} (15.35)
6 mo	25.17^{1,b} (12.95)	46.83^{2,b} (28.0)	25.83^{1,b} (16.54)	23.17^{1,b} (20.96)	27.50^{1,b} (30.20)
Δ	48.33^{A} (19.24)	24.50^{B} (26.32)	45.83^{A} (15.74)	46.00^{A} (23.71)	47.83^{A} (32.74)

Data are reported as mean (SD) score on a 0 to 100 VAS for pain intensity. OA = oral appliance; SS = saline solution; BoNT-A = botulinum toxin type A; L = low (dose); M = medium (dose); H = high (dose).
Values in the same row with different superscript numbers indicate significant differences between groups at the same time point ($P < .05$). Values in the same column with different lowercase superscript letters indicate significant within-group differences between time points ($P < .05$).
Different uppercase superscript letters describe differences between groups at $P < .05$.

Table 5 RDC/TMD Axis II Depressive Symptoms Scale (SCL-DEP) Scores for Each Group at Baseline and Final Time Point

Group	Baseline	6 mo
OA	0.90^{A,a} (0.85)	0.25^{B,b} (0.44)
SS	1.20^{A,a} (1.01)	1.40^{A,a} (0.94)
BoNTA-L	1.30^{A,a} (0.98)	0.50^{B,b} (0.83)
BoNTA-M	1.05^{A,a} (1.00)	0.50^{B,b} (0.89)
BoNTA-H	1.55^{A,a} (0.83)	0.30^{B,b} (0.73)

Table 6 RDC/TMD Axis II Somatic Symptoms Scale (SCL-SOM) Scores for Each Group at Baseline and Final Time Point

Group	Baseline	6 mo
OA	1.35^{A,a} (0.75)	0.20^{B,b} (0.41)
SS	1.60^{A,a} (0.75)	1.40^{A,a} (0.75)
BoNTA-L	1.60^{A,a} (0.60)	0.65^{B,b} (0.75)
BoNTA-M	1.30^{A,a} (0.86)	0.30^{B,b} (0.57)
BoNTA-H	1.75^{A,a} (0.55)	0.45^{B,b} (0.69)

Data are reported as mean (SD). OA = oral appliance; SS = saline solution; BoNT-A = botulinum toxin type A; L = low (dose); M = medium (dose); H = high (dose).
Values with different uppercase superscript letters indicate significant within-group differences between time points ($P < .05$). Values with different lowercase superscript letters indicate significant between-group differences at each time point ($P < .05$).

the BoNT-A and OA groups at the final assessment ($P > .05$; Table 4).

Regarding SCL-DEP scores, 64% of participants presented abnormal values, showing either severe (58%) or moderate (8%) depression symptom levels, while 36% presented normal scores. In the within-group comparisons, the SCL-DEP scores in the BoNT-A and OA groups improved significantly over time ($P < .0001$). In the between-group comparisons, no significant differences were found at the baseline assessment. The BoNT-A and OA groups showed significantly improved depressive symptom scores when compared to the SS group at the final follow-up ($P < .0001$). No significant differences were found between the BoNT-A groups or between the BoNT-A and OA groups over time ($P > .05$; Table 5).

Data analysis for the SCL-SOM values included pain items. Abnormal scores were found in 87% of the total population. Severe and moderate levels were found in 65% and 22% of the subjects, respectively, while only 13% reported normal scores (Table 6). In the within-group comparisons, SCL-SOM scores were significantly improved in the BoNT-A and OA groups over time ($P < .0001$). In the between-group comparisons, no significant differences were found at the baseline assessment. The BoNT-A and OA groups showed significantly improved somatic symptom scores when compared to the SS group ($P < .0001$) at the 6-month assessment ($P < .0001$). There were no significant differences between the BoNT-A groups or between the BoNT-A and OA treatments over time ($P > .05$; Table 6).

Discussion

To the best of the present authors' knowledge, this is the first study to demonstrate the positive effects of BoNT-A on the psychosocial aspects of patients with masticatory MFP. The results showed that most patients had low pain-related disability (GCPS grade II, 58%), followed by 26% presenting high disability with moderately limiting pain, and a minority (6%) presenting high disability with severely limiting pain. Likewise, 61% and 65% of patients presented severe levels

of depressive and somatic symptoms, respectively. BoNT-A and OA improved scores for pain-related disability, CPI, and depressive and somatic symptoms after 6 months. While there were no significant differences between the BoNT-A and OA approaches at the final follow-up, both treatments were significantly better than placebo (ie, SS injection) over time for all Axis II outcomes.

Epidemiologic studies on the GCPS show a 6% to 12% frequency of high disability with moderately limiting pain, and a 3% to 6% frequency of high disability with severely limiting pain.[10,11,27–29] Such data are not exactly in line with those from the present study population, which showed a higher proportion of grade III and IV scores. Different methods of patient recruitment, as well as treatment-seeking behavior strategies, could explain the differences from other studies in different countries.[11] In particular, the present study was restricted to a refractory chronic pain population (persistent masticatory MFP) prone to experiencing higher pain intensity and perceived disability.[30–33] Notwithstanding, only a few patients presented high pain-related disability negatively affecting their daily activities. As for the SCL-90R scores, moderate and severe levels of depressive and somatic symptoms were detected in 65% and 87% of the population, respectively, while the studies of Yap et al,[34] Manfredini et al,[35] Canales et al,[29] and De la Torre Canales et al[11] presented lower rates. Although ethnic background and socioeconomic issues could explain these differences, a systematic review[5] showed that TMD patients with the highest pain-related disability presented the highest levels of depressive and somatic symptoms, as demonstrated in the present study.

The present randomized clinical trial is one of the few investigations focusing on the effects of MFP treatments on the entire spectrum of symptoms included in the Axis II evaluation. In addition, to the knowledge of the present authors, this is the first study to assess the effects of BoNT-A on the psychosocial aspects of TMD patients and to compare this treatment to active (OA) and placebo (SS) control groups. Regardless of dose, BoNT-A improved pain disability (GCPS) over time. While all groups showed an improvement after 6 months, BoNT-A and OA were superior compared to the SS group. BoNT-A has shown peripheral and central analgesic effects in in vivo, in vitro, and clinical studies,[20,25,36,37] a finding that was corroborated by the present study with the significant decrease of CPI values after 6 months, as expected. On the other hand, in a crossover study,[38] GCPS scores were not different between BoNT-A and placebo groups after 3 months of follow-up, and treatments had no effect on pain-related disability. The small sample size, the use of a different protocol to inject the BoNT-A, and the short evaluation period compared to the present study may explain the different results.

As for the SCL-90R scores, the BoNT-A groups showed lower depressive and somatic symptom levels over time, with results comparable to the OA group. In addition, BoNT-A and OA treatments were significantly better than the SS treatment when it came to decreasing severe SCL-DEP and SCL-SOM scores. The present results differ from those of the studies by Ernberg et al[38] and Kurtoglu et al,[39] in which no treatment effects were found on depressive and somatic symptom scores. BoNT-A has been shown to decrease depressive symptoms in some chronic pain conditions like trigeminal neuralgia, indicating that this treatment improves depression by relieving pain.[40] These findings and the present results support the hypothesis that pain reduction can improve psychologic symptoms. However, a study assessing depression in chronic migraine patients[41] showed that BoNT-A diminished depression scores even in patients who did not have a meaningful reduction in headache after treatment. The study suggested that BoNT-A may have a secondary effect by modulating the central nuclei of the limbic system or by improving the patient's self-esteem through a social feedback mechanism as a result of improved appearance after relaxation of muscles in the glabellar region. Interestingly, recent clinical studies have shown that a single BoNT-A treatment in the glabellar region may lead to sustained alleviation of major depressive symptoms that did not improve sufficiently with previous antidepressant medication.[42–45] Although the mechanisms underlying this clinical effect are unknown, a disruption of proprioceptive facial feedback reinforcing negative emotions is supported by these studies. A retrospective study that analyzed postmarketing safety reports of the FDA Adverse Event Reporting System concluded that the antidepressant effects of BoNT-A are significant and observed for a broad range of injection sites.[46]

The OA group showed the same effects as BoNT-A on the GCPS, CPI, and the SCL-DEP and SCL-SOM scores. Although studies assessing OA effects on psychosocial features are few, oral appliances have been shown to diminish depression, anxiety, and catastrophizing symptoms.[15] Costa et al[15] found that OA effects are more related to a behavioral factor than to purely mechanical factors. Even though the exact mechanism for the positive effects of OA in the assessed psychosocial features is not well understood, studies evaluating the brain activity of patients using an OA showed significantly increased brain activation in the supplementary motor cortex (SMA) regions, temporal association area (TAA), prefrontal area (PFA), and the insular cortex, which control motor co-

ordination, memory, cognition, and emotions, respectively.[47–50] However, it should be considered that the pain reduction due to the OA could also have an important role in improving psychologic features. Since BoNT-A injections could cause severe adverse effects in muscle and bone tissues[51,52] and no adverse effects have been reported from OA treatment,[53] the present authors recommend that reversible conservative treatments like OA should be the first treatment option for this kind of patient.

As a final remark, it is important to mention the validity of the Axis II instruments to assess psychosocial changes over time. The main strength of the RDC/TMD Axis II lies in the importance given to the assessment of pain-related disability as well as of depressive and somatic symptom levels, with good psychometric properties.[54] Even though the usefulness of Axis II has been shown in the clinical setting,[55] a recent systematic review reported that most studies have been based on specific populations recruited in health care centers, not allowing a deeper insight into the psychosocial features that negatively influence TMD patients.[5] In addition, due to the few clinical trials on the subject,[15,16] the assessment of psychosocial features on TMD treatment in clinical studies is recommended in order to establish individualized approaches in the clinical setting. Finally, the low number of subjects presenting with combined myofascial TMD pain and arthralgia in the present study is related to the RDC/TMD protocol method, as this method diagnoses myofascial TMD pain with an acceptable validity but does not present desirable levels for the sensitivity and specificity for arthralgia, underestimating its rates.[56]

As limitations, the psychosocial aspects of participants were assessed by using validated questionnaires, but no clinical evaluation was performed. The study sample was very specific (patients unresponsive to previous treatments, no sex-matched controls), preventing the generalization of findings to other populations. Future studies should confirm these results and assess the effects of BoNT-A on other psychosocial aspects, such as anxiety and catastrophizing.

Conclusions

Regardless of dose, a single injection of BoNT-A was as effective as OA in improving pain-related disability, CPI, and depressive and somatic symptoms in participants with persistent masticatory MFP.

Clinical Implications

BoNT-A treatment can improve psychosocial factors in patients with masticatory MFP, but did not differ from treatment with an OA.

Acknowledgments

This study was supported by the São Paulo Research Foundation - FAPESP (grant number 2014/15863-7). G.D.T.C. was a recipient of a postdoctoral scholarship from FAPESP (grant 2017/21674-0), and R.L.P. was a recipient of a PhD scholarship from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – grant code 001 (process, 88887.195891/2018-00). The authors report no conflicts of interest.

Author contributions: G.D.T.C.: study conceptualization, data curation, data analysis, writing of the original draft; R.L.P.: study conceptualization and writing of the original draft; Y.N.A.P.: study conceptualization and data curation; P.C.R.C.: project management, supervision, and writing, review and editing of the manuscript; D.M.: project management, supervision, writing, review and editing of the manuscript; A.S-A.: statistical analysis and writing, review, and editing of the manuscript; C.M.R-B.: project management, supervision, and writing, review, and editing of the manuscript.

References

1. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
2. Manfredini D, Guarda-Nardini L, Winocur E, Piccotti F, Ahlberg J, Lobbezoo F. Research diagnostic criteria for temporomandibular disorders: A systematic review of axis I epidemiologic findings. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:453–462.
3. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. Pain 2020;161:1976–1982.
4. Loeser JD, Fordyce WE. Chronic pain. In: Carr JE, Dengerink HA (eds). Behavioral Science in the Practice of Medicine. New York: Elsevier, 1983:331–346.
5. De La Torre Canales G, Câmara-Souza MB, Muñoz Lora VRM, et al. Prevalence of psychosocial impairment in temporomandibular disorder patients: A systematic review. J Oral Rehabil 2018;45:881–889.
6. Poluha RL, De la Torre Canales G, Bonjardim LR, Conti PCR. Somatosensory and psychosocial profile of patients with painful temporomandibular joint clicking. J Oral Rehabil 2020;47:1346–1357.
7. Poluha RL, De la Torre Canales G, Bonjardim LR, Conti PCR. Clinical variables associated with the presence of articular pain in patients with temporomandibular joint clicking. Clin Oral Investig 2021;25:3633–3640.
8. Fillingim RB, Ohrbach R, Greenspan JD, et al. Psychological factors associated with development of TMD: The OPPERA prospective cohort study. J Pain 2013;14:75–90.
9. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for clinical and research applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache 2014;28:6–27.

10. Ohrbach R. Assessment and further development of RDC/TMD Axis II biobehavioural instruments: a research programme progress report. J Oral Rehabil 2010;37:784–798.
11. De la Torre Canales G, Bonjardim LR, Poluha RL, Carvalho Soares FF, Guarda-Nardini L, Conti PR, et al. Correlation between physical and psychosocial findings in a population of temporomandibular disorder patients. Int J Prosthodont 2020;33:155–159.
12. Ohrbach R, Dworkin SF. The evolution of TMD diagnosis: Past, present, future. J Dent Res 2016;95:1093–1101.
13. Gil-Martínez A, Paris-Alemany A, López-de-Uralde-Villanueva I, La Touche R. Management of pain in patients with temporomandibular disorder (TMD): Challenges and solutions. J Pain Res 2018;16:571–587.
14. Kuzmanovic Pficer J, Dodic S, Lazic V, Trajkovic G, Milic N, Milicic B. Occlusal stabilization splint for patients with temporomandibular disorders: Meta-analysis of short and long term effects. PLoS One 2017;12:e0171296.
15. Costa YM, Porporatti AL, Stuginski-Barbosa J, Bonjardim LR, Conti PC. Additional effect of occlusal splints on the improvement of psychological aspects in temporomandibular disorder subjects: A randomized controlled trial. Arch Oral Biol 2015;60:738–744.
16. De la Torre Canales G, Manfredini D, Grillo CM, Guarda-Nardini L, Machado Gonçalves L, Rizzatti Barbosa CM. Therapeutic effectiveness of a combined counseling plus stabilization appliance treatment for myofascial pain of the jaw muscles: A pilot study. Cranio 2017;35:180–186.
17. Roldán-Barraza C, Janko S, Villanueva J, Araya I, Lauer HC. A systematic review and meta-analysis of usual treatment versus psychosocial interventions in the treatment of myofascial temporomandibular disorder pain. J Oral Facial Pain Headache 2014;28:205–222.
18. Nazeri M, Ghahrechahi HR, Pourzare A, et al. Role of anxiety and depression in association with migraine and myofascial pain temporomandibular disorder. Indian J Dent Res 2018;29:583–587.
19. Matak I, Lacković Z. Botulinum toxin A, brain and pain. Prog Neurobiol 2014;119–120:39–59.
20. De la Torre Canales G, Alvarez-Pinzon N, Muñoz-Lora VRM, et al. Efficacy and safety of botulinum toxin type A on persistent myofascial pain: A randomized clinical trial. Toxins (Basel) 2020;12:395.
21. Zhang H, Zhang H, Wei Y, Lian Y, Chen Y, Zheng Y. Treatment of chronic daily headache with comorbid anxiety and depression using botulinum toxin A: A prospective pilot study. Int J Neurosci 2017;127:285–290.
22. Ceylan D, Erer S, Zarifoğu M, Türkeş N, Özkaya G. Evaluation of anxiety and depression scales and quality of LIFE in cervical dystonia patients on botulinum toxin therapy and their relatives. Neurol Sci 2019;40:725–731.
23. Weber A, Heger S, Sinkgraven R, Heckmann M, Elsner P, Rzany B. Psychosocial aspects of patients with focal hyperhidrosis. Marked reduction of social phobia, anxiety and depression and increased quality of life after treatment with botulinum toxin A. Br J Dermatol 2005;152:342–345.
24. Dong H, Fan S, Luo Y, Peng B. Botulinum toxin relieves anxiety and depression in patients with hemifacial spasm and blepharospasm. Neuropsychiatr Dis Treat 2018;15:33–36.
25. Patel AA, Lerner MZ, Blitzer A. IncobotulinumtoxinA injection for temporomandibular joint disorder. Ann Otol Rhinol Laryngol 2017;126:328–333.
26. Pereira FJ, Favilla EE, Dworkin SF, Huggins KH. Critérios de diagnóstico para pesquisa das desordens temporomandibulares RDC/TMD. International Network for Orofacial Pain and Related Disorders Methodology, 2002. https://ubwp.buffalo.edu/rdc-tmdinternational/tmd-assessmentdiagnosis/rdc-tmd/translations/. Accessed 7 October 2021.
27. John MT, Reissmann DR, Schierz O, Wassell RW. Oral health-related quality of life in patients with temporomandibular disorders. J Orofac Pain 2007;21:46–54.
28. Manfredini D, Winocur E, Ahlberg J, Guarda-Nardini L, Lobbezoo F. Psychosocial impairment in temporomandibular disorders patients. RDC/TMD axis II findings from a multicentre study. J Dent 2010;38:765–772.
29. Canales GT, Guarda-Nardini L, Rizzatti-Barbosa CM, Conti PCR, Manfredini D. Distribution of depression, somatization and pain- related impairment in patients with chronic temporomandibular disorders. J Appl Oral Sci 2019;27:e20180210.
30. Ozdemir-Karatas M, Peker K, Balık A, Uysal O, Tuncer EB. Identifying potential predictors of pain–related disability in Turkish patients with chronic temporomandibular disorder pain. J Headache Pain 2013;14:17.
31. Lorduy KM, Liegey-Dougall A, Haggard R, Sanders CN, Gatchel RJ. The prevalence of comorbid symptoms of central sensitization syndrome among three different groups of temporomandibular disorder patients. Pain Pract 2013;13:604–613.
32. Greenspan JD, Slade GD, Bair E, et al. Identified pain sensitivity risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case control study. J Pain 2011;12(suppl 11):T61–T74.
33. Campi LB, Jordani PC, Tenan HL, Camparis CM, Gonçalves DA. Painful temporomandibular disorders and central sensitization: Implications for management–a pilot study. Int J Oral Maxillofac Surg 2017;46:104–110.
34. Yap AU, Dworkin SF, Chua EK, List T, Tan KB, Tan HH. Prevalence of temporomandibular disorder subtypes, psychologic distress, and psychosocial dysfunction in Asian patients. J Orofac Pain 2003;17:21–28.
35. Manfredini D, Arveda N, Guarda-Nardini L, Segù M, Collesano V. Distribution of diagnoses in a population of patients with temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:35–41.
36. Muñoz-Lora VRM, Clemente-Napimoga JT, Ballassini H, Gomes-Macedo C, De la Torre Canales G, Rizzatti- Barbosa CM. Botulinum toxin type A reduces inflammatory hypernociception induced by arthritis in the temporomandibular joint of rats. Toxicon 2017;129: 52–57.
37. Matak I, Bach-Rojecky L, Filipović B, Lacković Z. Behavioral and immunohistochemical evidence for central antinociceptive activity of botulinum toxin A. Neuroscience 2011;186:201–207.
38. Ernberg M, Hedenberg-Magnusson B, List T, Svensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: A randomized, controlled, double-blind multicenter study. Pain 2011;152:1988–1996.
39. Kurtoglu C, Gur OH, Kurkcu M, Sertdemir Y, Guler-Uysal F, Uysal H. Effect of botulinum toxin-A in myofascial pain patients with or without functional disc displacement. J Oral Maxillofac Surg 2008;66:1644–1651.
40. Xia JH, He CH, Zhang HF, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. Int J Neurosci 2016;126:348–353.
41. Blumenfeld AM, Tepper SJ, Robbins LD, et al. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. J Neurol Neurosurg Psychiatry 2019;90:353–360.
42. Wollmer MA, de Boer C, Kalak N, et al. Facing depression with botulinum toxin: A randomized controlled trial. J Psychiatr Res 2012;46:574–581.
43. Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: A randomized, double-blind, placebo controlled trial. J Psychiatr Res 2014;52:1–6.
44. Magid M, Reichenberg JS, Poth PE, et al. Treatment of major depressive disorder using botulinum toxin A: A 24-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2014;75:837–844.

45. Hexsel D, Brum C, Siega C, et al. Evaluation of self-esteem and depression symptoms in depressed and nondepressed subjects treated with onabotulinumtoxinA for glabellar lines. Dermatol Surg 2013;39:1088–1096.
46. Makunts T, Wollmer MA, Abagyan R. Postmarketing safety surveillance data reveals antidepressant effects of botulinum toxin across various indications and injection sites. Sci Rep 2020;10:12851.
47. Otsuka T, Watanabe K, Hirano Y, et al. Effects of mandibular deviation on brain activation during clenching: An fMRI preliminary study. J Craniomandib Pract 2009;27:88–93.
48. Greven M, Otsuka T, Zutz L, Weber B, Elger C, Sato S. The amount of TMJ displacement correlates with brain activity. J Craniomandib Pract 2011;29:291–296.
49. Lotze M, Lucas C, Domin M, Kordass B. The cerebral representation of temporomandibular joint occlusion and its alternation by occlusal splints. Hum Brain Mapp 2012;33:2984–2993.
50. Ariji Y, Koyama S, Sakuma S, Nakayama M, Ariji E. Regional brain activity during jaw clenching with natural teeth and with occlusal splints: A preliminary functional MRI study. Cranio 2016;34:188–194.
51. Balanta-Melo J, Toro-Ibacache V, Kupczik K, Buvinic S. Mandibular bone loss after masticatory muscles intervention with botulinum toxin: An approach from basic research to clinical findings. Toxins 2019;11:84.
52. De la Torre Canales G, Poluha RL, Lora VM, et al. Botulinumtoxin type A applications for masticatory myofascial pain and trigeminal neuralgia: What is the evidence regarding adverse effects? Clin Oral Investig 2019;23:3411–3421.
53. Tuna SH, Celik OE, Ozturk O, et al. The effects of stabilization splint treatment on the volume of masseter muscle in sleep bruxism patients. Cranio 2018;36:286–293.
54. Dworkin SF, Sherman J, Mancl L, Ohrbach R, LeResche L,Truelove E. Reliability, validity, and clinical utility of the Research Diagnostic Criteria for Temporomandibular Disorders axis II scales: Depression, non-specific physical symptoms, and graded chronic pain. J Orofac Pain 2002;16:207–220.
55. Manfredini D, Ahlberg J, Winocur E, Guarda-Nardini L, Lobbezoo F. Correlation of RDC/TMD axis I diagnoses and axis II pain-related disability. A multicenter study. Clin Oral Investig 2011;15:749–756.
56. Truelove E, Pan W, Look JO, et al. The Research Diagnostic Criteria for Temporomandibular Disorders. III: Validity of Axis I diagnoses. J Orofac Pain 2010;24:35–47.