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Botulinum Toxin in Facial Aesthetics Affects the Emotion Process: A Meta-analysis of Randomized Controlled Trials

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This study aimed to conduct a meta-analysis of randomized controlled trials (RCTs) to evaluate the effects of the btulinum toxin-A (BT-A) in patiets with mood disorders. PubMed, Scopus, Web of Science, Cochrane Library and LILACS were searched without restrictions up to July 2022. The PICOS strategy was used for the selection of studies and risk-of-bias assessment was performed using Cochrane's tool for RCTs. RCTs were included if they compared BT-A treatment on facial muscles in patients with mood disorders to placebo. After assessment of the full texts, seven studies were selected. Five studies had low risk of bias for the generation of random sequence and blinding of participants and professional domains. A total of four studies showed a low risk of bias for the allocation concealment and blinding of the evaluation of the domain results. The domain of selective reports showed a low risk of bias in all included studies. However, four studies presented a high risk of bias for the domain of other biases. The meta-analysis was based on the mean difference or standardized mean difference between the BT-A and placebo groups for each selected trial and revealed that the BT-A group showed a significant improvement in the symptoms of depression when compared to placebo. This study revealed that the BT-A application into mimic muscles of the upper third of the face improves the mood disorders, but it was not possible to guarantee whether the aesthetic benefits can contribute to reducing the severity of the depressive state.

KEY WORDS: Botulinum toxin; Facial expression; Emotions; Major depressive disorder; Mood disorders; Randomized controlled trial.

INTRODUCTION

Botulinum toxins (BT) are potent neurotoxins produced by anaerobic bacteria of the genus Clostridium and that have eight different serotypes: A, B, C, D, E, F, G, and H [1]. It is responsible for botulism, a serious condition characterized by paralysis of the facial, limb and even respiratory muscles, giving this disease a high severity [2]. Despite its toxicity, BT has been used since the 1970s as a therapeutic alternative in clinical situations such as strabismus and blepharospasm [3].

Since its approval by the Food and Drugs Administration, botulinum toxin type A (BT-A) has been widely used in aesthetic treatments, such as smoothing wrinkles and hyperkinetic facial lines [4]. It acts by inhibiting the release of acetylcholine in the synaptic cleft and consequently preventing the depolarization of the postsynaptic terminal, thus causing the blocking of muscle contracture in a competitive and dose-dependent manner [5].

In addition to the aesthetic benefit, studies have shown that the application of BT-A in the corrugator muscle of the eyebrow and procerus in the glabella region is able to favor positive changes in mood [6]. It is known that its action on the upper third of the face is associated to emotions as anger, worry and anxiety. Furthermore, other authors describe that such a cosmetic approach has been associated with improvements in patients' emotional well-being and that this is associated with the inhibition of limbic system activation generated by involuntary muscle contraction [7-11].

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Although there are currently numerous therapeutic modalities for the treatment of depressive disorders [12], a large proportion of patients do not achieve satisfactory results [13]. In addition, the discomfort of side effects resulting from most pharmacological therapies makes this approach even more challenging, showing the importance of investigating different adjuncts to the mood disorders treatment [14]. Thus, the aim of this meta-analysis was to investigate how the use of BT-A in facial esthetics interferes with mood disorders.

METHODS

Protocol and Registration

This study was registered in the PROSPERO database (CRD42020211737). The reporting of this study is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Strategy

The main search was performed in the following electronic databases until March 2021: PubMed, Scopus, Web of Science, Cochrane Library and LILACS. In July 2022, the main search was updated. Unpublished literature was searched on ClinicalTrials.gov, Google Scholar and Open Grey. A combination of the Boolean operators AND/OR and the following MeSH/non-MeSH terms was used to identify relevant studies: "Botulinum Toxins", "Botulinum Toxins, Type A", "Emotions", "Positive Mood", "Low Mood", "Depression", "Anxiety", "Facial Feedback". The reference lists of all eligible studies were consulted manually to identify any relevant additional articles (Supplementary Table 1; available online).

Study Selection

Two independent authors (ACFC; DVG) selected the study that comprised the steps of reading the title, the abstract and the full text. After excluding duplicate and ineligible studies, the full reports considered by either one of the authors eligible for inclusion, were independently assessed. Discrepancies were resolved by a discussion between the two authors (ACFC; DVG). The Cohen κ test was used to assess the level of agreement between the reviewers (ACFC; DVG).

Eligibility Criteria

The eligibility criteria were adopted according to the PICOS (Patients, Intervention, Control, Outcomes, Study Design) strategy:

- Patients (P): adult patients.
- Intervention (I): BT-A treatment for facial aesthetic.
- Control (C): placebo or saline solution.
- Outcome (O): changes in the mood disorders.
- Study design (S): for a higher level of scientific evidence, all study designs were randomized controlled trials.

There was no restriction on language or date of publication. Aiming a high level of scientific evidence, literature reviews, opinion articles, case reports, case series, cross-sectional studies, observational studies and non-randomized clinical trials were excluded.

Data Extraction

The two authors (ACFC; ECS) extracted the relevant data from the included studies independently. Any differences were discussed with a third author (DVG). The information from the included studies was synthesized tabulating the general information of the studies, including author, year of publication, research location, study design, number of participants along with their age and sex, groups and patient's condition, application area, number of units, monitoring methods and evaluation times. Finally, the main outcomes and conclusions of the studies were synthesized.

Risk of Bias in Individual Studies

The two authors (ACFC; ECS) independently performed the risk of bias in individual studies by the Cochrane Collaboration Risk of Bias tool. A third author (DVG) resolved doubts and disagreements. The criteria analyzed were: (a) generation of random sequence - selection bias, (b) allocation concealment - selection bias, (c) blinding of participants and professionals - performance bias, (d) blinding of the evaluation of results - detection bias, (e) incomplete result data - attrition bias, (f) selective reports - reporting bias and (g) and other biases. After a rigorous analysis of these criteria, the studies were classified as low, high or uncertain risk of bias.

Meta-analysis

The meta-analysis was performed to evaluate the intensity of depressive symptoms between two groups (BT-

A and placebo) at the visits after six weeks versus baseline. For this, the mean difference or standardized mean difference (SMD) between the groups for each selected trial was extracted. In some studies, it was necessary to extract the mean difference or SMD directly from graphs using the Web Plot Digitizer software (version 4.5) [6,11,15]. The measure of effect was synthesized by the inverse variance method, using different scales and through the synthesis of reduction of the scores of the same scale. It is noteworthy that the mean difference was used in the meta-analysis in studies that applied only one type of scale to assess the depression parameters [6,11,15], and for those that applied different scales, the SMD was used [6,15-17]. Two studies were excluded from the meta-analysis, as they presented incomplete outcome data [8] or a different rating scale when compared to the selected articles [18].

Analyzes were performed using R software (version 4.1.1 and meta package). As the study samples were heterogeneous and from different populations, we adopted the random effects model. To assess the statistical heterogeneity of the studies, we used I^2, Q test, and tau^2. It is noteworthy that the significance level adopted in the analyzes was 5% ($p < 0.05$).

RESULTS

Study Selection

A total of 774 references was identified in the initial search. After removing duplicates, 551 studies remained. Based on the eligibility criteria, 541 studies were excluded after assessment of titles and abstracts. The full texts of 10 articles were retrieved. At the end of the study selection, 7 studies were included for the qualitative synthesis (Fig. 1).

General Characteristics of the Included Studies

All studies eligible to compose this meta-analysis were published in the last ten years. Three researches were performed in the United States of America, one was performed in Iran, one was performed in England and two simultaneously were performed in Switzerland and Germany.

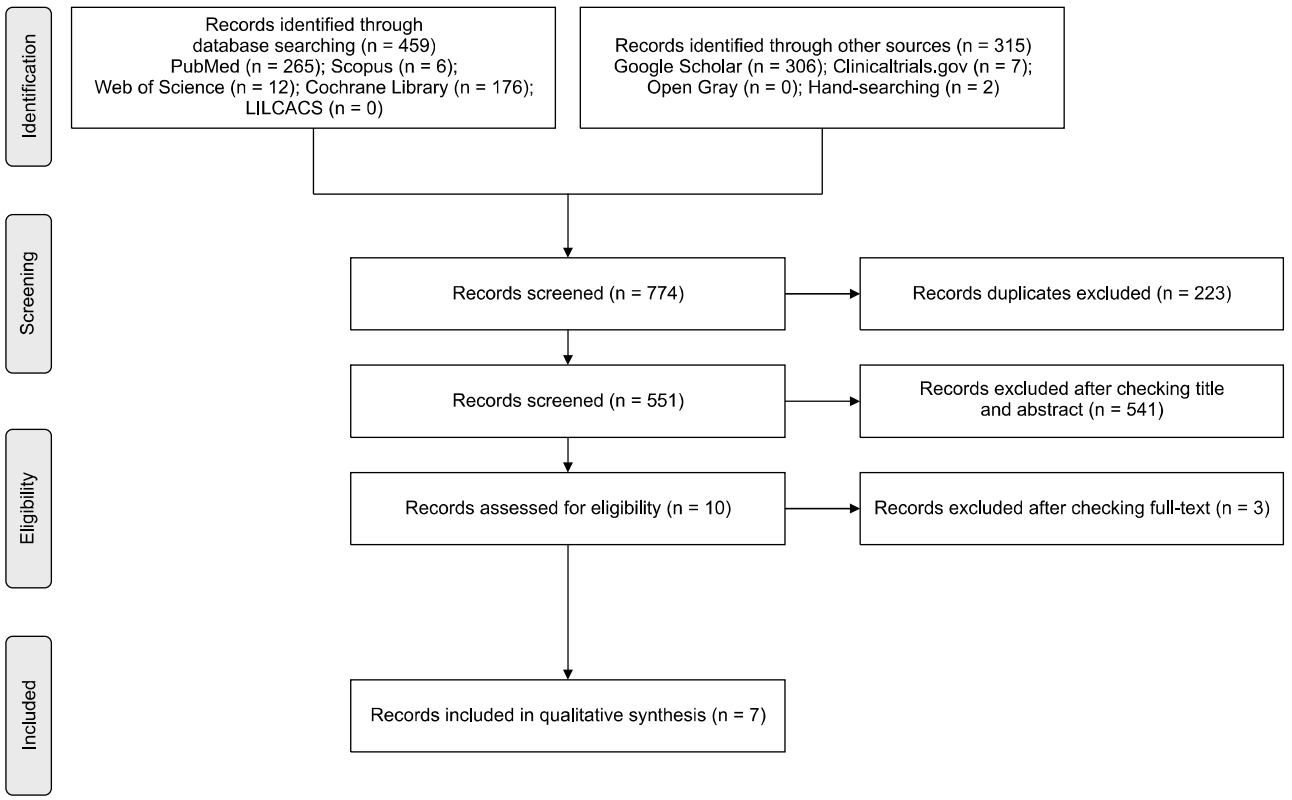

Fig. 1. PRISMA flowchart.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The samples of the studies ranged from 30 to 255 patients. Most samples were composed of female subjects aged between 18 and 65 years in control and BT-A groups. In all studies, patients had some mood disorder, with major depressive disorder being the most common condition.

The effects of botulinum toxin application in the treatment of major depressive disorder (MDD) were assessed by five of the seven studies [6,11,15-17], while the others investigated the effects of BT-A in the treatment of wrinkles and expression lines [18] and in the treatment of moderate unipolar depression, as well as in the treatment of expression lines [8]. The glabella was the application region adopted by four studies [6,8,11,15]. The corrugator muscles of the brow and frontal [16] and orbicularis orbital [18] muscles were also investigated. One study did not report the application site [17]. The volume of application of BT-A ranged between 29 units (U) and 50 U in six studies [6,8,11,15,16,18] and only one did not report the application volume [17].

The measures used to assess mood symptoms in the selected studies were Montgomery-Asberg Depression Rating Scale, Clinical Global Impressions (CGI) -Severity, Hamilton Depression Rating Scale, Hospital Anxiety and Depression Scale, Facial Emotion Recognition test, Reading the Mind in the Eyes test, Female Sexual Function Index, Patient Health Care Questionnaire-9, Beck Depression Inventory, self-rating questionnaire, and CGI Scale [6,8,11,15-18]. As for the evaluation time, the studies used periods that ranged from six to 24 weeks [6,8,11,15-18] (Table 1).

Risk of Bias in Individual Studies

The Cochrane Collaboration risk of bias tool revealed that five studies had low risk of bias for the generation of

Table 1. General characteristics of the included studies

Study	Location	Study design	Sample (size, sex, age)	Groups	Patient's condition	Application area	Units	Monitoring methods	Evaluation times
Brin *et al.*, 2020 [15]	United States of America	RCT	255; female; 18−65 years	Placebo (30 U); BT-A (30 U); Placebo (50 U); BT-A (50 U)	MDD	Glabellar region	30 U or 50 U	MADRS, CGI, and HDRS-17	Weeks 3, 6, 9, 12, 15, 18, 21, and 24
Finzi and Rosenthal, 2014 [16]	United States of America	RCT	74; female and male; 18−65 years	Placebo; BT-A	MDD	Corrugator and procerus frown muscles	29 U for females and 40 U for males	MADRS	Weeks 6 and 9
Lewis, 2018 [18]	England	RCT	36; female; 28−65 years	Non-BT-A; BT-A frown lines; BT-A crow's feet and frown lines	Depression and anxiety	Orbicularis oculi muscles	Not reported	HADS, Facial Emotion Recognition test, Reading the Mind in the Eyes test, and Female Sexual Function Index	Baseline and between the fourth and eighth week
Magid *et al.*, 2014 [11]	United States of America	RCT	30; female and male; 18−65 years	Placebo; BT-A	MDD	Glabellar region	29 U for females and 39 U for male	Patient Health Care Questionnaire-9, BDI and HDRS-21	Baseline, 3, 6, 12, 15, 18, and 24 weeks
Zamanian *et al.*, 2017 [17]	Iran	RCT	28; sex or age not reported	Control; BT-A	MDD	Not reported	Not reported	BDI	Baseline, 2 and 6 weeks
Wollmer *et al.*, 2012 [6]	Switzerland and Germany	RCT	30; female; 25−65 years	Control; BT-A	MDD	Glabellar region	29 U	HDRS-17, BDI, and CGI	Baseline, 2, 4, 6, 8, 12, and 16 weeks
Wollmer *et al.*, 2014 [8]	Switzerland and Germany	RCT	30; female and male; 50−57 years	Control; BT-A	Resistant unipolar depression	Glabellar region	29 U	HDRS-17, BDI, and CGI	Baseline, 2, 4, 6, 8, 12, and 16 weeks

RCT, randomized clinical trial; BT-A, botulinum toxin type A; U, units; MDD, major depressive disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, 17-item Hamilton Depression Rating Scale; HADS, Hospital Anxiety and Depression Scale; BDI, Beck Depression Inventory; HDRS-21, 21-item Hamilton Depression Rating Scale; CGI, Clinical Global Impressions Scale.

random sequence and blinding of participants and professional domains. A total of four studies showed a low risk of bias for the allocation concealment and blinding of the evaluation of the domain results. The domain of selective reports showed a low risk of bias in all included studies. However, four studies presented a high risk of bias for the domain of other biases, as they were funded research (Supplementary Table 2; available online).

Outcomes and Meta-analysis Data

The RCTs showed a reduction in the depression parameters after BT-A treatment [6,8,11,15-18]. However, Lewis [18] found that the application of BT-A in the laugh lines are associated with a reduction in the ability to recognize emotions and even sexual function (Table 2).

The results of the studies were quantitatively synthesized, and a meta-analysis was performed through 5 studies [6,11,15-17]. We can see in Figure 2 that the measure of effect shows a significant difference in the scores in different scales for MDD (SMD = −0.63 [95% confidence interval, 95% CI −1.04 to −0.22], $p = 0.0026$), evidencing a reduction of the same in the group treated with botulinum toxin (Fig. 2A). It is important to highlight that the data were homogeneous, since low heterogeneity was detected ($I^2 = 38\%$, $p = 0.18$). It was also possible to synthesize the data referring to the amount of reduction in the Hamilton Rating Scale for Depression-17 (HAM-D17) (Fig. 2B), whose meta-analysis showed greater values of

Table 2. Main outcomes and conclusions of the included studies

Study	Outcomes	Conclusions
Brin *et al.*, 2020 [15]	BT-A 30 U application reduced MADRS total scoreat week 6 from baseline ($p = 0.053$) and reached significance least-squares mean differences: −3.6 to −4.2; $p < 0.05$ (two-sided) at 3 and 9 weeks. A single application of BT-A 30 U showed a efficacy signal across multiple depression symptom scales for 12 or more weeks. BT-A 30 U/placebo MADRS differences of ≥ 4.0 points (up to week 15) and ≥ 2.0 points (weeks 18–24).	BT-A is not associated with systemic effects of conventional antidepressants and may be a treatment option for depression.
Finzi and Rosenthal, 2014 [16]	Response rates at week 6 after BT-A were 52%in the group that received BT-A and 15% in the placebo group (chi-square = 11.2, $p < 0.001$, Fisher $p < 0.001$). BT-A group showed lower MADRS score of 10 or less (chi-square = 5.1, $p < 0.02$, Fisher $p < 0.03$). Six weeks after a BT-A single treatment, MADRS scores in BT-A group were reduced on average by 47%, and 21% to the placebo group.	A BT-A single application in the upper third muscles induces a significant and sustained antidepressant effect in patients with major depression.
Lewis, 2018 [18]	There was animprovement in mood (lower HADS scores) when BT-A was applied only to frown lines ($p < 0.01$). There was not significant difference in HADS scores when BT-A was applied in frown lines and crow's feet from baseline ($p > 0.05$). There was a reduction in the emotion recognition ability and the overall orgasm satisfaction score after BT-A treatment.	The application of BT-A in the frown lines improved the MDD scores. In addition, BT-A treatment was associated with reduced emotion recognition and sexual function.
Magid *et al.*, 2014 [11]	There was a significant reduction in MDD symptoms in the groups that received BT-A. HDRS-21 response rates were 55% in the group that received BTA- at week 0.24% in the group that received BTA at week 12, and 0% in the placebo group ($p < 0.0001$). HDRS-21 remission rates were 18%, 18%, and 0%, respectively ($p = 0.057$). HDRS-21 scores dropped −46% and −35% in the BTA-week 0 and BTA-week 12 versus −2% in the placebo group ($p < 0.0001$). The BDI response rate was 45% (5/11) in the BTA-week 0, 33% in the BTA-week 12 group, and 5% in the placebo group ($p = 0.0067$). BDI remission rates were 27%, 33%, and 5%, respectively ($p = 0.09$). BDI scores dropped −42% and −35% in the BTA-week 0 and -week 12, respectively, versus −15% in the placebo group ($p < 0.0001$).	BT-A injection in the glabellar region was associated with significant improvement in depressive symptoms in the MDD.
Zamanian *et al.*, 2017 [17]	BDI was stastistically different after 6 weeks of the BT-A application ($p = 0.004$), but at baseline and after two weeks, there was no significant difference ($p > 0.05$).	BT-A was effective and safe for treating patients with major depression.
Wollmer *et al.*, 2012 [6]	There was a reduction in the HAM-D17 scores at the visit after 6 weeks versus baseline in the BT-A group (47,1%) when compared to the placebo group (9,2%) ($p = 0.002$) Treatment-dependent clinical improvement was also reflected in the BDI, and in the CGIS.	The application of BT-A can be an effective and safe intervention in the treatment of depression.
Wollmer *et al.*, 2014 [8]	Participants with higher agitation scores at baseline showed a greater improvement in the HAM-D17 score (Δ HAM-D17) compared to those with lower agitation scores ($p = 0.01$), while no other single item of the HAM-D or the BDI was associated with treatment response.	Patients with agitated depression may particularly benefit from BT-A treatment.

BT-A, botulinum toxin-A; U, units; MADRS, Montgomery-Åsberg Depression Rating Scale; HADS, Hospital Anxiety and Depression Scale; MDD, major depressive disorder; HDRS-21, 21-item Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; CGI, Clinical Global Impressions Scale; HAM-D, Hamilton Depression Rating Scale.

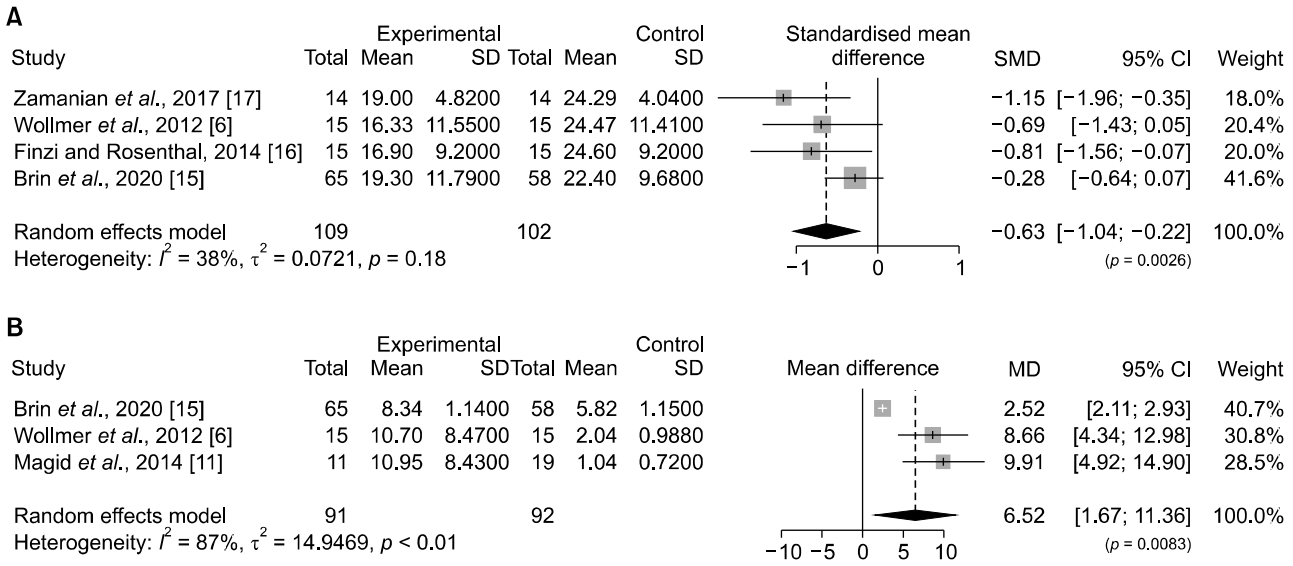

Fig. 2. (A) Meta-analysis for different scales of MDD after six weeks of botulinum toxin application. (B) Meta-analysis for MDD scale considering score reduction data.
MDD, major depressive disorder; SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; MD, mean difference.

reduction in the MDD scores of the group that received the treatment compared to the untreated group (mean deviation [MD] = 6.52 [95% CI 1.67 to 11.36], p = 0.0083). It is noteworthy that in this case, the data were heterogeneous (I^2 = 87%, $p < 0.01$).

DISCUSSION

This study identified seven RCTs and evaluated the effect of the BT-A in patients with mood disturbs [6,8,11, 15-18]. BT-A application was not associated with systemic effects of conventional antidepressants [15] and was effective and safe for treating patients with major depression. Its application in the glabellar region induced a significant antidepressant effect [6,11,15].

The analysis of the selected studies for the meta-analysis [6,11,15-17] showed that the use of BT-A in facial muscles can contribute to the reduction of depressive symptoms, being an interesting therapeutic strategy for patients with mood disorders. Wollmer *et al.* [6] showed that a single treatment with BT-A in the glabellar region can improve the depression in patients and suggested that the facial muscles not only express our emotions, but also modulate the states mood.

Clinical studies using the glabellar application of BT-A in patients diagnosed with major depressive disorder have shown a reduction in symptoms of this condition when compared to patients who received placebo treatment [8,11]. Recent investigations show that BT-A applied on the glabella region reduces muscle inputs necessary to the development and maintenance of the emotional state [16,17,19,20]. These findings show the cosmetic BT-A application as a potential therapeutic alternative for treating emotional disorders.

Chugh *et al.* [21] showed that the improvement in the state of depression after BT-A application was 53% after 3weeks of application of the toxin and that 100% of the patients reported continued improvement in the symptoms of depression in the follow-up period. The authors highlighted that there is a direct relationship between the intensity of glabellar frown lines and the state of depression, the greater severity of the wrinkles, the greater the emotional damage [21]. In this way, reducing the glabellar muscle activity by toxin application creates a smoothing of the expression markers in this region and consequently, an improvement in the depression state.

It is known that the management of mood disorders is carried out through pharmacological approaches and their side effects cause tolerance and dependence, and the limited effectiveness leads treatment dropout. Thus, it is important to investigate and adopt effective adjuvant therapies, mainly for difficult-to treat mood disorder pa-

tients [22]. Studies reinforce that BT-A may be a sustainable intervention in the depression treatment and that it may offer a high safety and tolerability advantages when compared to antidepressant treatments [11,15,16].

In this way, despite the aesthetic effect obtained by BT-A injections in muscles of facial expression, especially those located in the upper third of the face, the finding of improvement in mood disorders opens the possibility of its application. BT-A in the glabellar frown lines showed an antidepressant effect [6] and this fact has been associated to the facial feedback theory, in other words, mimic expressions can modulate an emotional behavior [23]. Soussignan [24] suggested that BT-A could disrupt emotional cognitive process due the feedback facial failure.

In addition, Hennenlotter *et al.* [25] showed, through magnetic resonance, that there was a reduction of the activity of the left amygdala, and of the stem brain regions associated to the autonomic response of emotional states in patients treated with BT-A during the manifestation of anger facial expression.

There is a bidirectional way of the information from the face that traffics through the brain stem to the amygdala and from this region to the face. Periaqueductal gray, reticular formation, and parabrachial nucleus receive axonal projections from the amygdala region. It is important to highlight that these nuclei also project inputs to the amygdala, conducting peripheral sensorial information of the face from the principal sensory nucleus of the trigeminal tract. In this way, the denervation of the mimic muscles by BT-A causes a lower activation of the amygdala, altering the emotional state [25].

Nestor *et al.* [26] brought an important reflection about the psychosocial impairment of the frequent use of masks during the social interactions in the Covid-19 pandemic. The author argues that the mask hinders the emotional interpretation based on the facial expression, enabling the exposure of the upper third of the face. It reinforces the perception of negative emotions, as anger, fear, anxiety, suffering and sadness. The author suggests that BT-A application in procerus and corrugator muscles can reduce negative emotions in patients treated with toxin, as well as, in other people who are in contact with these patients, promoting well-being.

Negative emotions can be present in other mood disorders associated to panic, fear or anxiety [27], due to the modulation of facial feedback in muscles, improving the negative emotional experience and reducing negative feelings or thoughts. Dong *et al.* [28] evaluated the BT-A effect in anxiety and depression in patients with hemifacial spasm and blepharospasm. The authors showed that these patients show motor-symptoms associated to emotional problems and that the BT-A application can help them, reducing the motor symptoms, as well as reducing anxiety and depression, which can aggravate the motor symptoms. This study also evidences the importance to investigate BT-A mechanisms in the central nervous system.

The evaluation of well-being promoted by BT-A application goes beyond the aesthetic benefits. The potential therapeutic in the emotional states shown in several clinical studies toward the new use of BT-A, mainly in patients who do not respond to antidepressant medications [29,30]. It is important to consider that different symptoms and depression grades can contribute to heterogeneity of the improvement of depression statements, and it is not clear if the severity of the mood state requires higher BT-A dosages (units/muscle). However, the BT-A off-label effect may be observed in long term after a single dose application and this may justify its use in patients with mood disturbances [6].

In summary, the studies selected showed reduction of the depression parameters, but it was not possible to relate whether the aesthetic benefits can contribute to reducing the severity of the depressive state. Thus, it is important to carry out well-designed clinical studies and to investigate the BT-A mechanisms involved in the antidepressant effects.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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