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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.

Trial Registration: clinicaltrials.gov Identifier: NCT01556971.

1. Introduction

Major depressive disorder (MDD) is common, costly, and disabling (Greden, 2001; Nierenberg and DeCecco, 2001; Ustün 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; Adelmann 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 $\geq$ 26 at screening, and a Clinical Global Impression – Severity (CGI-S) (Guy, 1976) score $\geq$ 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 ± 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 ± standard deviation.