

Treatment of Major Depressive Disorder Using Botulinum Toxin A: A 24-Week Randomized, Double-Blind, Placebo-Controlled Study

Michelle Magid, MD; Jason S. Reichenberg, MD; Poppy E. Poth, BS; Henry T. Robertson, PhD; Amanda K. LaViolette, MD, MPH; Tillmann H. C. Kruger, MD; and M. Axel Wollmer, MD

ABSTRACT

Objective: To determine whether a single treatment of botulinum toxin A in the forehead (glabellar) region can improve symptoms of depression in patients with major depressive disorder (MDD), as defined by *DSM-IV* criteria.

Method: Thirty participants were randomly assigned to receive either placebo or botulinum toxin A (BTA; onabotulinumtoxinA) injections in the forehead. Female participants received 29 units; male participants received 39 units. At week 12, the groups were crossed over. Participants were evaluated at weeks 0, 3, 6, 12, 15, 18, and 24 for improvement in MDD symptoms using the Patient Health Care Questionnaire-9, Beck Depression Inventory (BDI), and 21-Item Hamilton Depression Rating Scale (HDRS-21) objective measurement scales. The primary outcome was the rate of HDRS-21 response, defined as $\geq 50\%$ score reduction from baseline. The study occurred from July 2011 to November 2012.

Results: Patients who received BTA at week 0 (BTA-first group) and at week 12 (BTA-second group) had a statistically significant reduction in MDD symptoms as compared to placebo. Improvement in MDD continued over 24 weeks in the group that received BTA first even though the cosmetic effects of BTA wore off at 12 to 16 weeks. HDRS-21 response rates were 55% (6/11) in the BTA-first group, 24% (4/17) in the BTA-second group, and 0% (0/19) in the placebo group ($P < .0001$). HDRS-21 remission rates (score ≤ 7) were 18% (2/11), 18% (3/17), and 0% (0/19), respectively ($P = .057$). HDRS-21 scores dropped -46% and -35% in the BTA-first and -second groups versus -2% in the placebo group ($P < .0001$). The BDI response rate ($\geq 50\%$ reduction from baseline) was 45% (5/11) in the BTA-first group, 33% (6/18) in the BTA-second group, and 5% (1/19) in the placebo group ($P = .0067$). BDI remission rates (score ≤ 9) were 27% (3/11), 33% (6/18), and 5% (1/19), respectively ($P = .09$). BDI scores dropped -42% and -35% in the BTA-first and -second groups versus -15% in the placebo group ($P < .0001$).

Conclusions: Botulinum toxin A injection in the glabellar region was associated with significant improvement in depressive symptoms and may be a safe and sustainable intervention in the treatment of MDD.

Trial Registration: ClinicalTrials.gov identifier: NCT01392963

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Corresponding author: Michelle Magid, MD, 1600 West 38th St, Ste 404, Austin, TX 78731 (michellemagidmd@gmail.com).

Major depressive disorder (MDD) is an illness that affects 16% of the US population and more than 350 million people worldwide.¹ MDD is also the leading cause of disability internationally.² A relevant proportion of patients do not sufficiently improve with medication management and psychotherapy and are then left with fewer therapeutic options. There is a great need to develop further and alternative treatment strategies.

Three preliminary studies have suggested that treating the frown muscles of depressed patients with botulinum toxin A (BTA; onabotulinumtoxinA) may improve symptoms of MDD.^{3–5} Several theories have been put forth to explain the mechanism of action behind this treatment, the most notable being the facial feedback hypothesis. This hypothesis suggests that facial expression influences emotional perception; producing an expression that is characteristic of a particular emotion can lead to experiencing that emotion (eg, smiling can lead to happiness, scowling can lead to anger). One study showed that mimicking facial expressions of anger or fear, even with no emotional valence attached to the expression, can lead to significant changes in heart rate and temperature.⁶ Perhaps by inhibiting the muscles responsible for expressions of anguish and sadness, one may decrease the patient's experience of these feelings.^{7,8}

We recruited 30 patients who were able to produce moderate to severe frown lines by maximum activation of the glabellar muscles, and BTA was injected into this area in a crossover design. This 24-week study was conducted to determine whether BTA can treat MDD and whether these effects last beyond the cosmetic effects (usually 12 weeks).

METHOD

Study Design

The study protocol was approved by our hospital's Institutional Review Board and Steering Committee. The trial was registered at ClinicalTrials.gov (identifier: NCT01392963).

This double-blind, placebo-controlled pilot study occurred from July 2011 to November 2012 at the Seton Family of Hospitals/University of Texas Southwestern Department of Psychiatry outpatient clinic in Austin, Texas. The study protocol consisted of 7 visits over 24 weeks (weeks 0, 3, 6, 12, 15, 18, and 24). At baseline visit (week 0), patients were randomly assigned to receive either onabotulinumtoxinA at a concentration of 40 units (U)/1 mL dissolved in 0.9% NaCl saline solution or placebo, 0.9% NaCl saline solution. Identical volumes of placebo or active substance were placed in 30-gauge syringes

- There is increasing evidence that patients suffering from major depressive disorder (MDD) may benefit from injections of botulinum toxin A into the frown lines.
- Psychotherapy and medication management remain the mainstay for the treatment of MDD. Further studies of botulinum toxin A for MDD are warranted before this treatment can be recommended either for monotherapy or as an augmentation strategy.

and were injected into the glabellar region at 5 specific points chosen to correlate with the configuration used in previous studies.^{3–5} Women received 29 U: 7 U in the procerus, 6 U bilaterally to the corrugator muscles, and 5 U bilaterally to the lateral corrugator muscles (Figure 1A). Men received 39 U in the same injection sites, to account for increased muscle mass. At week 12, those who initially received BTA were given placebo, and those who initially received placebo were given BTA (ie, BTA-second group).

At each visit, patients were assessed with the following measurement scales: the Hamilton Depression Rating Scale 21 (HDRS-21) (physician administered),⁹ the Beck Depression Inventory (BDI) (self-rating),¹⁰ and the Patient Health Questionnaire-9 (PHQ-9) (self-rating; a quick instrument that can be easily used by a dermatologist or primary care physician).¹¹ Patient photographs were taken at each visit, both at rest and at maximum frowning. The photographer was not involved in psychometric rating. All patients were assessed by the same psychiatrist throughout the study, to minimize interrater variability. The psychiatrist was blinded to the intervention by having patients wear surgical caps, which covered the entire forehead region (Figure 1B), during visits. This technique concealed any visual signs of BTA versus placebo. Topics that provided a hint to treatment allocation (ie, side effects, cosmetic effects, satisfaction with treatment) were not discussed.

A power analysis (power = 80% and $\alpha = .05$, for a 3-point change in HDRS score [standard deviation = 4]) revealed that 28 patients would be needed for statistical significance (N = 30 would allow for some attrition).

Participants

Participants were recruited from local outpatient psychiatry and primary care practices and through Internet advertisements and media appearances. Patients meeting the inclusion criteria were men and women ages 18–65 years with a history of MDD (296.3x or 296.2x) for at least 6 months, as defined by *DSM-IV* criteria. Patients must have already been diagnosed with MDD by a previous physician prior to study enrollment. The diagnosis was confirmed by a trained psychiatrist (M.M.) via structured clinical interview using *DSM-IV* criteria based on the Mini-International Neuropsychiatric Interview.¹² Patients who were in a current major depressive episode and who scored 14 or greater on the 21-Item Hamilton Depression Rating Scale (HDRS-21) at screening were included. The severity of patients'

glabellar folds during maximum voluntary frowning were rated on a scale of 0–10, with those having a score of 7 or more (indicating moderate to severe frown lines) included in the study. They were also rated on a scale of 0–3 according to the 4-point clinical severity score for glabellar frown lines (CSS-GFL) used in other onabotulinumtoxinA studies^{4,13} to allow for a later comparison. Exclusion criteria included active substance abuse, bipolar disorder, pregnancy (positive urine pregnancy test on initial evaluation), an unstable medical condition, previous onabotulinumtoxinA treatment, and treatment with more than 3 psychotropic medications at the time of enrollment. Current psychiatric medications must have been stable for 60 days prior to study enrollment. Patients with potential secondary gain or with significant Axis II comorbidity revealed on interview were excluded. This included patients who were overly invested in cosmetic treatments, patients with a formal Axis II diagnosis, or patients with significant interpersonal difficulties on clinical interview.

Demographic information, including age, education, duration of MDD, current psychotropic medications, and living situation, was collected. At baseline visit, patients were asked to rate how much they expected their mood to improve with botulinum toxin A (0%, 25%, 50%, 100%), in order to better account for placebo effects.¹⁴ Patients were subjected to a full psychiatric intake and brief neurologic examination at screening visit. Written informed consent was provided by all participants after the study was completely explained.

Outcome Measures

The primary end point was change in HDRS-21 score at week 6 after injection, similar to previous trials of BTA for depression.^{4,5} The definition of clinical response as measured by the HDRS-21 was categorized as nonresponse (<25% reduction), partial response (25%–49% reduction), response ($\geq 50\%$ reduction), or remission (HDRS-21 score ≤ 7). The Structured Interview Guide for the Hamilton Depression Rating Scale was used.¹⁵

Secondary and tertiary measures were a change in BDI and PHQ-9 scores at week 6 after injection. The definition of clinical response was the same as with HDRS-21 above.

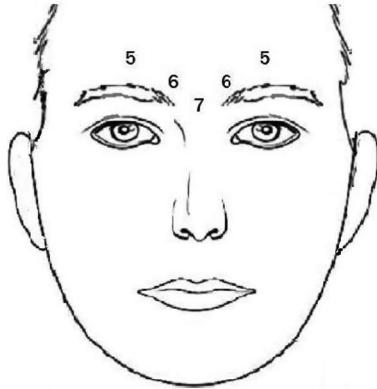
BDI remission was defined as a score ≤ 9 . Photographs of patients' faces at rest and at maximum frowning were taken at each visit. At the end of the study, these photographs were randomized and rated by 2 physicians (M.M. and J.S.R.) using both the 0–3 CSS-GFL and the 0–10 frowning severity scale to determine the physical effects of the intervention versus placebo.

Randomization and Blinding

Participants were randomized using a simple unrestricted randomization method to allocate treatment arms. (Two cards, 1 labeled "placebo" and 1 labeled "BTA," were placed in an envelope. At enrollment visit, a card was randomly selected by the study coordinator [P.E.P.], which determined initial arm allocation.) The onabotulinumtoxinA was mixed by the study coordinator and injected by the dermatologist (J.S.R.),

Figure 1. Botulinum Toxin A Configuration and Method Used for Blinding

A. Botulinum toxin A configuration^a



B. Blinding method^b



^aWomen received 29 units: 7 into the procerus, 6 bilaterally into the medial corrugator supercili muscles, and 5 bilaterally into the lateral corrugator supercili muscles, as illustrated. Men received 39 units (2 more units into each injection site) to account for higher muscle mass.

^bPatients wore surgical caps covering the forehead (glabellar) region during their visits. Technique modeled here by a staff member who consented to the use of her image in this article.

neither of whom participated in psychometric rating of the participants for response to treatment. The placebo and onabotulinumtoxinA syringes were indistinguishable from one another. The psychometric rater (M.M.) was blinded, as all participants wore surgical caps which covered the forehead region during visits, preventing visualization of cosmetic changes (Figure 1B). This method was used in a previous study.⁴

Statistical Analysis

Two-way analysis of variance (ANOVA) models were fitted with random-effect intercepts for each patient. Two ANOVA models were used: (1) cell means model and (2) time-since-BTA model. The former model allowed us to determine any significant changes in MDD scores from baseline for each combination of time point and treatment group. The latter model allowed us to separate the effect of time in study versus the effect of time since BTA injection. At crossover, week 0 (baseline) scores were used in statistical analysis. Week 12 scores as a covariate were assessed, and the *P* values were nonsignificant and did not influence the results. The analyses were conducted using the nlme package in the R programming language, version 3.0.1.¹⁶ Other secondary analyses were conducted using logistic regression.

RESULTS

Patient Characteristics

A total of 101 patients were screened via telephone, 39 received a face-to-face screening interview, and 30 were enrolled in the study. The majority of patients who did not qualify for the study had either a bipolar diagnosis or no previous diagnosis of MDD (see Supplementary eFigure 1 [CONSORT diagram] at PSYCHIATRIST.COM). Of the 210 potential visits, data points were collected for 196 visits. Nine data points were filled in using the last observation point carried forward, if patients missed an appointment.

Eleven patients initially received BTA (BTA-first group), and 19 initially received placebo. Data analysis included 11 patients in the BTA-first group, 19 patients in the placebo group, and 17 patients in the BTA-second group (1 patient was terminated due to becoming pregnant and 1 dropped out at crossover).

Table 1. Efficacy Outcome Measures at 6 and 24 Weeks After Intervention and Change in Frown Scores (CSS-GFL) at 3 and 24 Weeks After Intervention

Measure	Placebo (n = 19)			BTA-First (n = 11)			BTA-Second (n = 17) ^a			BTA-First (n = 9) ^b			
	Mean Score Baseline	Mean Score 6 wk	Change in Score (%)	Mean Score Baseline	Mean Score 6 wk	Change in Score (%)	Mean Score Baseline	Mean Score 6 wk	Change in Score (%)	Mean Score Baseline	Mean Score 24 wk	Change in Score (%)	<i>P</i> Value ^c
HDRS-21	23.7	23.3	-0.4 (-1.7)	27.9	15.2	-12.7 (-45.5)	23.7	15.3	-8.4 (-35.4)	14.1	13.8 (-49.5)	13.8 (-49.5)	<.0001
PHQ-9	13.5	11.7	-1.8 (-13.3)	16.1	10.7	-5.4 (-33.5)	13.5	9.5	-4.0 (-29.5)	6.7	9.4 (-58.4)	9.4 (-58.4)	<.0001
BDI	23.7	20.1	-3.6 (-15.2)	27.5	16	-11.5 (-41.8)	23.7	15.4	-8.3 (-35.0)	11.9	15.6 (-56.7)	15.6 (-56.7)	<.0001
CSS-GFL	2.5	2.3	0.2 (-8.0)	2.7	0.7	2.0 (-74.1)	2.5	0.9	1.6 (-64.0)	2.7	0 (0) ^d	0 (0) ^d	

^aTwo patients in the placebo group (n = 19) dropped out at crossover (1 terminated due to pregnancy, and 1 filled out the PHQ-9 and BDI measurements [n = 18] but left before HDRS-21 administration [n = 17]).

^bTwo patients in the BTA-first group dropped out at crossover and were therefore not included in the 24-week analysis.

^c*P* values are based on a repeated-measures 2-way analysis of variance model. See Supplementary eTable 3.

^dAt 24 weeks, frown scores (CSS-GFL) were back to baseline; however, PHQ-9, HDRS-21, and BDI scores continued to improve. Abbreviations: BDI = Beck Depression Inventory, BTA = botulinum toxin A, CSS-GFL = Clinical Severity Score for Glabellar Frown Lines, HDRS-21 = 21-Item Hamilton Depression Rating Scale, PHQ-9 = Patient Health Questionnaire-9.

Active and placebo groups did not differ in age, education, number of psychotropic medications, or duration of MDD. There was no statistically significant difference in HDRS-21 and BDI scores between the groups (Supplementary eTables 1 and 2).

Efficacy Outcomes

The following 3 groups were compared: (1) patients who received placebo at week 0 (placebo), (2) patients who received BTA at week 0 (BTA-first), and (3) patients who received BTA at crossover week 12 (BTA-second) (Table 1).

The group that received placebo at crossover was not included in analysis, since the CSS-GFL scores had not yet returned to baseline and there was a possibility that the botulinum toxin was still active. Rather, in this group, protocol continued as usual, and data were collected throughout the 24-week period to determine if antidepressant effects were sustained even when the cosmetic effects of BTA wore off.

The ANOVA results are shown in Supplementary eTable 3. There were significant decreases in all 3 scales after patients received BTA. Both models found a statistically significant effect of time at week 3 on the decline in scores among patients who received placebo first; this decline in scores regressed to zero in the following weeks of measurement. After receiving BTA, the scores continued to drop throughout the duration of the study. The psychotropic effects of BTA were found to be more persistent than expected, lasting at least 24 weeks.

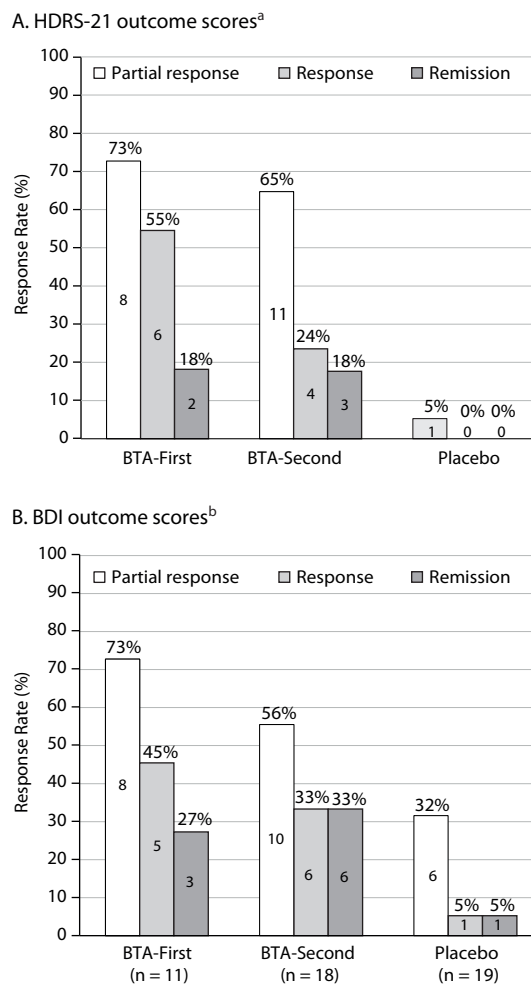
HDRS scoring. At week 6, response rate was 55% in the BTA-first group, 24% in the BTA-second group, and 0% in the placebo group ($P < .0001$ by logistic regression). Remission rates were 18%, 18%, and 0%, respectively ($P = .057$). Partial response rates were 73%, 65%, and 5%, respectively (Figure 2A). There was a significant improvement in MDD symptoms in the BTA-first and BTA-second groups (vs placebo group) with a large effect size; -46% , -35% , -2% reduction in HDRS-21 scores, respectively ($P < .0001$ by repeated measures 2-way ANOVA model) (Table 1, Figure 3A and 3B).

BDI scoring. At week 6, response rate was 45% in the BTA-first group, 33% in the BTA-second group, and 5% in the placebo group ($P = .0067$). Remission rates were 27%, 33%, and 5%, respectively ($P = .09$). Partial response rates were 73%, 56%, and 32%, respectively (Figure 2B). There was a significant improvement in MDD symptoms in the BTA-first and BTA-second groups (vs placebo group), with a -42% , -35% , and -15% reduction in BDI rating scores, respectively ($P < .0001$) (Table 1, Figure 3C).

PHQ-9 scoring. There was a significant improvement in MDD symptoms in the BTA-first and BTA-second groups (vs placebo group), with a -34% , -30% , and -13% reduction in PHQ-9 rating scores, respectively ($P = .0006$) (Table 1, Figure 3D).

CSS-GFL scoring. Changes in glabellar frown lines at maximum frowning were evaluated throughout the study. At 3 weeks after injection (the most likely point of maximum BTA effect), BTA versus placebo injections caused

Figure 2. Partial Response, Response, and Remission Rates



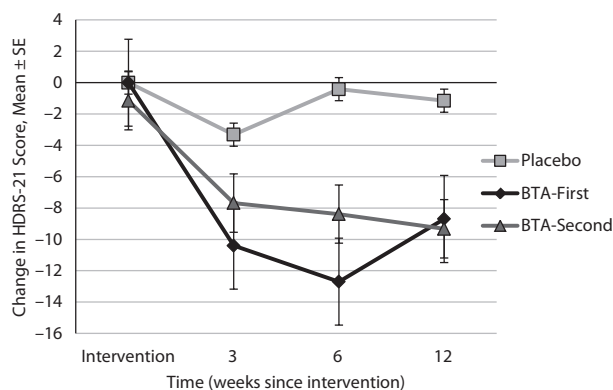
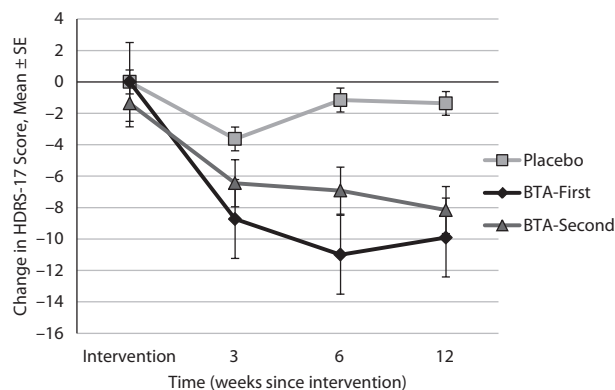
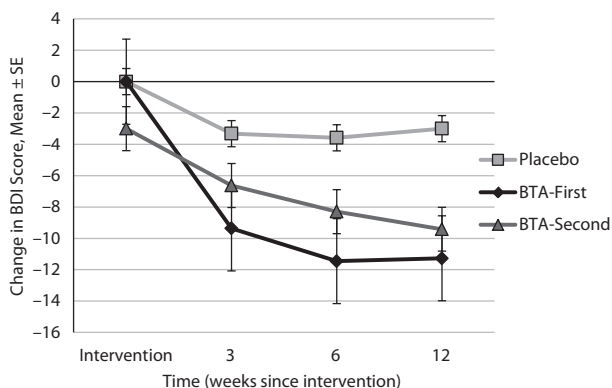
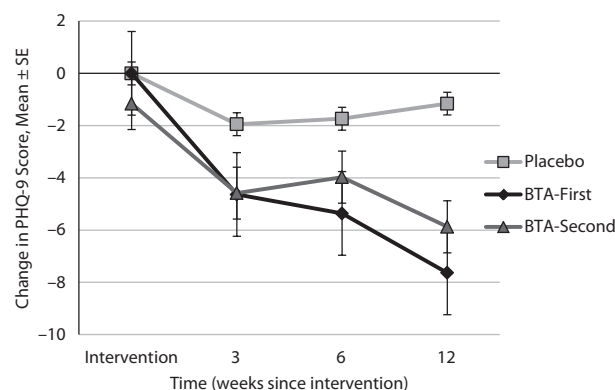
^aPartial response, response, and remission rates are presented as both a number and percentage of participants in the placebo (n = 19), BTA-first (n = 11), and BTA-second (n = 17) groups at the 6-week visit. Significant group differences were observed. Originally, response rate as defined as a 30% reduction in HDRS-21 score was registered as the primary endpoint (ClinicalTrials.gov, NCT01392963), which is obviously also positive. For comparability with other studies, the primary endpoint was changed to 50% reduction in HDRS score.

^bPartial response, response, and remission rates are presented as both a number and percentage of participants in the placebo (n = 19), BTA-first (n = 11), and BTA-second (n = 18) groups at the 6-week visit. Again, significant group differences were observed.

Abbreviations: BDI = Beck Depression Inventory, BTA = botulinum toxin A, HDRS-21 = 21-Item Hamilton Depression Rating Scale.

a mean change of 1.6 versus 0.2 points on CSS-GFL scores, respectively (Table 1), indicating that BTA treatments were active and significantly changed one's ability to frown. During treatment with BTA, CSS-GFL scores maximally dropped at 3 weeks and slowly increased toward baseline afterward.

Week 24. At week 24, the mean CSS-GFL score in the group that received BTA first was back to baseline. Nonetheless, all 3 measurement scales showed continued reduction in MDD scores throughout the 24 weeks, indicating that mood continued to improve despite the BTA effects wearing off. At week 24 in the group that received BTA first, there was a 50% reduction in HDRS-21 scores, a 57% reduction in BDI

Figure 3. Efficacy Outcomes Presented as Change in HDRS-21, HDRS-17, BDI, and PHQ-9 Scores^a**A. HDRS-21****B. HDRS-17****C. BDI****D. PHQ-9**

^aThe groups compared are the placebo group (n = 19), BTA-first group (n = 11), and BTA-second group (n = 17 for HDRS, n = 18 for BDI and PHQ-9). For the BTA-second group, all scores listed are for change from week 0 (even though the intervention occurred at week 12), explaining why the BTA-second group starts from below zero at "intervention." There was a statistically significant difference between the placebo and BTA groups in reduction of major depressive disorder scores in all 3 rating scales.

Abbreviations: BDI = Beck Depression Inventory, BTA = botulinum toxin A, HDRS-17 = 17-Item Hamilton Depression Rating Scale, HDRS-21 = 21-Item Hamilton Depression Rating Scale, PHQ-9 = Patient Health Questionnaire-9.

scores, and a 59% reduction in PHQ-9 scores ($P < .0001$) (Table 1, Figure 4).

Expectancy to improve. The mean rating of "expectancy to improve with BTA" was 50% in patients who responded to the intervention and 47% in patients who did not respond, indicating that "expectancy to improve with BTA" did not correlate with a placebo response to BTA ($P = .40$ by linear regression).

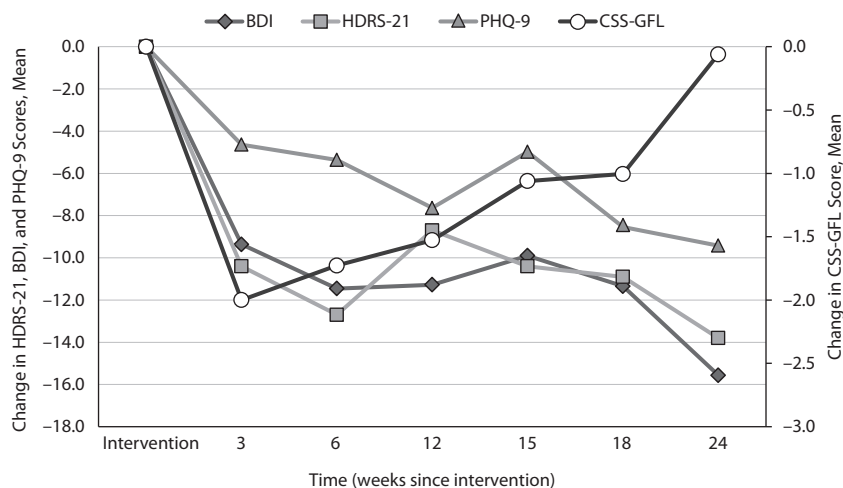
DISCUSSION

This study shows a statistically significant reduction in depressive symptoms in those who received botulinum toxin A versus placebo injections in the frown muscles. This is the third double-blind, placebo-controlled study to date that has shown efficacy in the treatment of MDD with botulinum toxin A, and it is the first to show continued improvement over a 24-week period, which is longer than any prior study has shown. This finding is particularly thought-provoking given that the neuromuscular effects of BTA last approximately 12–16 weeks. This indicates that the treatment of MDD is not wholly dependent on the paralytic effects of BTA. It does

not just keep symptoms at bay as long as the paralytic effect is active; it also leads to a sustainable improvement in MDD beyond the cosmetic effect.

There are several theories as to why botulinum toxin A injections may improve mood.¹⁷ One suggestion is that the mere cosmetic effect of the procedure makes people feel better about themselves. Although we cannot rule this out, we excluded patients who were cosmetically concerned about their frown lines. Moreover, the fact that the psychotropic effect outlasted the cosmetic effect strongly argues against the possibility that the latter may drive the former. In fact, in the trial by Wollmer et al,⁴ 1 patient disliked the esthetic results of botulinum toxin but still attained remission in MDD. A study¹⁸ in 2009 compared patients treated with botulinum toxin A in the glabellar region to those receiving cosmetic procedures such as glycolic peels, laser treatments, or Restylane. While both groups perceived improvement in attractiveness, those receiving BTA had a statistically significant improvement in depression and anxiety scores.

Another suggestion is that people who look happier are received more favorably by those around them, leading to

Figure 4. Change in BDI, HDRS-21, and PHQ-9 Scores in the BTA-First Group^a

^aAt week 24, the mean frown score (CSS-GFL) in the BTA-first group was back to baseline (baseline score = 2.7, week 24 score = 2.7), indicating that the BTA had worn off. Nonetheless, all 3 measurement scales showed continued reduction in major depressive disorder scores throughout the 24 weeks, indicating that mood continued to improve even though the BTA effects wore off. Abbreviations: BDI = Beck Depression Inventory, BTA = botulinum toxin A, HDRS-21 = 21-Item Hamilton Depression Rating Scale, PHQ-9 = Patient Health Questionnaire-9.

positive social feedback and in turn a happier mood for the subject. Heckmann et al⁷ showed that patients who received BTA in the frown muscles were perceived by others as happier when compared to themselves prior to the procedure.

A final suggestion is that the facial muscles send peripheral feedback to the brain. The simple act of frowning may lead to a reduction in neurotransmission, for instance, whereas smiling can up-regulate the system. Hennenlotter et al¹⁹ showed via functional magnetic resonance imaging that patients treated with BTA in the frown muscles had decreased activity in the left amygdala when mimicking angry facial expressions. The theory suggests that motor denervation of face muscles reduces afferent sensory information from the trigeminal tract to the brain stem, which then reduces coupled functioning between the brainstem and left amygdala. These findings are important as hyperactivity in the left amygdala has been linked to anxiety, depression, posttraumatic stress disorder, and heightened fear responses.²⁰ In one study,²¹ depressed patients showed exaggerated left amygdala activity when shown pictures of emotional faces, especially fearful faces. After antidepressant treatment, left amygdala hyperactivity normalized.

This theory is not in contradiction to the preceding theory, which focuses on facial mimicry during social interactions; rather, it may biologically explain what happens when we “read faces” during social interactions. In other words, reducing facial feedback to the brain via BTA injections may “normalize” the depressed person’s emotional response to other people’s facial cues.

As we often talk about depression as a vicious cycle of biological changes affecting psychosocial functioning and vice versa, BTA may be breaking this cycle by inhibiting a negative emotional circuitry *and* improving social interaction, which might explain why improvement in

mood lasts beyond the maximal cosmetic effects of the intervention.

The treatment of MDD using BTA is safe and effective and may decrease both direct costs (eg, medications, physician visits) and indirect costs (loss of work productivity) of this disease. Preliminary cost-effectiveness analysis has shown that BTA may be a *less* expensive intervention than psychotherapy or medications in specific patient populations.²² Given that a third of patients show some form of treatment resistance to antidepressants, this alternative treatment may be a viable option.

Our study design has several advantages versus previous BTA studies. Since the placebo group improved after they were switched to BTA, we can largely exclude that hidden variables (selection bias) between the groups may explain the different course. Hence, during the 12-week pre-run in the placebo group, there was no clinical change prior to BTA treatment, indicating a causal relation between the BTA treatment and improvement of mood.

A number of limitations should be emphasized. Although patients were blinded to the treatment intervention, patients may have become unblinded due to the obvious cosmetic effects of BTA. This may have contributed to the smaller than expected placebo response in our study, which can be up to 30% in antidepressant medication trials.²³ We are currently evaluating better placebo controls (ie, BTA in the occiput, often used in migraine prophylaxis, vs BTA in the forehead) for future studies.

In addition, HDRS scores showed slightly better responses than BDI scores, although this difference was not statistically significant. Some may be concerned that any face-to-face psychometric assessment would be susceptible to inadvertent unblinding of the rater. To allay these concerns in future studies, one may consider more complete facial coverings

(eg, full-faced masks) in lieu of surgical caps during HDRS administration. Another option would be to choose a psychometric rater who was unaware of the intervention being studied, to avoid the potential for unintended rater bias. Our study protocol did not include asking raters and participants to guess which intervention was received before unblinding. However, this would be a helpful means to evaluate blinding efficacy. Future studies should be designed this way. It is of note that in Finzi and Rosenthal's study,⁵ in which this question was asked beforehand, 52% of BTA-treated patients (n = 41) and 46% of placebo-treated patients (n = 44) guessed their arms correctly. Of the raters, 73% guessed treatment arms correctly. This indicates that blinding is possible for glabellar treatment with botulinum toxin and that unblinding is not a prerequisite for the mood-lifting effect.

HDRS scores were based on the HDRS-21, whereas most MDD studies are done using the HDRS-17, which takes into consideration only the first 17 questions of the HDRS-21. Patients with a milder form of MDD were therefore included. This is not necessarily a limitation, as this allowed us to determine the effects of treatment on less severe forms of the illness, which many of the population suffer from.

Three patients reported changes to their psychotropic medication regimen during the trial (Supplementary eTable 2). Patient 16 added aripiprazole at week 6, patient 17 stopped fluoxetine at week 3, and patient 24 increased mirtazapine at week 3. In all 3 cases, time point or direction (increase or reduction) of the change in medication as well as the subsequent response or nonresponse of MDD argue against a significant confounding role of medication changes in the outcome of the study.

Ninety-three percent of participants were female. This did not allow for statistical analysis based on gender (ie, whether males or females are more likely to respond to the intervention). The proportions of female and male subjects may also suggest that the study was more appealing to women, whether due to cultural reasons (BTA being more acceptable in the female population) or cosmetic reasons. Patients were asked about current medications, previous number of episodes, and length of past and present episodes (Supplementary eTable 2). They were not asked about current or past psychotherapy and/or past medication trials. Future studies should analyze these data to determine the level of "treatment resistance" within the study population and whether those with higher treatment resistance respond differently to the intervention.

The sample size of this study was small. Although statistically significant findings were possible, further studies should include a larger patient population.

Finally, the sample only included those with moderate to severe frown lines in the glabellar region. Although only 2 patients were not included because they were not able to produce an at least moderate frown line at maximum voluntary contraction of the corrugator muscles, it remains to be established how the baseline muscle activity influences treatment outcome. The recent randomized, controlled trial

by Finzi and Rosenthal⁵ indicates that the presence of frown lines is not a prerequisite for response of MDD to botulinum toxin treatment.

In summary, this trial adds to the growing body of evidence that botulinum toxin A in the glabellar region can treat MDD. Furthermore, the effects on mood last beyond the maximal cosmetic effects of BTA, suggesting that this intervention may break a cycle. Additional studies are warranted on larger sample sizes, with improved placebo controls, and should focus on demographic/disease findings that may predict a positive response to this treatment option. If future trials substantiate current study findings, botulinum toxin A can potentially be an additional or alternative novel treatment option for people suffering with depression.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), mirtazapine (Remeron and others), onabotulinumtoxinA (Botox).

Author affiliations: Departments of Psychiatry (Dr Magid), Dermatology (Dr Reichenberg), and Internal Medicine (Dr LaViolette), University of Texas Southwestern at Seton Family of Hospitals, Austin; Departments of Dermatology (Ms Poth) and Analytics (Dr Robertson), Seton Family of Hospitals, Austin, Texas; Department of Psychiatry, Social Psychiatry, and Psychotherapy, Hannover Medical School, Hannover, Germany (Dr Kruger); and Asklepios Clinic North, Ochsenzoll, Asklepios Campus Hamburg; Medical Faculty, Semmelweis University, Hamburg, Germany; and Psychiatric Clinics of the University of Basel, Basel, Switzerland (Dr Wollmer).

Potential conflicts of interest: Dr Magid received a research grant from the Brain and Behavior Institute, National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator award, to fund this study (grant number: 17648). The grant went to Seton Family of Hospitals, which then provided salary support to Dr Magid for this research. After completion and as a result of the study, Dr Magid became a consultant with Allergan in November 2012 to discuss study findings. Dr Reichenberg's spouse (Dr Magid) became a consultant with Allergan in November 2012. Dr Kruger received honoraria for talks from Servier and Lundbeck. These activities were unrelated to the study. In April 2012, after completion and as a result of his initial study on botulinum toxin for depression, he became a member of an advisory board with Allergan. Dr Wollmer has received financial support for research through his institution, Asklepios Hamburg, GmbH. Dr Wollmer received honoraria for talks from Merz, Novartis, and Eli Lilly. These activities were unrelated to the study. In April 2012, after completion and as a result of his initial study on botulinum toxin for depression, he became a consultant and a member of an advisory board with Allergan. Drs Reichenberg, Robertson, and LaViolette and Ms Poth have no financial disclosures.

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