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Botulinum toxin therapy of bipolar depression: A case series

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A B S T R A C T

We and others have recently found that botulinum toxin injected into the brow muscles has significant antidepressant properties as compared to placebo in randomized controlled trials in patients with major depressive disorder. However, data for the treatment of bipolar depression with botulinum toxin is lacking. We report here six patients with bipolar disorder experiencing moderate to severe depressive episodes who were treated on a compassionate basis with botulinum toxin given their persistent depressive symptoms and adverse side effects from medications. Four of six patients with bipolar depression experienced a remission following treatment with botulinum toxin, and the other two patients experienced a reduction of depressive symptoms. When the effect of botulinum toxin on the frown muscles began to wear off, depressive symptoms returned and retreatment with botulinum toxin provided successful relief of depressive symptoms again.

1. Introduction

Bipolar disorder is a major cause of disability, affecting an estimated 60 million people worldwide (Merikangas et al., 2011). It is divided into bipolar I (at least one manic episode with or without depression) and bipolar II (at least one hypomanic episode and one depressive episode). Depressive episodes are frequent and can be difficult to treat (Frye et al., 2014).

Recently, botulinum toxin (BT) of the glabellar region has been studied as an antidepressant (Finzi and Wasserman, 2006; Wollmer et al., 2012; Finzi and Rosenthal, 2014; Magid et al., 2014; Zamanian et al., 2017; Magid et al., 2015; Parsaik et al., 2016). However, all patients suffered from unipolar depression. Successful treatment of bipolar depression with BT has not been reported.

This report is the first to show sustained remission of depressive symptoms in four of six patients with bipolar depression treated with BT injections into their frown muscles. In addition, the two patients who did not go into remission experienced a reduction of depressive symptoms.

2. Methods

Consecutive female (1) and male (5) patients aged 39 to 87, with a diagnosis of bipolar depression, received BT treatment with 29–46 units of onabotulinumtoxinA at 5 to 7 injection points in the glabellar region between January 2015 and August 2017 at Hannover Medical School (N = 1), Asklenios Clinic North Ochsenzoll (N = 2), and at George Washington University School of Medicine (N = 3) (Finzi and Rosenthal, 2014). In all six patients, previous and current pharmacologic and psychotherapeutic treatments had been insufficient or were discontinued secondary to side effects. The different scales used to assess the severity of depression were the Beck Depression Inventory (BDI I and II), MADRS(Montgomery Asberg Depression Rating Scale (MADRS) and QIDS SR-16 (Quick Inventory of Depressive Symptoms (Self-Report).

3. Results

Four of six patients had a strong response and went into remission (Fig. 1, Table 1). The remaining two patients also improved, with one able to avoid a second round of ECT.

In most instances, the antidepressant effects of BT began to wear off after about 3 months. However, occasionally the antidepressant effect began to wear off earlier (for example, once at 5 weeks for case 4, and once at 60 days for case 5). Four of the six patients have continued to repeat BT treatments and have maintained their improvement.

To assess the change in depression severity after BT therapy in all six patients, we calculated depression scores into relation with the

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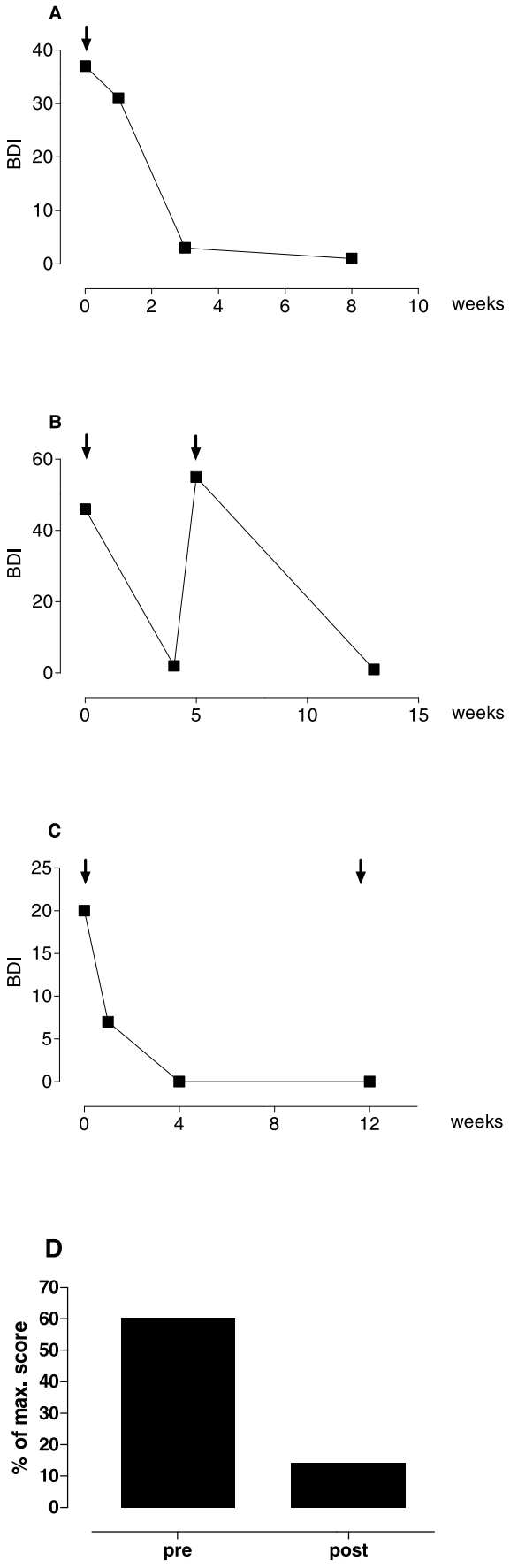

Fig. 1. Improvement of Bipolar Depressive Symptoms Following Glabellar Botulinum Toxin Treatment[a]

[a]↓ = time point of BT injection. (A) This 49-year-old (case 1) with a 3 year depressive episode that was treatment resistant began to improve within 1 week after injection and went into remission within 4 weeks. Subsequently he discontinued all other medications. (B) After discontinuing Lithium secondary to kidney side effects, the 55-year-old patient (case 4) received BT injection. Within 4 weeks he experienced almost a complete remission in depressive symptoms as measured by the Beck Depression Inventory II. However, 10 days later his frown began to be active again, and his depression returned. He was retreated with a greater dose (48 units), which replicated treatment success. (C) This 51-year-old (case 2) began improvement one week after injection. One month after receiving BT his BDI-II was 0. He has been retreated every 3 months with BT, and his remission has been maintained for 18 months. (D) *Relative Depression score Change*. To visualize the change in depression severity after BT therapy across all six patients described in this case series, we scaled depression scores relative to the maximum scores of the respective scales (QIDS SR16, 27, n = 1; BDI II, 63, n = 4, MADRS, 60, n = 1) and compared the percentaged values between the beginning (**pre**) and the end (**post**) of the observation period according to Table 1.

Table 1
Depression scores before and after Botulinum Toxin treatment.

Case	Bipolar Type	Scale	Baseline Score	Score after most recent BT tx
1	I	BDI	37	1
2	I	BDI II	20	0
3	I	BDI	32	8
4	I	BDI II	46	2
5	II	QIDS SR16	26	12
6	I	MADRS	35	19

maximum scores of the respective scales (QIDS SR16, 27, n = 1; BDI II, 63, n = 3, MADRS, 60, n = 2) and compared the percentaged values between the beginning (**pre**) and the end (**post**) of the observation period according to Table 1. Depression severity dropped significantly after BT therapy (Fig. 1D).

4. Discussion

This is the first report of successful BT therapy of bipolar depression in six patients.

Several lines of reasoning suggest BT played a role in patient improvement.

First, depressive episodes of all patients were moderate to severe and failed to respond to conventional pharmacologic and psychotherapeutic therapy. Second, patients had suffered from depressive symptoms for an extended time. Third, when the BT effect on the frown muscles began to wear off depressive symptoms returned and retreatment with BT provided successful relief of depressive symptoms again.

The interval between BT injection and the return of depressive symptoms (about 3 months), corresponds well to the documented length of BT inhibition of the glabellar frown (Giordano et al., 2017). BT has been used for over 20 years in millions of people for a wide variety of medical and cosmetic indications, with an excellent safety profile (Giordano et al., 2017).

How BT therapy might exert its antidepressant effect is unknown. The most plausible explanation involves underlying neuroanatomical circuitry in the emotional proprioceptive pathway (Finzi, 2013; Finzi and Rosenthal, 2016). Frowning influences proprioceptive fibers of the optic branch of the trigeminal nerve, which, in turn sends a signal to the amygdala and prefrontal cortex (Matsuo et al., 2015). BT treatment of normal subjects results in decreased amygdala activity (Hennenlotter et al., 2009; Kim et al., 2014). Thus BT may, in part, affect depressive symptoms through the amygdala (Heller et al., 2014).

This study has some inherent limitations. The data presented are only observational. There were no controls; patient improvement could

have been influenced by expectation and placebo bias. These results await confirmation in a controlled trial.

Source of funding

No funding was received for this work.

Conflicts of interest

Dr. Finzi is a named inventor on patents to treat depression with botulinum toxin. Dr. Kels, Shaver and Eberlein and J. Axelowitz have no conflicts to report.

Dr. Kruger has received honoraria for talks and/or advisory board activities from Allergan, Lilly, Lundbeck, Otsuka, Schwabe, Servier, and Trommsdorf. Dr. Wollmer has received a honorarium for a talk for Ipsen and a grant from the Asklepios Hamburg GmbH Forschungsförderung. Drs. Kruger and Wollmer were members of an advisory board of Allergan.

References

Finzi, E., 2013 September. Antidepressant effects of botulinum toxin A: scientific rationale. J. Psychiatry Neurosci. 38 (5), 29.

Finzi, E., Rosenthal, N.E., 2014. Treatment of depression with onabotulinumtoxinA: a randomized,double-blind, placebo controlled trial. J. Psychiatr. Res. 52, 1–6.

Finzi, E., Rosenthal, N.E., 2016. Emotional proprioception: treatment of depression with afferent facial feedback. J. Psychiatr. Res. 80, 93–96.

Finzi, E., Wasserman, E., 2006. Treatment of depression with botulinum toxin a: a case series. Dermatol. Surg. 32, 645–650.

Frye, M.A., Prieto, M.L., Bobo, W.V., Kung, S., Veldic, M., Alarcon, R.D., Moore, K.M., Choi, D.S., Biernacka, J.M., Tye, S.J., 2014. Current landscape, unmet needs, and future directions for treatment of bipolar depression. J. Affect. Disord. 169 (Suppl. 1), S17–S23.

Giordano, C.N., Matarasso, S.L., Ozog, D.M., 2017. Injectable and topical neurotoxins in dermatology: basic science, anatomy, and therapeutic agents. J. Am. Acad. Dermatol. 76 (6), 1013–1024.

Heller, A.S., Lapate, R.C., Mayer, K.E., Davidson, R.J., 2014 Sep. The face of negative affect: trial-by-trial corrugator responses to negative pictures are positively associated with amygdala and negatively associated with ventromedial prefrontal cortex activity. J. Cognit. Neurosci. 26 (9), 2102–2110.

Hennenlotter, A., Dresel, C., Castrop, F., Ceballos-Baumann, A.O., Wohlschla€ger, A.M., Haslinger, B., 2009. The link between facial feedback and neural activity within central circuitries of emotion-new insights from botulinum toxin-induced denervation of frown muscles. Cerebr. Cortex 19, 537–542.

Kim, M.J., Neta, M., Davis, F.C., Ruberry, E.J., et al., 2014. Botulinum toxin-induced facial muscle paralysis affects amygdala responses to the perception of emotional expressions: preliminary findings from an A-B-A design. Biol. Mood Anxiety Disord. 4, 11.

Magid, M., Finzi, E., Kruger, T.H., Robertson, H.T., Keeling, B.H., Jung, S., Reichenberg, J.S., Rosenthal, N.E., Wollmer, M.A., 2015. Treating depression with botulinum toxin: a pooled analysis of randomized controlled trials. Pharmacopsychiatry 48 (6), 205–210.

Magid, M., Reichenberg, J.S., Poth, P.E., Robertson, H.T., LaViolette, A.K., Kruger, T.H., Wollmer, M.A., 2014. Treatment of major depressive disorder using botulinum toxin A: a 24-week randomized, double-blind, placebo-controlled study. J. Clin. Psychiatr. 75 (8), 837–844.

Matsuo, K., Ban, R., Hama, Y., Yuzuriha, S., 2015. Eyelid opening with trigeminal proprioceptive activation regulates a brainstem arousal mechanism. PLoS One 10 (8), e0134659.

Merikangas, K.R., Jin, R., He, J., Kessler, R.C., et al., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatr. 68 (3), 241–251.

Parsaik, A., Mascarenhas, S., Hashmi, A., et al., 2016. Role of botulinum toxin in depression. J. Psychiatr. Pract. 22 (2), 99–110.

Wollmer, M.A., de Boer, C., Kalak, N., Beck, J., Götz, T., Schmidt, T., et al., 2012. Facing depression with botulinum toxin: a randomized controlled trial. J. Psychiatr. Res. 46 (5), 574–581.

Zamanian, A., Jolfaei, A.G., Mehran, G., Azizian, Z., 2017. Efficacy of botox versus placebo for treatment of patients with major depression. Iran. J. Public Health 46 (7), 982–984.