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# *Botulinum*

# *toxin*: Emerging psychiatric indications

Botulinum toxin has shown promising antidepressant effects, and might be helpful for several other indications

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Botulinum toxin, a potent neurotoxic protein produced by the bacterium *Clostridium botulinum*, has been used as treatment for a variety of medical indications for more than 25 years (Box,<sup>1-12</sup> page 10). Recently, researchers have been exploring the role of botulinum toxin in psychiatry, primarily as an adjunctive treatment for depression, but also for several other possible indications. Several studies, including randomized controlled trials (RCTs), have provided evidence that glabellar botulinum toxin injections may be a safe and effective treatment for depression. In this article, we provide an update on the latest clinical trials that evaluated botulinum toxin for depression, and also summarize the evidence regarding other potential clinical psychiatric applications of botulinum toxin.

## Several RCTs suggest efficacy for depression

The use of botulinum toxin to treat depression is based on the facial feedback hypothesis, which was first proposed by Charles Darwin in 1872<sup>13</sup> and further elaborated by William James,<sup>14,15</sup> who emphasized the importance of the sensation of bodily changes in emotion. Contrary to the popular belief that emotions trigger physiological changes in the body, James postulated that peripheral bodily changes secondary to stimuli perception would exert a sensory feedback, generating emotions. The manipulation of human facial expression with an expression that is associated with a particular emotion (eg, holding a pen with teeth, leading to





**Botulinum toxin**

### Clinical Point

The use of botulinum toxin to treat depression is based on the facial feedback hypothesis: changes in facial expression can influence affect



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### Box

## Therapeutic uses of botulinum toxin

**B**otulinum toxin is a potent neurotoxin from *Clostridium botulinum*. Its potential for therapeutic use was first noticed in 1817 by physician Justinus Kerner, who coined the term botulism.<sup>1</sup> In 1897, bacteriologist Emile van Ermengem isolated the causative bacterium *C. botulinum*.<sup>2</sup> It was later discovered that the toxin induces muscle paralysis by inhibiting acetylcholine release from presynaptic motor neurons at the neuromuscular junction<sup>3</sup> and was then mainly investigated as a treatment for medical conditions involving excessive or abnormal muscular contraction.

In 1989, the FDA approved botulinum toxin A (BTA) for the treatment of strabismus, blepharospasm, and other facial nerve disorders. In 2000, both BTA and botulinum toxin B (BTB) were FDA-approved for the treatment of cervical dystonia, and BTA was approved for the cosmetic treatment of frown lines (glabellar, canthal, and forehead lines).<sup>4</sup> Other approved clinical indications for BTA

include urinary incontinence due to detrusor overactivity associated with a neurologic condition such as spinal cord injury or multiple sclerosis; prophylaxis of headaches in chronic migraine patients; treatment of both upper and lower limb spasticity; severe axillary hyperhidrosis inadequately managed by topical agents; and the reduction of the severity of abnormal head position and neck pain.<sup>5</sup> Its anticholinergic effects have been also investigated for treatment of hyperhidrosis as well as sialorrhea caused by neurodegenerative disorders such as amyotrophic lateral sclerosis.<sup>6-8</sup> Multiple studies have shown that botulinum toxin can alleviate spasms of the gastrointestinal tract, aiding patients with dysphagia and achalasia.<sup>9-11</sup> There is also growing evidence supporting the use of botulinum toxin in the treatment of chronic pain, including non-migraine types of headaches such as tension headaches; myofascial syndrome; and neuropathic pain.<sup>12</sup>

risorius/zygomaticus muscles contraction and a smile simulation) was found to influence participants' affective responses in the presence of emotional stimuli (eg, rating cartoons as funnier), reinforcing the facial-feedback hypothesis.<sup>16,17</sup>

From a neurobiologic standpoint, facial botulinum toxin A (BTA) injections in rats were associated with increased serotonin and norepinephrine concentrations in the hypothalamus and striatum, respectively.<sup>18</sup> Moreover, amygdala activity in response to angry vs happy faces, measured via functional magnetic resonance imaging (fMRI), was found to be attenuated after BTA applications to muscles involved in angry facial expressions.<sup>19,20</sup> Both the neurotransmitters as well as the aforementioned brain regions have been implicated in the pathophysiology of depression.<sup>21,22</sup>

More than a century after Charles Darwin's initial proposal, Wollmer et al<sup>23</sup> conducted the first RCT exploring the effect of BTA as an adjunctive treatment to antidepressants in 30 patients with depression. BTA or normal saline injections were given at 5 points in the glabellar region (*Figure*,<sup>24</sup> *page 11*). Positive effects on mood were measured at 7 points over 16 weeks using the 17-item version of the Hamilton Depression

Rating Scale (HAM-D17; administered using the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement [SIGH-ADS]); the Beck Depression Inventory (BDI) self-rating questionnaire; and the Clinical Global Impression Scale (CGI). Changes in glabellar frown lines were tracked at each study visit using the 4-point Clinical Severity Score for Glabellar Frown Lines (CSS-GFL) and standardized photographs of the face with maximum frowning.

Compared with those in the placebo group, participants in the BTA group had a higher response rate as measured by the HAM-D17 at 6 weeks after treatment ( $P = .02$ ), especially female patients ( $P = .002$ ). Response to BTA, defined as  $\geq 50\%$  reduction on the HAM-D17, occurred within 2 weeks, and lasted another 6 weeks before slightly wearing off. Assessment of the CSS-GFL showed a statistically significant change at 6 weeks ( $P < .001$ ). This small study failed, however, to show significant remission rates (HAM-D17  $\leq 7$ ) in the BTA group compared with placebo.

In a second RCT involving 74 patients with depression, Finzi and Rosenthal<sup>25</sup> observed statistically significant response and remission rates in participants who

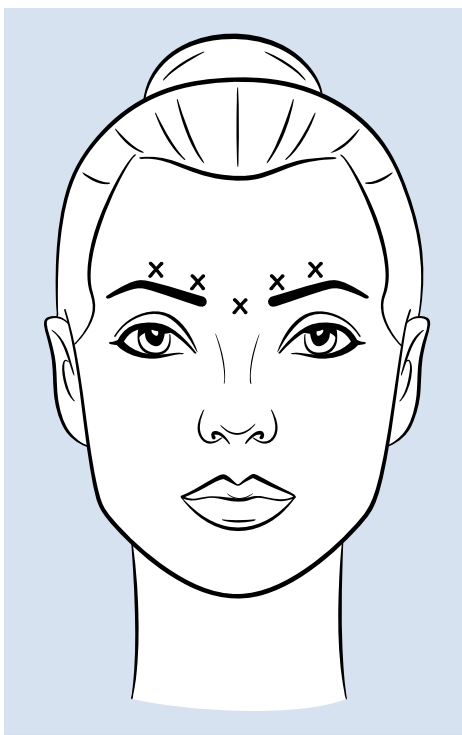
received BTA injections, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). Participants were given either BTA or saline injections and assessed at 3 visits across 6 weeks using the MADRS, CGI, and Beck Depression Inventory-II (BDI-II). Photographs of participants' facial expressions were assessed using frown scores to see whether changes in facial expression were associated with improvement of depression.

This study was able to reproduce on a larger scale the results observed by Wollmer et al.<sup>23</sup> It found a statistically significant increase in the rate of remission (MADRS  $\leq 10$ ) at 6 weeks following BTA injections (27%,  $P < .02$ ), and that even patients who were not resistant to antidepressants could benefit from BTA. However, although there was an observable trend in improvement of frown scores associated with improved depression scores, the correlation between these 2 variables was not statistically significant.

In a crossover RCT, Magid et al<sup>26</sup> observed the response to BTA vs placebo saline injections in 30 patients with moderate to severe frown lines. The study lasted 24 weeks; participants switched treatments at Week 12. Mood improvement was assessed using the 21-item Hamilton Depression Rating Scale (HDRS-21), BDI, and Patient Health Questionnaire-9 (PHQ-9). Compared with patients who received placebo injections, those treated with BTA injections showed statistically significant response rates, but not remission rates. This study demonstrated continued improvement throughout the 24 weeks in participants who initially received BTA injections, despite having received placebo for the last 12 weeks, by which time the cosmetic effects of the initial injection had worn off. This suggests that the antidepressant effects of botulinum toxin may not depend entirely on its paralytic effects, but also on its impact on the neurotransmitters involved in the pathophysiology of depression.<sup>18</sup> By demonstrating improvement in the placebo group once they were started on botulinum toxin, this study also was able to exclude the possibility that other variables may be responsible for the

Figure

### Botulinum toxin injection sites in the glabellar region



Source: Adapted from reference 24

difference in the clinical course between the 2 groups. However, this study was limited by a small sample size, and it only included participants who had moderate to severe frown lines at baseline.

Zamanian et al<sup>27</sup> examined the therapeutic effects of BTA injections in 28 Iranian patients with major depressive disorder (MDD) diagnosed according to DSM-5 criteria. At 6 weeks, there were significant improvements in BDI scores in patients who received BTA vs those receiving placebo. However, these changes were demonstrated at 6 weeks (not as early as 2 weeks), and patients didn't achieve remission.

A large-scale, multicenter U.S. phase II RCT investigated the safety, tolerability, and efficacy of a single administration of 2 different doses of BTA (30 units or 50 units) as monotherapy for the treatment of moderate to severe depression in 258 women.<sup>28</sup> Effects on depression were measured at 3, 6, and 9 weeks using the MADRS. Participants who received the 30-unit injection showed

### Clinical Point

The antidepressant effects of botulinum toxin may not depend entirely on its paralytic effects



## Botulinum toxin

### Clinical Point

A large RCT found no dose-effect relationship when using botulinum toxin A to treat depression

**Table 1**

## RCTs of botulinum toxin A for depression

Study	Patients	Study method
Wollmer et al <sup>23</sup> (2012)	30 patients (23 women), mean age 50. DSM-IV diagnosis of current MDD, HDRS $\geq 15$ at screening. Stable treatment with 1 or 2 antidepressants for $\geq 4$ weeks prior to study. Moderate to severe vertical glabellar line in maximum voluntary frowning per CSS-GFL	16 weeks. 15 patients received BTA (39 units for men, 29 units for women). Response defined as $\geq 50\%$ reduction in HAM-D-17 score from baseline to Week 6
Finzi and Rosenthal <sup>25</sup> (2014)	74 patients (69 women), mean age 48. DSM-IV diagnosis of current MDD, MADRS $\geq 26$ and CGI-S $\geq 4$ at screening. Details of antidepressant use unknown	6 weeks. 33 patients received BTA (40 units for men, 29 units for women). Response defined as $\geq 50\%$ reduction in MADRS score from baseline to Week 6
Magid et al <sup>26</sup> (2014)	30 patients (28 women), mean age 49.5 years. DSM-IV diagnosis of MDD. HDRS-21 $\geq 14$ at screening. History of depression for $\geq 6$ months. Score $\geq 6$ on a frowning severity 0 to 10 scale for photographs of negative/melancholic facial expressions. Approximately 86% were taking $\geq 1$ antidepressant	24 weeks; crossover at 12 weeks. 11 BTA-first group (39 units for men, 29 units for women) vs 19 placebo group. 17 given BTA in second group. Response defined as $\geq 50\%$ reduction in HDRS-21 score from baseline to Week 6
Zamanian et al <sup>27</sup> (2017)	28 patients (14 women). Mean age 35 years in BTA group vs 43 years in placebo group. DSM-5 diagnosis of MDD, in addition to BDI (threshold not specified). All patients were receiving antidepressants	6 weeks. 14 patients received BTA. Primary outcome was reduction in BDI score from baseline to Week 6
Allergan Phase II trial <sup>28</sup> (2017)	258 patients (all women), age 18 to 65 years. Moderate to severe depression defined by MADRS $\geq 18$ and CGI-S $> 4$ . No antidepressant use	24 weeks. Patients received 30 units or 50 units of BTA. Primary outcome change in MADRS at Week 6

BDI: Beck Depression Inventory; BTA: botulinum toxin A; CGI: Clinical Global Impressions scale; CGI-S: Clinical Global Impressions-Severity scale; CSS-GFL: Clinical Severity Score for Glabellar Frown Lines; HAM-D-17: 17-item Hamilton Depression Rating Scale; HDRS: Hamilton Depression Rating Scale; HDRS-21: 21-item Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9

statistically significant improvement at 3 weeks ( $-4.2$ ,  $P = .005$ ) and at 9 weeks ( $-3.6$ ,  $P = .049$ ). Although close, the primary endpoint at 6 weeks was not statistically significant ( $-3.7$ ,  $P = .053$ ). Surprisingly, the 50-unit injection failed to produce any significant difference from placebo and thus no superiority from the 30-unit group; this finding calls into question the dose-response relationship. Both doses were, however, well tolerated. Allergan is planning to move forward with BTA injections for depression in larger phase III trials.<sup>29</sup>

More recently, in a case series, Chugh et al<sup>30</sup> examined the effect of BTA in 42 patients (55% men) with severe treatment-resistant depression. Participants were given BTA injections in the glabellar region as an adjunctive treatment to

antidepressants and observed for at least 6 weeks. Depression severity was measured using HAM-D17, MADRS, and BDI at baseline and at 3 weeks. Changes in glabellar frown lines also were assessed using the CSS-GFL. The authors reported statistically significant improvements in HAM-D17 ( $-9.0 \pm 3.5$ ,  $P < .001$ ), MADRS ( $-12.7 \pm 4.0$ ,  $P < .001$ ), and BDI ( $-12.5 \pm 4.2$ ,  $P < .001$ ) scores at 3 weeks. BTA's antidepressant effects did not differ between male and female participants ( $R^2 \leq .042$ ), demonstrating for the first time in the largest male sample to date that botulinum toxin's effects are independent of gender. However, this study was limited by its lack of placebo control.

A summary of the RCTs of BTA for treating depression appears in *Table 1*.<sup>23,25-28</sup>

## Findings

Significant improvement in HAMD-17 ( $-10.07 \pm 8.16$ ,  $P < .001$ ), BDI ( $-10.67 \pm 10.77$ ,  $P = .002$ ), and CGI ( $1.40 \pm 1.24$ ,  $P < .001$ ) at 6 weeks. Significantly higher HAMD-17 partial (25% to 49% reduction) response rate (86.7% vs 26.7%,  $P = .003$ ) and response rate (60% vs 13.3%,  $P = .02$ ) in BTA group. Significant change in CSS-GFL ( $-0.87 \pm 0.35$ ,  $P < .001$ ) at 6 weeks

Significantly higher MADRS response rate (52% vs 15%,  $P < .001$ ) in BTA group after 6 weeks. Significantly higher remission rate (27% vs 7%,  $P < .02$ ) in BTA group after 6 weeks. Significant MADRS score reduction (47% vs 20.6%,  $P < .0005$ ) in BTA group 6 weeks after single treatment. No significant association ( $P = .07$ ) between reduction in frown scores and mood improvement after BTA injection

Statistically significant difference in HDRS-21 response rate in BTA-first (55%) and BTA-second (24%) groups vs placebo at 6 weeks ( $P < .0001$ ). No statistically significant difference in remission rate between groups ( $P = .057$ ). No statistically significant difference in HDRS-21 partial response (25% to 49% reduction) rate in both groups ( $P = .27$ ). Significant reduction in HDRS-21 ( $-46\%$ ,  $-35\%$  vs  $-2\%$ ,  $P < .0001$ ) at 6 weeks. Statistically significant difference in BDI response rate in BTA-first (45%) and BTA-second (5%) groups ( $P = .0067$ ). No statistically significant difference in remission rate between groups ( $P = .09$ ). No statistically significant difference in BDI partial response (25% to 49% reduction) rate between groups ( $P = .95$ ). No statistically significant difference in PHQ-9 response rate ( $P = .46$ ) or remission rate ( $P = .23$ ) between groups. Continued reduction in HDRS-21 (50%), BDI (57%), and PHQ-9 (59%) scores in BTA-first group after 24 weeks. CSS-GFL scores showed average change of 1.6 in BTA group vs 0.2 in placebo group at 3 weeks. CSS-GFL scores returned to baseline after 24 weeks

Significant difference in BDI score between BTA and placebo groups at 6 weeks ( $19.00 \pm 4.82$  vs  $24.29 \pm 4.04$ ;  $P = .004$ ) but not at 2 weeks ( $27.29 \pm 6.14$  vs  $25.07 \pm 4.16$ ;  $P = .274$ )

Change in HAMD-17 scores in the 30-unit group ( $-13.4$ ) and 50-unit group ( $-17.4$ ) after 24 weeks. Change in CGI-S scores in the 30-unit group ( $-1.9$ ) and 50-unit group ( $-2.9$ ) after 24 weeks

## Clinical Point

**BTA injections in the glabellar region were effective for treatment-resistant symptoms of borderline personality disorder**

## Benefits for other psychiatric indications

**Borderline personality disorder.** In a case series of 6 women, BTA injections in the glabellar region were reported to be particularly effective for the treatment of borderline personality disorder symptoms that were resistant to psychotherapy and pharmacotherapy.<sup>31</sup> Two to 6 weeks after a 29-unit injection, borderline personality disorder symptoms as measured by the Zanarini Rating Scale for Borderline Personality Disorder and/or the Borderline Symptom List were shown to significantly improve by 49% to 94% from baseline ( $P \leq .05$ ). These findings emphasize the promising therapeutic role of BTA on depressive symptoms concomitant with the emotional lability, impulsivity, and negative emotions that usually characterize

this personality disorder.<sup>31,32</sup> A small sample size and lack of a placebo comparator are limitations of this research.

**Neuroleptic-induced sialorrhea.** Botulinum toxin injections in the salivary glands have been investigated for treating clozapine-induced sialorrhea because they are thought to directly inhibit the release of acetylcholine from salivary glands. One small RCT that used botulinum toxin B (BTB)<sup>33</sup> and 1 case report that used BTA<sup>34</sup> reported successful reduction in hypersalivation, with doses ranging from 150 to 500 units injected in each of the parotid and/or submandibular glands bilaterally. Although the treatment was well tolerated and lasted up to 16 weeks, larger studies are needed to replicate these findings.<sup>33-35</sup>

continued



## Botulinum toxin

### Clinical Point

Several case reports of orofacial tardive dyskinesia have found improvements in hyperkinetic movements following BTA injections

**Table 2**

## Reports of botulinum toxin for other psychiatric disorders

Disorder	Study	Details
Borderline personality disorder	Kruger et al <sup>31</sup> (2016; case series)	6 women, age 20 to 59, who were refractory to previous pharmacologic and psychotherapeutic treatments received 29 units of BTA at 5 injection sites in the glabellar region
Neuroleptic-induced sialorrhea	Kahl et al <sup>34</sup> (2004; case report)	Man, age 50, with sialorrhea from clozapine (250 mg/d, subsequently increased to 600 mg/d to control psychosis) without improvement from atropine (2 mg/d) received 150 IU of BTA injected into each parotid gland
	Steinlechner <sup>33</sup> et al (2009; RCT)	8 patients (7 men; median age 71) with neuroleptic or Parkinson's disease-induced sialorrhea. Four received 500 units of BTB into each parotid gland and 250 units into each submandibular gland and 4 received placebo
Orofacial tardive dyskinesia	Slotema et al <sup>38</sup> (2007; non-placebo-controlled single-blind [raters] study)	12 patients (4 women), mean age 51. Each patient had tardive dyskinesia following antipsychotics for ≥3 months. BTA injected into 4 sites in orbicularis oris muscles at 3, 6, and 9 months from baseline. Forty Mu injected at 3 months. Up to 60 Mu injected at 6 months. Up to 80 Mu injected at 9 months (mean dosage 72.8 Mu)
	Hennings et al <sup>37</sup> (2008; case report)	Patient, age 28, with tardive dystonia caused by flupentixol (20 mg IM every 2 weeks) and biperiden (regimen unknown) for 1 year. Tardive dystonia did not improve with amisulpride (300 mg/d), olanzapine (2.5 mg/d), and ziprasidone (120 mg/d). Symptoms worsened with aripiprazole (10 mg/d). Clozapine (regimen unknown) not tolerated due to severe hypotension and syncope. Fifty units of BTA injected into each genioglossal muscle. Second smaller injection (total of 80 units) 16 weeks later
	Tschopp et al <sup>36</sup> (2009; case report)	Woman, age 81, with tardive dyskinesia since 1997. Unclear history of antipsychotic and antidepressant use. History of tetrabenazine use (100 mg/d) for 3 years. History of reserpine use (4 mg/d, reduced to 1 mg/d) for unknown duration. 25 units of BTA injected into each genioglossal muscle

BTA: botulinum toxin A; BTB: botulinum toxin B; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; RCT: randomized controlled trial

**Orofacial tardive dyskinesia.** Several case reports of orofacial tardive dyskinesia, including lingual dyskinesia and lingual protrusion dystonia, have found improvements in hyperkinetic movements following muscular BTA injections, such as in the genioglossus muscle in the case of tongue involvement.<sup>36-39</sup> These cases were, however, described in the literature before the recent FDA approval of the vesicular monoamine transporter 2 inhibitors valbenazine and deutetrabenazine for the treatment of tardive dyskinesia.<sup>40,41</sup>

Studies examining botulinum toxin's application in areas of psychiatry other than depression are summarized in *Table 2*.<sup>31,33,36-38</sup>

### Promising initial findings but multiple limitations

Although BTA injections have been explored as a potential treatment for several psychiatric conditions, the bulk of recent evidence is derived from studies in patients with depressive disorders. BTA injections in the glabellar regions have been shown in small RCTs to be well-tolerated with overall promising improvement of depressive symptoms, optimally 6 weeks after a single injection. Moreover, BTA has been shown to be safe and long-lasting, which would be convenient for patients and might improve adherence to therapy.<sup>42-44</sup> BTA's antidepressant effects were shown to be independent of frown line severity or patient



Findings

49% to 94% improvement in Zanarini Rating Scale for Borderline Personality Disorder and/or Borderline Symptom List at 2 to 6 weeks
Subjective reduction in hypersalivation after 2 weeks lasting until 12-week follow-up
Change in saliva weight (-2.43 ± 0.412 g) at 4 weeks. Change in salivary IgA (-1.28 ± 4.58 mg/dL), salivary IgG (4.92 ± 2.11 mg/dL), salivary IgM (0.01 ± 3.63 mg/dL), albumin (36.80 ± 3.55 mg/dL), and total protein (19.65 ± 24.73 mg/dL) at 4 weeks. Improvement in Drooling Severity and Drooling Frequency Scales (1.75 ± 1, 1.00 ± 0.8) at 4 weeks. Drooling severity worsened at 8 weeks (-0.24) and 16 weeks (-0.15). Drooling frequency worsened at 16 weeks (-0.41). Change in Global Assessment of Functioning scores (2.50 ± 13) at 4 weeks
Significant improvement in Abnormal Involuntary Movement Scale scores at 33 weeks in patients with stable antipsychotic regimen (1.8 ± 2.4, <i>P</i> = .035)
Subjective improvement in tongue protrusion within 3 days lasting 10 weeks. Subjective improvement with second injection lasting 3.5 months
Subjective reduction in pain and lingual dyskinesia persisting for 2 months, evidenced by amelioration of orolingual movements and improvement of symptoms, mainly pruritus and burning sensation

Clinical Point

In small RCTs, BTA injections in the glabellar region resulted in promising improvement of depressive symptoms

satisfaction with cosmetic effects.<sup>45</sup> The trials by Wollmer et al,<sup>23</sup> Finzi and Rosenthal,<sup>25</sup> and Magid et al<sup>26</sup> mainly studied BTA as an adjunctive treatment to antidepressants in patients with ongoing unipolar depression. However, Finzi and Rosenthal<sup>25</sup> included patients who were not medicated at the time of the study.

Pooled analysis of these 3 RCTs found that patients who received BTA monotherapy improved equally to those who received it as an adjunctive treatment to antidepressants. Overall, on primary endpoint measures, a response rate of 54.2% was obtained in the BTA group compared with 10.7% among patients who received placebo saline injections (odds ratio

[OR] 11.1, 95% confidence interval [CI], 4.3 to 28.8, number needed to treat [NNT] = 2.3) and a remission rate of 30.5% with BTA compared with 6.7% with placebo (OR 7.3, 95 % CI, 2.4 to 22.5, NNT = 4.2).<sup>46</sup> However, remission rates tend to be higher in the augmentation groups, and so further studies are needed to compare both treatment strategies.

Nevertheless, these positive findings have been recently challenged by the results of the largest U.S. multicenter phase II RCT,<sup>28</sup> which failed to find a significant antidepressant effect at 6 weeks with the 30-unit BTA injection, and also failed to prove a dose-effect relationship, as the 50-unit injection wasn't superior to the lower dose and



## Botulinum toxin

### Clinical Point

The high unblinding rates in botulinum toxin trials remains a significant limitation because it may lead to underestimation of the placebo effect

didn't significantly differ from placebo. One hypothesis to explain this discrepancy may be the difference in injection sites between the treatment and placebo groups.<sup>47</sup> Future studies need to address the various limitations of earlier clinical trials that mainly yielded promising results with BTA.

A major concern is the high rate of unblinding of participants and researchers in BTA trials, as the cosmetic effects of botulinum toxin injections make them easy to distinguish from saline injections. Ninety percent of participants in the Wollmer et al study<sup>23</sup> were able to correctly guess their group allocation, while 60% of evaluators guessed correctly. Finzi and Rosenthal<sup>25</sup> reported 52% of participants in the BTA group, 46% in the placebo group, and 73% of evaluators correctly guessed their allocation. Magid et al<sup>26</sup> reported 75% of participants were able to guess the order of intervention they received. The high unblinding rates in these trials remains a significant limitation. There is a concern that this may lead to an underestimation of the placebo effect relative to clinical improvement, thus causing inflation of outcome differences between groups. Although various methods have been tried to minimize evaluator unblinding, such as placing surgical caps on participants' faces during visits to hide the glabellar region, better methods need to be implemented to prevent unblinding of both raters and participants.

Furthermore, except for the multicenter phase II trial, most studies have been conducted in small samples, which limits their statistical power. Larger controlled trials will be needed to replicate the positive findings obtained in smaller RCTs.

Another limitation is that the majority of the well-designed RCTs were conducted in populations that were predominantly female, which makes it difficult to reliably assess treatment efficacy in men. This may be because cosmetic treatment with botulinum toxin injection is more favorably received by women than by men. A recent comparison<sup>48</sup> of the studies by Wollmer et al<sup>23</sup> and Finzi and Rosenthal<sup>25</sup> discussed an interesting observation. Wollmer et al did not explicitly mention botulinum toxin

when recruiting for the study, while Finzi and Rosenthal did. While approximately a quarter of the participants in the Wollmer et al study were male, Finzi and Rosenthal attracted an almost entirely female population. Perhaps there is a potential bias for females to be more attracted to these studies due to the secondary gain of receiving a cosmetic procedure.

In an attempt to understand predictors of positive response to botulinum toxin in patients with depression, Wollmer et al<sup>49</sup> conducted a follow-up study in which they reassessed the data obtained from their initial RCT using the HAM-D agitation item scores to separate the 15 participants who received BTA into low-agitation ( $\leq 1$  score on agitation item of the HAM-D scale) and high-agitation ( $\geq 2$  score on agitation item of the HAM-D scale) groups. They found that the 9 participants who responded to BTA treatment had significantly higher baseline agitation scores than participants who did not respond ( $1.56 \pm 0.88$  vs  $0.33 \pm 0.52$ ,  $P = .01$ ). All of the participants who presented with higher agitation levels experienced response, compared with 40% of those with lower agitation levels ( $P = .04$ ), although there was no significant difference in magnitude of improvement ( $14.2 \pm 1.92$  vs  $8.0 \pm 9.37$ ,  $P = .07$ ). The study added additional support to the facial feedback hypothesis, as it links the improvement of depression to facial muscle activation targeted by the injections. It also introduced a potential predictor of response to botulinum toxin treatment, highlighting potential factors to consider when enrolling patients in future investigations.

The case series of patients with borderline personality disorder<sup>31</sup> also shed light on the potential positive effect of BTA treatment for a particular subtype of patients with depression—those with comorbid emotional instability—to consider as a therapeutic target for the future. Hence, inclusion criteria for future trials might potentially include patient age, gender, existence/quantification of prominent frown lines at baseline, severity of MDD, duration of depression, and personality characteristics of enrolled participants.

In conclusion, BTA injections appear promising as a treatment for depression as well as for other psychiatric disorders. Future studies should focus on identifying optimal candidates for this innovative treatment modality. Furthermore, BTA dosing and administration strategies (monotherapy vs adjunctive treatment to antidepressants) need to be further explored. As retrograde axonal transport of botulinum toxin has been demonstrated in animal studies, it would be interesting to further examine its effects in the human CNS to enhance our knowledge of the pathophysiology of botulinum and its potential applications in psychiatry.<sup>50</sup>

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#### Drug Brand Names

Alprazolam • Xanax	Imipramine • Tofranil
Aripiprazole • Abilify	Olanzapine • Zyprexa
Biperiden • Akineton	Reserpine • Serpalan,
Botulinum toxin A • Botox	Serpasil
Botulinum toxin B • Myobloc	Tetrabenazine • Xenazine
Clozapine • Clozaril	Valbenazine • Ingrezza
Deutetrabenazine • Austedo	Ziprasidone • Geodon
Flupentixol • Prolixin	

#### Clinical Point

**Botulinum toxin might be beneficial for patients with depression and comorbid emotional instability**

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continued

## Bottom Line

Botulinum toxin shows promising antidepressant effects and may have a role in the treatment of several other psychiatric disorders. More research is needed to address limitations of previous studies and to establish an adequate treatment regimen.



## Botulinum toxin

### Clinical Point

**Botulinum toxin dosing and administration strategies (as monotherapy or an adjunct) need to be further explored**

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