



Treatment of depression with onabotulinumtoxinA: A randomized, double-blind, placebo controlled trial



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ABSTRACT

Converging lines of evidence suggest a role for facial expressions in the pathophysiology and treatment of mood disorders.

To determine the antidepressant effect of onabotulinumtoxinA (OBA) treatment of corrugator and procerus muscles in people with major depressive disorder, we conducted a double blind, randomized, placebo-controlled trial. In an outpatient clinical research center, eighty-five subjects with DSM-IV major depression were randomized to receive either OBA (29 units for females and 40 units for males) or saline injections into corrugator and procerus frown muscles (74 subjects were entered into the analysis). Subjects were rated at screening, and 3 and 6 weeks after OBA treatment. The primary outcome measure was the response rate, as defined by $\geq 50\%$ decrease in score on the Montgomery–Asberg Depression Rating Scale (MADRS). Response rates at 6 weeks from the date of injection were 52% and 15% in the OBA and placebo groups, respectively (Chi-Square (1) = 11.2, $p < 0.001$, Fisher $p < 0.001$). The secondary outcome measure of remission rate (MADRS score of 10 or less) was 27% with OBA and 7% with placebo (Chi-square (1) = 5.1, $p < 0.02$, Fisher $p < 0.03$). Six weeks after a single treatment, MADRS scores of subjects were reduced on average by 47% in those given OBA, and by 21% in those given placebo (Mann–Whitney U , $p < 0.0005$).

In conclusion, a single treatment with OBA to the corrugator and procerus muscles appears to induce a significant and sustained antidepressant effect in patients with major depression.

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1. Introduction

Major depressive disorder (MDD) is common, costly, and disabling (Greden, 2001; Nierenberg and DeCecco, 2001; Ustun et al., 2004). The World Health Organization has concluded that MDD is the greatest cause of disease burden in North America (Mathers and Loncar, 2006). The large scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study indicated that up to a third of depressed patients may not reach remission despite multiple drug trials. In addition, troubling side effects, such as decreased libido, anorgasmia, insomnia and nausea, are often reported with current antidepressants, and they are a major reason why patients discontinue treatment and subsequently relapse (Pollack and Rosenbaum, 1987; Remick et al., 1989; Baldessarini and Marsh, 1990; Clayton et al., 2006). Thus, there is a need for the

development of new effective and better-tolerated treatments for depression.

Charles Darwin (1872) and William James (1890) proposed a novel theory of emotion: that the facial expressions feed information back to the brain, thereby influencing emotions positively or negatively. Multiple experimenters have subsequently confirmed aspects of this so-called “facial feedback hypothesis” (Strack et al., 1988; Adelman and Zajonc, 1989; Larsen et al., 1992). For example, voluntary contraction of facial muscles into a smile or a frown can induce feelings of happiness or sadness respectively (Soussignan, 2002; Lewis, 2012), influence the emotional appraisal of events (Flack, 2006; Neal and Chartrand, 2011), and cause specific changes in the autonomic nervous system (Ekman et al., 1983).

Facial expressions of negative emotions such as fear, sadness and anger, all involve contraction of the corrugator muscles (Ekman, 2007). Multiple lines of evidence specifically implicate the corrugator muscles in depression. Thus, corrugator activity is greater and fails to decrease normally with happy imagery in depressed subjects (Schwartz et al., 1976). Normal subjects who

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viewed unhappy imagery had an increase in both depressed mood and corrugator activity, two variables that are highly correlated (Teasdale and Bancroft, 1977). Facial electromyography has been shown to be a predictor of treatment outcome in depression (Carney et al., 1981; Greden et al., 1985). Nevertheless, these correlations do not demonstrate a causal role for corrugator muscles in depression, which has not been researched until recently.

Botulinum toxin injection of muscles reversibly blocks acetylcholine release from neuronal axons into the synapse, inhibiting neuromuscular transmission (Burgen et al., 1949). OnabotulinumtoxinA (OBA) is one distinct subtype of botulinum toxin, and was the first botulinum toxin subtype to be FDA approved for the treatment of frown lines. OBA is now one of several botulinum toxins that are commercially available. Injection of OBA into the corrugator and procerus muscles (between the eyebrows) reversibly inhibits frowning for about three months (Carruthers and Carruthers, 1992) and provides a method for specifically and reversibly inhibiting frown facial expressions. Medical indications now outnumber cosmetic ones for the use of OBA. If the facial feedback hypothesis is correct and, specifically, if corrugator muscle activity is capable of propagating or enhancing sad or depressed feelings, we hypothesize that OBA injections into these muscles should have antidepressant properties.

In an open study of OBA injected into the frown muscles of ten depressed patients, Finzi and Wasserman, 2006, reported that eight out of ten went into remission after one treatment with OBA. Their study was limited, however, by its small sample size, lack of controls, and lack of blinding. Wollmer et al., 2012, in a small ($N = 30$) randomized, placebo controlled trial of OBA in depressed patients found a statistically significant (60%) response rate in OBA-treated subjects versus 13% in controls, but remission rates were not significantly different. They confined their study to patients who had both observable frowns and treatment-resistant depression. To evaluate the general therapeutic efficacy of OBA as a treatment for major depression, we have conducted a larger study with a broader clinical spectrum of patients. As in the study of Wollmer et al., we used a randomized double-blind design in which subjects received either OBA or placebo injections into the corrugator and procerus muscles as a treatment for major depressive disorder (MDD).

2. Methods

2.1. Patients

Subjects were recruited from advertisements placed in the local newspapers in the Washington, DC metropolitan area; from the Internet; and from local physicians. The study protocol and advertisements were approved by the Institutional Review Board, Quorum Review Seattle, Washington. Advertisements stated that we were recruiting depressed people for a double blind randomized clinical trial of OBA for depression. No mention was made as to any expected efficacy. Male or female outpatients aged 18–65 years, with a DSM-IV diagnosis of current MDD (APA, 1994), based on the MINI (Sheehan et al., 1998), administered by a trained research psychiatrist, were eligible to participate. Subjects received no monetary compensation for participation.

Subjects were required to have a MADRS (Montgomery and Asberg, 1979) score ≥ 26 at screening, and a Clinical Global Impression – Severity (CGI-S) (Guy, 1976) score ≥ 4 at screening. Women of childbearing potential were required to be on an acceptable form of birth control, and neither pregnant nor lactating. Subjects were only included if judged by the investigator to be able to comply with all the requirements of the study.

Subjects were excluded if they had another Axis I disorder as a principal diagnosis in the 6 months prior to screening, had a history

of substance abuse or dependency in the 2 months prior to screening, tested positive for illicit drugs on urine drug screen, endorsed MADRS item 10 (suicidal ideas) at a level of 5 or more or had attempted suicide in the six months prior to screening, were considered to be at a significant risk of committing homicide, or had an unstable medical condition. Patients were excluded from the study if they had been treated with OBA in the 12 months prior to screening. Subjects were also excluded if there had been a change in their medication or psychotherapy treatment regimen in the month preceding screening, or had been refractory to three or more adequate antidepressant treatments with methods that have different mechanisms of action.

All subjects provided written informed consent after complete description of the study and before their inclusion.

2.2. Study design

Eligible subjects were randomly assigned, at the time of screening, to receive either OBA (Botox Cosmetic, Allergan) or placebo (0.9%NaCl) injections. Injections were made using insulin syringes with 30 gauge needles at five specific injection points into the corrugator and procerus muscles, as previously described (Finzi and Wasserman, 2006). The 100 unit vial of OBA was reconstituted with 1.0 ml of 0.9% NaCl. The 0.29 ml total injection volume (29 units) for females was divided into five injections: 0.07 ml (7 units) in the procerus muscle, 0.06 ml (6 units) in the medial part of the corrugator muscle, and 0.05 ml (5 units) in the middle part of the corrugator muscle. The injection sites are standard for the treatment of frowning (Carruthers and Carruthers, 1992). Higher dosages of OBA were given to male (Supplemental Fig. 2) vs. female subjects (40 vs 29 units), as per usual clinical protocol, because of the greater average corrugator and procerus muscle mass generally found in men. The study lasted 6 weeks and patients were assessed psychiatrically at screening, and 3 and 6 weeks after injection with OBA or placebo.

Syringes prepared for OBA or placebo injection were optically indistinguishable from each other. Patients were randomly assigned to either group in blocks of 4. Syringes were prepared by a study nurse, under the direction of a physician who did not have contact with the patients. Patients and clinicians who had patient contact were blind to treatment allocation. A single clinician, who had no contact with psychiatrists, performed all injections. Injections were performed at a separate building location from

Table 1
Baseline characteristics of patient groups [Mean \pm standard deviation].

	OBA	Placebo
Age, Y	47.9 + 10.3	48.9 + 9.3
Sex, No. (%) F	32 (96)	37 (90)
Age at first depressive episode, mean	27.1 + 12.1	27.2 + 13.5
Duration of current episode, months, mean	19.5 + 18.9	34.6 + 44.5
Patients on current antidepressants, No. (%)	14 (42)	17 (41)
Current antidepressants, mean	0.5 + 0.7	0.5 + 0.6
Patients treated with antidepressants, No. (%)	31 (94)	32 (78)
Number of different antidepressants tried in lifetime, mean	2.2 + 1.2	1.8 + 1.3
Number of previous depressive episodes, mean	5.9 + 5.9	6.9 + 7.8
Patients with recurrent depression, no. (%)	30 (91)	33 (80)
Days between visit 1 and injection, mean	8.8 + 7.2	9.0 + 7.4
BDI-II, mean	30.4 + 9.7	28.8 + 8.1
MADRS, mean	31.6 + 3.8	31.2 + 3.6
CGI – S, mean	4.6 + 0.5	4.6 + 0.5
Baseline frown score	0.52 + 0.5	0.49 + 0.5

Abbreviations: BDI-II, Beck Depression Inventory II, MADRS, Montgomery-Asberg Depression Rating Scale, CGI-S, Clinical Global Impression – Scale. Data are presented as the mean \pm standard deviation.

ratings, which led to a mean time lag of 9 days between screening and injections (Table 1). No instructions were given to either subjects or to rating psychiatrists as to what physical changes in facial expression might occur. All patients were assessed photographically, at the time of injection and at the final patient visit, at rest and after maximal voluntary frowning (effortful). Photographs of subjects were rated blindly by two Board-certified dermatologists who did not know or treat any of the study subjects, according to a standardized four-point frown clinical severity score, with 0 signifying no frown, and 3 signifying maximal frown (Honeck et al., 2003). Frown data were categorized as follows: BL-R (initial visit, at rest), BL-E (initial visit, effortful), 6W-R (6 weeks, at rest), and 6WE (6 weeks, effortful). Only the injecting clinician photographed subjects and photographs were reviewed only after the clinical trial was completed. Subjects' medication and psychotherapy regimens remained unchanged throughout the course of the trial.

To help assess the blinding of the trial, after completion of the trial psychiatric raters were shown photographs of subjects taken during their initial and final visit. They were then asked to guess which treatment they thought subjects had received. Subjects were also asked, after trial completion, to state which treatment they thought they had received.

2.3. Outcome measures

All patients were assessed at three visits (screening, and 3- and 6-weeks post injection) with the MADRS and, with the CGI, by trained research psychiatrists, and completed the Beck Depression Inventory II (BDI) (Beck et al., 1961, 1996). The primary outcome measure was response to treatment, as defined as a 50% or greater decrease in MADRS from baseline. Secondary outcome measures included remission rate, as defined by a MADRS score of 10 or lower. Other secondary outcome measures included changes in BDI and CGI scores.

3. Statistical analysis

All subjects who met inclusion criteria and had at least one visit value in addition to a screening value were entered into the analysis. Chi square statistics and Fisher exact tests were used to assess response rates, and differences in response rates were assessed with the non-parametric Mann–Whitney *U* test. Descriptive statistics were obtained and tests for the statistical assumptions of normality and homogeneity of variance were made. These statistical assumptions were satisfied.

The time point data were analyzed using mixed model analysis of variance to assess the difference in MADRS scores between the two treatment groups over time. This method, designed for repeated measures, does not require complete data. Thus all subjects who satisfied inclusion conditions and had a least one visit value in addition to screening, were entered into the analysis. Any variation in group size reports (in the text or figures) are the result of varying numbers of data points per subject post screening. The mixed model ANOVA produces three statistical *F* tests. There is a test between the two treatment groups, OBA vs. placebo, a test of the time profile (baseline vs. week 3 vs. week 6) and the treatment group interaction over time. The Akaike Information criterion (AIC) was used in comparing model covariance structures. Statistical significance was set at the 0.05 level (two-tailed), with the Bonferroni correction applied as statistically necessary to correct for multiple comparisons where applicable. We analyzed CGI data by considering those who were judged to be much improved on the CGI scale (a score of 2 or less). To assess the relationship between frown variables and MADRS response to OBA, we analyzed the

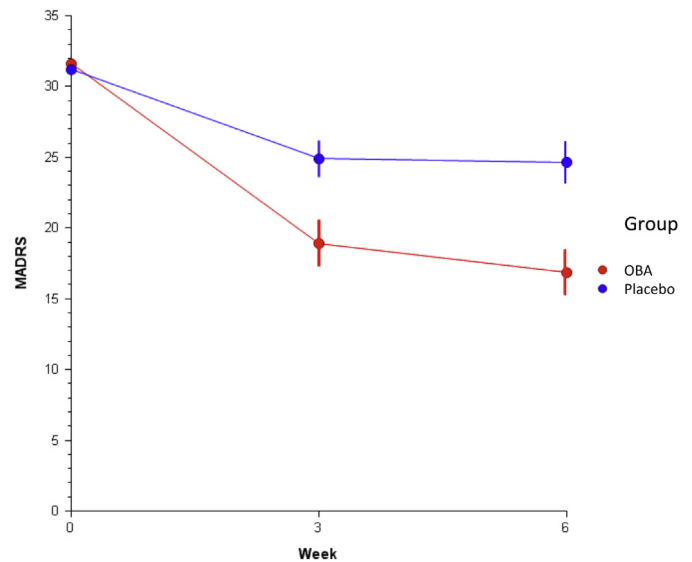


Fig. 1. MADRS scores over time (mean \pm standard error of the mean), in the OBA(33) and placebo(41) groups at 3 and 6 weeks versus baseline.

difference in scores between baseline (BL) and week 6(6W) for both effortful and resting frown by means of logistic regression.

We calculated the percentage of subjects who correctly guessed their treatment condition. Since the majority of subjects guessed their treatment condition correctly at the end of the study, we investigated whether the results of the study might have been biased by this potential breach of the blind. In order to do so we performed a two by three ANOVA on MADRS scores. The two groups were OBA and placebo, and the three categories of guessers were those who guessed correctly, those who guessed incorrectly, and those who did not guess at all.

4. Results

4.1. Patients

121 subjects were screened. 36 subjects were excluded as they did not meet inclusion/exclusion criterion. The 85 subjects who met DSM-IV criteria for MDD were randomized, 41 subjects were randomized to receive OBA and 44 to receive placebo. Eleven patients were excluded: 8 patients in the OBA group; 3 for withdrawal of consent, 1 for protocol violation (starting a new antidepressant), 4 were lost to follow-up; and 3 in the placebo group; 2 for protocol violations (starting new antidepressants), 1 was lost to follow-up. Thus there were 33 subjects in the OBA group and 41 in the placebo group. Of the 74 subjects used in the analysis, 69 had complete data; the other five subjects had incomplete data but were used in the mixed model ANOVA. Of these five subjects, four placebo subjects missed the second visit (week 3), and one OBA subject missed week 3. Fisher's exact test did not reveal any significant differences in dropout rate between the two arms of the study.

As expected by randomization, OBA and placebo groups did not differ significantly in any of the demographic or clinical baseline variables (Table 1). After screening, subjects received their injections a mean of 8.8(OBA) or 9.0(placebo) days later (N.S.). 91% of the OBA, and 80% of the placebo subjects suffered from recurrent depression. 42% of OBA, and 41% of placebo subjects were currently on antidepressants. The mean resting baseline frown score (scale 0–4) was low for both OBA and placebo groups, 0.52 and 0.49, respectively (N.S.) (Table 1). 3 patients complained of temporary

side effects: one placebo complained of vivid dreams and headaches, one placebo patient complained of headaches, and one OBA patient complained of headaches.

4.2. Efficacy

Response rates at 6 weeks from the date of injection were 52% and 15% in the OBA and placebo groups, respectively (Chi-Square (1) = 11.2, $p < 0.001$, Fisher $p < 0.001$). The remission rate at 6 weeks, as judged by MADRS, was significantly higher in the OBA group, 27% (9 of 33), than in the placebo group, 7% (3 of 41), (Chi-square (1) = 5.1, $p < 0.02$, Fisher $p < 0.03$). There was an 7.7 difference in the MADRS scores between the two treatment groups at week 6 (Table 3). The effect size, or Cohen's d , was 0.84.

The MADRS mixed model ANOVA interaction test which assesses the three time period MADRS response profile for the two treatment groups was $F(2,139) = 10.03$, $p < 0.0001$ (See Fig. 1). The difference between the OBA least square mean of 18.9 and the placebo least square mean of 24.9 at week 3 was statistically significant, $F(1,159) = 11.2$, $p < 0.001$. Likewise the difference at week 6, was also statistically significant, $F(1,160) = 19.4$, $p < 0.0001$ (See Fig. 1). Comparing the scores at the six-week visit versus baseline, there was a significant improvement in the OBA group compared to the placebo group; there was a 47.0% reduction in MADRS scores for OBA, versus a 20.6% reduction for placebo subjects, (Mann–Whitney U, $p < 0.0005$).

Secondary measures of mood and clinical status with other measures corroborated the results seen in the MADRS analyses. For the BDI, a significant mixed model interaction was observed between the drug and depression scores over time (ANOVA, $F(2,139) = 11.3$, $p < 0.0001$). At week 6, the difference between the two groups viz 6.8 was statistically significant, $F(1,150) = 11.4$, $p < 0.001$. Analysis of the CGI data at 3 weeks showed that for the OBA subjects, 16 of 32 were much improved vs 9 of 38 placebo subjects, Fisher p value of 0.03. At the 6 week visit, 21 of 33 OBA subjects vs 8 of 41 placebo subjects were much improved, Fisher p value of 0.0001.

4.3. Frown analysis

Logistic regression of the changes in frown scores from baseline (BL) to 6W for resting(R) and effortful(E) frown scores was used to assess the association between these changes and OBA response profile (i.e. responders versus non-responders). Frown score differences were associated with 57% of the non-responders (8 of 14) and 69% of the responders (11 of 16) (See Table 2). The overall total association (19 of 30; 63%) as compared to the benchmark 50% association, has a statistical difference via the binomial test with a P value of 0.07 (trending towards significance). In other words, there was a trend towards changes in frown scores predicting improvement following OBA treatment.

Table 2
Logistic regression means and classification matrices using frown difference scores to predict MADRS responders.

Classification OBA subjects			
Actual	Estimated		Total
	Non-responder	Responder	
Non responder	8	6	14
Responder	5	11	16
Total	13	17	30

Percent correctly classified = 63.3%

8/14 Non-Responders were correctly classified. 11/16 Responders were correctly classified. Thus 19/30 (63.3%) were correctly classified.

Table 3
MADRS scores over time.

	MADRS [mean (SD)]		
	Week 0	Week 3	Week 6
OBA	31.6 (3.9)	18.9 (9.3)	16.9 (9.2)
Placebo	31.2 (3.7)	24.9 (7.9)	24.6 (9.2)

The difference between the OBA mean of 18.9 (9.3) and the placebo mean of 24.9 (7.9) at week 3 was statistically significant, via the Bonferroni corrected individual comparison hypothesis, $F(1,159) = 11.2$, $p < 0.001$. Likewise the difference at week 6, Botox mean 16.9 (9.2), placebo mean 24.6 (9.2) was also statistically significant, $F(1,160) = 19.4$, $p < 0.0001$ (See Fig. 1) and Table 3. Comparing the scores at the six-week visit versus baseline, there was a significant improvement in the OBA group compared to the placebo group; there was a 47.0% reduction in MADRS scores for OBA, versus a 20.6% reduction for placebo subjects, (Mann–Whitney U, $p < 0.0005$).

As expected (Carruthers and Carruthers, 1992), the OBA group had a decreased ability to form an effortful frown at 6 weeks. The mean effortful frown at baseline, 1.9, decreased to 0.43 at 6 weeks, in the OBA group. Non-parametric Wilcoxon Signed Rank Test, $p < 0.0001$.

After completion of the clinical trial psychiatric evaluators correctly guessed 73% of group allocations. Among those subjects who received OBA, 52% correctly guessed treatment, 33% incorrectly guessed, and 15% made no guess. Among those who received placebo, 46% guessed correctly, 39% incorrectly, and 15% made no guess. To assess whether unblinding might have influenced the outcome of different groups (those who guessed correctly, incorrectly or did not guess at all), we assessed MADRS scores in a two-treatment by three-guess categories ANOVA. In the two-by-three interaction F -test, F was 2.68 ($P = 0.36$). While the overall MADRS outcome for the two treatments was preserved, the pattern over the three guess categories was statistically flat within both the OBA and placebo groups. In other words, there was no difference in the change in MADRS between those who guessed their condition correctly and those who did not.

5. Discussion

The present study supports earlier research suggesting that OBA injected into the corrugator and procerus muscles can have antidepressant effects in people with major depressive disorder (Finzi and Wasserman, 2006; Wollmer et al., 2012; Finzi, 2013). The present study takes these findings further in a few ways: First, it is the largest controlled study to date; second, we found a significant increase in remissions following OBA vs. placebo; third, the patient population was not selected for treatment resistance (less than half were on antidepressants).

To the extent that our study covers the same territory as that of Wollmer et al. (2012), our results are similar. Specifically, they observed a 47.1% vs. 9.2% reduction in Hamilton D 17 scores, in the OBA versus placebo groups whereas we observed a 47.3% vs. 20.6% reduction in MADRS scores in the corresponding groups. Similarly, Wollmer et al., 2012, reported a 60.0% vs. 13.3% response in the OBA vs placebo group, as measured by Hamilton D 17 scores, while we observed, as measured by MADRS, a 52% vs 15% response.

In the current findings, there was some suggestion of differential efficacy between OBA as a monotherapy (remission rate of 21%) versus OBA as an augmentation of ongoing antidepressant treatment (remission rate of 36%). The higher remission rate when OBA is used as an augmentation treatment vs. monotherapy may suggest that the treatment is more effective in the latter context. This point will need to be confirmed in larger studies.

In contrast to the earlier study, our trial did not require subjects to have any specific facial characteristics, such as the ability to form

a frown or the presence of a resting frown, in order to be included. An observable frown at rest was not found necessary for improvement in major depression with OBA. In analyzing the relationship between frown data and response, we found that 5 of 13 patients who had no discernible frown at rest at their baseline visit nevertheless experienced full remission after receiving OBA.

Although there was no significant correlation between change in frown scores and change in mood, there was a trend in that direction ($P = 0.07$). If this trend is borne out in subsequent studies or proves significant in larger N studies, that would support the facial feedback hypothesis. We do need to acknowledge the limitations of snapshots in assessing ever-changing facial expressions that might influence mood.

Psychiatrists who saw photographs of the subjects taken before and after the study were able to guess correctly in about three quarters of cases which treatment condition had been given. However, this does not necessarily mean that the blind was vitiated in the actual clinical situation. Guessing the treatment condition of subjects from snapshots presented to clinicians side by side is a poor reflection of the realities of a clinic situation in which raters saw patients three weeks apart interspersed with many other patients in a busy clinic setting. In the latter scenario, it seems highly unlikely that minor frown changes (the change in baseline frown scores across the study was not statistically significant) would be discerned. Patients, reviewing their own experiences in the study, reached similar conclusions to those reached by the raters. Although this could suggest a breach of the blind, it is also possible that patients who felt happier might have been more likely to guess the active condition correctly based on their mood improvement. Even if the blind were breached, however, the question arises as to whether that was of consequence to treatment outcome. Results of the ANOVA that examined the relationship between direction of guessing versus MADRS response yielded no significant findings. This could be construed to suggest that guessing correctly does not in and of itself influence treatment outcome. This question will need to be clarified by further studies and we have provided specific details of our protocol to facilitate replication by others.

It is worth noting that unblinding has been a common problem in many so-called double-blind clinical trials, where several investigators have reported that at least three-quarters of participants correctly guessed their treatment assignment after the trial was over (Rabkin et al., 1986; Bang et al., 2004; Perlis et al., 2010).

The placebo response in the present study was lower than has been reported for many depression trials. Possible explanations for this are: (1) We offered no reimbursement to study subjects, which might have helped in the selection of appropriate subjects; (2) Placebo response has been shown to correlate with the number of psychiatric assessment visits (Rutherford et al., 2009), and our study had only two follow-up visits compared to the usual four to six; and (3) It is of course possible that unblinding might have weakened the placebo effect notwithstanding the absence of an association between guess status and MADRS responses.

If OBA proves to be an effective treatment for depression, it would be particularly useful insofar as it should have no adverse interactions with concurrent medications, since OBA injected as per the current protocol is not absorbed systemically. Since the action of OBA in preventing muscle contraction is temporary, lasting on average about three months, we would anticipate that patients may need to receive repeated treatments in order to maintain the improvement.

There are several possible mechanisms by which OBA may help alleviate depression. First, frowning may affect the way people feel about themselves when they look in the mirror and the way others respond to them. OBA, by reducing the level of frowning may cause others to respond in a way that influences mood favorably. Happier

facial expressions may influence mood by facilitating more positive social interactions with others (Heckmann et al., 2003). Finally, in line with the facial feedback hypothesis that inspired this study, frowning may in and of itself be depressogenic. Thus, reduction in frowning may be in and of itself therapeutic.

We suggest that the brain continuously monitors the relative valence of facial expressions and that mood responds accordingly. We term this *emotional proprioception* (Finzi, 2013), and suggest that it represents an important pathway for the brains' evaluation of emotional states. According to this model, the brain continuously assesses the extent of facial muscle contraction and muscle tension by proprioception. One can view the state of corrugator muscle tension as part of a neuronal circuit involving the brainstem, with motor input from the facial nerve and sensory afferents from facial and trigeminal cranial nerves. OBA treatment of the corrugator muscle, would interrupt the normal circuitry, reduce distress signals to the brain and thereby influence mood in a favorable way. This model is also supported by work showing that OBA treatment of the frown muscles modifies emotional perception (Niedenthal et al., 2009; Neal and Chartrand, 2011) and amygdala activation (Hennenlotter et al., 2009).

We acknowledge the following limitations of our study: (1) Too few men were included for us to draw conclusions about the value of OBA in men with depression; (2) We followed subjects for only six weeks; and (3) There was an average delay of 9 days after screening before subjects received their injections. It is possible that depression levels changed in the 9 days between screening and injection. However, there was no difference in the duration of the delay between those receiving OBA vs placebo, and no apparent reason why the delay in being injected should have favored one condition over the other. Future studies should obtain the baseline rating, randomize, and begin treatment all on the same day.

Potential advantages of OBA treatment for MDD include: (1) An excellent safety record for OBA injections into the corrugator and procerus muscles (Brin et al., 2009); (2) The long-lasting effect of a single dose should help compliance, which can be a problem in the treatment of depression (Serna et al., 2010); (3) Because of expected long treatment intervals, it is reasonably cost-effective (Beer, 2010); and (4) There are few drug interactions with locally injected OBA.

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Conflict of interest

Eric Finzi has been awarded a patent for the treatment of depression with botulinum toxin. The Chevy Chase Cosmetic Center, which provided funding for this study, is solely owned by Eric Finzi. Norman Rosenthal has no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.jpsychires.2013.11.006>

References

- American Psychiatric Association. The diagnostic and statistical manual of mental disorders, DSM IV; 1994.
- Adelmann PK, Zajonc RB. Facial efference and the experience of emotion. *Annu Rev Psychol* 1989;40:249–80.
- Baldessarini RJ, Marsh E. Fluoxetine and side effects. *Arch Gen Psychiatry* 1990;47(2):191–2.
- Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;25:143–56.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
- Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory*. 2nd ed. San Antonio, Tex: Psychological Corp; 1996.
- Beer K. Cost effectiveness of botulinum toxins for the treatment of depression: preliminary observations. *J Drugs Dermatol* 2010;9:27–30.
- Brin MF, Boodhoo TI, Pogoda JM, James LM, Demos G, Terashima Y, et al. Safety and tolerability of OBA in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. *J Am Acad Dermatol* 2009;61:961–70.
- Burgen ASV, Dickens F, Zatman LJ. The action of botulinum toxin on the neuromuscular junction. *J Physiol* 1949;109:10–24.
- Carney RM, Hong BA, O'Connell MF, Amano H. Facial electromyography as a predictor of treatment outcome in depression. *Br J Psychiatry* 1981;138:485–9.
- Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *Journal of Dermatologic Surgery & Oncology* 1992;18:17–21.
- Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. *J Affect Disord* 2006;91(1):27–32.
- Darwin CR. *The expression of emotion in man and animals*. London: Murray; 1872.
- Ekman P. *Emotions revealed: recognizing faces and feelings to improve communication*. New York: Owl Books; 2007.
- Ekman P, Levenson PW, Friesen WV. Autonomic nervous system activity distinguishes among emotions. *Science* 1983;4616:1208–10.
- Finzi E, Wasserman E. Treatment of depression with botulinum toxin A: a case series. *Dermatol Surg* 2006;32:645–9.
- Finzi E. *The face of emotion: how Botox affects moods and relationships*. New York: Palgrave-Macmillan; 2013.
- Flack Jr W. Peripheral feedback effects of facial expressions, bodily postures, and vocal expressions on emotional feelings. *Cognition and Emotion* 2006;20:177–95.
- Greden JF. The burden of disease for treatment-resistant depression. *J Clin Psychiatry* 2001;62(Suppl. 16):26–31.
- Greden JF, Genero N, Price HL. Agitation-increased electromyogram activity in the corrugator muscle region: a possible explanation of the "Omega sign"? *Am J Psychiatry* 1985;142:348–51.
- Guy W. *The clinical global severity and impression scales*. In: ECDEU assessment manual for psychopharmacology. Washington(DC): Superintendent of Documents, US Government Printing Office, US Department of Health, Education and Welfare Publication; 1976. pp. 218–22. No. 76-338.
- Heckmann M, Teichmann B, Schröder U, Sprengelmeyer R, Ceballos-Baumann AO. Pharmacologic denervation of frown muscles enhances baseline expression of happiness and decreases baseline expression of anger, sadness, and fear. *J Am Acad Dermatol* 2003;49:213–6.
- Hennenlotter A, Dresel C, Castrop F, Ceballos-Baumann AO, Wohlshläger AM, Haslinger B. The link between facial feedback and neural activity within central circuitries of emotion-new insights from botulinum toxin-induced denervation of frown muscles. *Cereb Cortex* 2009;19:537–42.
- Honeck P, Weiss C, Sterry W, Rzany B, Gladys study group. Reproducibility of a four-point clinical severity score for glabellar frown lines. *Br J Dermatol* 2003;10:149–306.
- James W. *The principles of psychology*. New York: Holt; 1890.
- Larsen RJ, Kasimatis M, Frey K. Facilitating the furrowed brow: an unobtrusive test of the facial feedback hypothesis applied to unpleasant affect. *Cognition and Emotion* 1992;6:321–38.
- Lewis MB. Exploring the positive and negative implications of facial feedback. *Emotion* 2012;12:852–9.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3(11):e442.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
- Neal DT, Chartrand TL. Embodied emotion perception: amplifying and dampening facial feedback modulates emotion perception accuracy. *Social Psychological and Personality Science* 2011;2(6):673–8.
- Niedenthal PM, Winkielman P, Mondillon L, Vermeulen N. Embodiment of emotion concepts. *J Pers Soc Psychol* 2009;96(6):1120–36.
- Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry* 2001;62(Suppl. 16):5–9.
- Perlis RH, Ostacher M, Fava M, Nierenberg AA, Sachs GS, Rosenbaum JF. Assuring that double-blind is blind. *Am J Psychiatry* 2010;167:250–2.
- Pollack MH, Rosenbaum JF. Management of antidepressant-induced side effects: a practical guide for the clinician. *J Clin Psychiatry* 1987;48(1):3–8.
- Rabkin JG, Markowitz JS, Stewart J, McGrath P, Harrison W, Quitkin FM, et al. How blind is blind? assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. *Psychiatry Res* 1986;19:75–86.
- Remick RA, Froese C, Keller FD. Common side effects associated with monoamine oxidase inhibitors. *Progress in Neuropsychopharmacology & Biological Psychiatry* 1989;13(3–4):497–504.
- Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome? The effects of placebo control and treatment duration in antidepressant trials. *Psychother Psychosom* 2009;78:172–81.
- Schwartz GE, Fair PL, Salt P, Mandel MR, Klerman GL. Facial muscle patterning to affective imagery in depressed and nondepressed subjects. *Science* 1976;192:489–91.
- Serna MC, Cruz I, Real J, Gascó E, Galván L. Duration and adherence of antidepressant treatment (2003–2007) based on prescription database. *Eur Psychiatry* 2010;25:206–13.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl. 20):22–33. quiz 34–57.
- Soussignan R. Duchenne smile, emotional experience, and autonomic reactivity: a test of the facial feedback hypothesis. *Emotion* 2002;2:52–74.
- Strack F, Martin LL, Stepper S. Inhibiting and facilitating conditions of the human smile: a nonobtrusive test of the facial feedback hypothesis. *J Pers Soc Psychol* 1988;54(5):768–77.
- Teasdale J, Bancroft J. Manipulation of thought content as a determinant of mood and corrugator EMG activity in depressed patients. *J Abnorm Psychol* 1977;86:235–41.
- Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br J Psychiatry* 2004;184:386–92.
- Wollmer MA, de Boer C, Kalak N, Beck J, Götz T, Schmidt T, et al. Facing depression with botulinum toxin: a randomized controlled trial. *J Psychiatr Res* 2012;46(5):574–81.