Treating Depression with Botulinum Toxin: A Pooled Analysis of Randomized Controlled Trials

Introduction

Affecting more than 350 million individuals worldwide, depression is one of the greatest medical challenges of our time [1]. There are several effective psychotherapeutic, pharmacological, and somatic options for the treatment of depression, but still a considerable proportion of patients do not attain remission. Thus, there is a need to develop further methods of treatment.

The injection of botulinum toxin A (BTA) into the glabellar frown muscles of the forehead is an emerging novel approach in the treatment of depression: after an auspicious first case series, we recently conducted 3 independent randomized, controlled trials and consistently showed that a single glabellar treatment with BTA reduces symptoms of depression [2–5].

The treatment of glabellar frown lines for cosmetic reasons is an approved indication for BTA and is the most frequent intervention in aesthetic medicine [6]. Several studies have shown that this particular cosmetic treatment may exert psychological effects, which may contribute to its popularity [7–11]. In one study, BTA in the forehead was compared to other cosmetic treatments (i.e., BTA in other regions besides the forehead, Restylane, glycolic peels, and laser treatments) [9]. Those who received BTA in the forehead reported feeling less depressed, irritable, and anxious, as compared to the control group, despite both groups feeling “equally attractive” after the intervention. This indicates that BTA in the forehead has positive mood effects above and beyond the euphoria that one gets from improved appearance.

The mood-lifting effect of such a BTA treatment may be explained by the facial feedback hypothesis, which dates back to Charles Darwin and William James in the 19th century and has been substantiated in several experimental studies [12–14]. In theory, contraction of facial muscles sends a message to the emotional centers of the brain. Smiling can reinforce and maintain feelings of well-being, whereas frowning can lead to the opposite. We assume that the paralysis of the injected frown muscles interrupts a proprioceptive feedback loop from the face to the emotional brain, therefore reducing the ability to feel negative emotions [15–17]. In depression, there is a...
relative over-activity of frown muscles, which has been confirmed electrophysiologicaly, and whose elimination by BTA treatment could potentially soften the correspondent experience of fear, anger, and sadness [18, 19].

In order to further corroborate the evidence of a role for BTA in the treatment of depression, we conducted a conjoint analysis of pooled individual patient data from our 3 trials.

Methods

Studies

The 3 studies from which we pooled data were all investigator-initiated, randomized controlled trials that were carried out free of any commercial entity. The studies were initiated and conducted independently from each other, however MM et al. adapted the protocol of MAW et al. to facilitate their comparison. All studies were approved by the responsible regulatory authorities and ethic committees. All patients gave written informed consent to take part in the study. All studies are registered at ClinicalTrials.gov (NCT00934687, NCT01556971, NCT01392963). Detailed descriptions of the studies are provided in the respective original articles [3–5] and key points are highlighted in Supplemental Table 1.

In summary all studies included female and male adult patients suffering from unipolar major depressive disorder (DSM-IV). The inclusion criteria, scales, and data pooling for our conjoint analysis are included baseline variables and outcome measures that were shared by all 3 studies (Table 1). These variables were markedly similar throughout all 3 studies, allowing for pooling. Of note the BDI score was 4 points higher (p=0.009) in the study by EF and NER than in the other studies; the CSS-GFL was lower (p<0.0001) in this study than in the other studies (Supplemental Table 1). In the pooled sample (n=134), the BTA (n=59) and the placebo (n=75) did not differ in any of the shared baseline variables, including BDI score and CSS-GFL scores (Table 1). These 2 variables, along with other baseline variables, were accounted for using random effects models (see statistics below), presenting evidence against confounding.

In MAW et al. and MM et al. studies, patients needed to produce “moderate to severe frown lines” in order to be included. This was not an inclusion criteria in EF’s study. Of note, very few people (n=5) were excluded on this basis, as most people, except for very young adults, are able to produce at least moderate frown lines at maximum frowning.

All 3 trials studied BTA as an adjunctive treatment to antidepressant medications and particularly the study by EF also BTA as a change in the symptoms of depression 6 weeks thereafter. By means of a systematic literature search in PubMed, Web of Science, the Cochrane Controlled Trials Register using “[depression OR major depressive disorder] AND [botulinum toxin A OR botulinum toxin type-A OR Botox]” as key words, and Medical Subject Headings (MeSH) no other comparable studies (i.e., randomized placebo-controlled study of BTA as a treatment for depression) have been published up to December 2014.

Inclusion criteria, scales, and data pooling

Table 1 Pooled analysis baseline variables and efficacy outcomes.

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Placebo (N=75)</th>
<th>BTA (N=59)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age</td>
<td>49.35</td>
<td>49.14</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Sex, % female</td>
<td>86.67 %</td>
<td>93.22 %</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td># of years with depression, mean</td>
<td>19.72</td>
<td>18.78</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Duration of current episode in months, mean</td>
<td>28.91</td>
<td>19.81</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>% of patients on current antidepressants</td>
<td>64.00 %</td>
<td>64.41 %</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td># of current antidepressants, mean</td>
<td>0.89</td>
<td>0.85</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>% of patients with recurrent depression</td>
<td>84.00 %</td>
<td>86.44 %</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>% of patients with mild depression</td>
<td>13.33 %</td>
<td>8.47 %</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>% of patients with moderate depression</td>
<td>46.67 %</td>
<td>45.76 %</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>% of patients with severe depression</td>
<td>38.67 %</td>
<td>44.07 %</td>
<td>0.53</td>
</tr>
<tr>
<td>BDI</td>
<td>Baseline score, mean</td>
<td>26.28</td>
<td>28.98</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Week 6 score, mean</td>
<td>21.23</td>
<td>14.73</td>
<td>&lt;0001</td>
</tr>
<tr>
<td></td>
<td>Change in score, mean</td>
<td>5.05</td>
<td>14.25</td>
<td>&lt;0001</td>
</tr>
<tr>
<td></td>
<td>% change in score</td>
<td>-16.19 %</td>
<td>-47.38 %</td>
<td>&lt;0001</td>
</tr>
<tr>
<td></td>
<td>% patient responders</td>
<td>8.00 %</td>
<td>52.54 %</td>
<td>&lt;0001</td>
</tr>
<tr>
<td></td>
<td>% patient remitters</td>
<td>8.00 %</td>
<td>42.37 %</td>
<td>&lt;0001</td>
</tr>
<tr>
<td>HAM-D/MADRS</td>
<td>% change in score</td>
<td>-14.60 %</td>
<td>-45.69 %</td>
<td>&lt;0001</td>
</tr>
<tr>
<td></td>
<td>% patient responders</td>
<td>10.67 %</td>
<td>54.24 %</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>% patient remitters</td>
<td>6.67 %</td>
<td>30.51 %</td>
<td>0.03</td>
</tr>
<tr>
<td>CSS-GFL</td>
<td>Baseline frown score, mean</td>
<td>2.08</td>
<td>2</td>
<td>0.589</td>
</tr>
<tr>
<td></td>
<td>Week 6 frown score, mean</td>
<td>2.20</td>
<td>0.73</td>
<td>&lt;0001</td>
</tr>
</tbody>
</table>

aP-values were determined by t-test for scalar outcomes and chi-square test for binary outcomes

bComparison of baseline features revealed no differences in the study participants

cThere were statistically significant differences in all outcome measures (% reduction in mean score, response rates, and remission rates) with both self-rating (Beck Depression Inventory, BDI) and expert rating (Hamilton Depression Rating Scale, HAM-D; Montgomery-Asberg Depression Rating Scale, MADRS) scales between the placebo and botulinum toxin A (BTA) intervention groups

dFrown scores, the severity of patients’ glabellar folds at maximum voluntary frowning, were measured on a scale of 0–3 by 4-point Clinical Severity Score for Glabellar Frown Lines (CSS-GFL). At week 6, those who received BTA had a statistically significant reduction in frown scores compared to those who received placebo
monotherapy (patients not taking antidepressants) (Supplemental Table 1). Pooled data analysis allowed for comparison of BTA as an adjunct vs. a monotherapy.

Tolerability and side effect data were reported in the studies done by EF et al. and MAW et al., and were collected from raw data by MM et al.

The primary end point was a reduction in depressive symptoms 6 weeks after the baseline. This was measured by the Hamilton Depression Rating Scale (HAM-D) in MAW et al. and MM et al. studies and by the Montgomery-Asberg Depression Rating Scale (MADRS) in EF et al. study. We used continuous (% change in score) and categorical (response, ≥50% improvement from baseline scores; remission, score ≤7 for the HAM-D scales, ≤10 for the MADRS) changes on these scales as common outcome variables, thus eliminating confounding factors that may have arisen from using different rating scales. Specifically, the cut-off values for remission allow for optimal comparability of the HAM-D and the MADRS (r = 0.82–0.94) and have an identical point range, we used them as one scale (BDI) [21]. All studies used the same Clinical Severity Score for Glabellar Frown Lines (CSS-GFL) to assess frown scores at baseline and week 6 [22]. One of the trials involved a cross-over of the BTA and the placebo group after 12 weeks. The crossover data was not included in our conjoint analysis.

Statistical analysis

Multiple regression models incorporating random effects for each study were evaluated for the following outcomes: 1) BDI score change, 2) BDI % change, 3) BDI response rate, 4) BDI remission rate, 5) HAM-D/MADRS % change, 6) HAM-D/MADRS response rate, 7) HAM-D/MADRS remission rate, 8) CSS-GFL score change. Models 1, 2, 5 and 8 were calculated using linear mixed models. The remaining were calculated as logistic mixed models. Each model was adjusted for age, sex, baseline CSS-GFL scores, and baseline depression severity for each of the 3 studies. Other variables such as the use of antidepressants were fitted and found to be non-significant in all cases. Possible interactions between the predictor variables were also tested; none were found to be significant. Odds ratios (OR) and numbers needed to treat (NNT) were calculated based on adjustments for age, sex, and baseline depression severity. All models found that patients who received the BTA intervention had significantly better outcomes, with p-values below 0.001; the effect of the intervention was invariant and no significant interactions were found with respect to baseline score, age, and sex. Random effect models compensated for any unobserved differences between the 3 studies.

Results

BTA was superior to placebo in all psychopathological efficacy outcomes (p < 0.0001–0.03, Table 1):

As for the primary end point, i.e., the improvement in the HAM-D or MADRS expert rating scale, recipients of BTA experienced an overall score reduction of 45.7% vs. 14.6% in the placebo group. This corresponds to a response rate of 54.2% (vs. 10.7%, OR 11.1, 95% CI 4.3–28.8, NNT = 2.3) and a remission rate of 30.5% (vs. 6.7%, OR 7.3, 95% CI 2.4–22.5, NNT = 4.2; Fig. 1a).

On the BDI, the BTA group improved by 14.3 points (47.4%) compared to 5.1 points (16.2%; Cohen’s d = 1.07, Fig. 2), corresponding to a response rate of 52.5% (vs. 8.0%, OR 11.1, 95% CI 4.3–28.8, NNT = 2.2) and a remission rate of 42.4% (vs. 8.0%, OR 15.7, 95% CI 4.8–50.9, NNT = 2.9; Fig. 1b).

The response rates did not differ significantly between patients receiving BTA as a monotherapy vs. patients receiving it as an adjunctive treatment in addition to an established treatment with psychotropic medications (BDI: p = 0.61) (Supplemental Table 2).

In the pooled analysis, approximately 9.3% (n = 7) of the placebo group and 13.6% (n = 8) of the BTA reported temporary headaches after the intervention. No severe adverse reactions were
Discussion

As expected and in concordance with the 3 individual trials, which all had positive findings, the pooled data showed with greater statistical power and a higher significance level, that a single treatment of BTA in the glabellar region can produce a strong reduction in the symptoms of major depression. With large effect sizes, this applied for all continuous and categorical efficacy outcome measures.

Our 3 studies are the only previously published randomized controlled trials on the use of BTA in the treatment of depression and they are well comparable with respect to the shared demographic and clinical baseline variables. The higher baseline scores in the BDI data in the study by EF and NER may indicate that patients with more severe depression were included in this study. However, when the data was pooled, there was no statistical difference in BDI scores or any other baseline variables between the placebo and BTA arms in this study.

In the pooled sample, patients who received BTA as a monotherapy and patients who received BTA as an adjunctive treatment improved equally. As such, there is potential for both treatment strategies. However, given the small sample size in each group (adjunctive, n = 86; monotherapy, n = 49), and the results from EF and NER’s original study showing a superior remission rate for BTA augmentation vs. monotherapy (36% vs. 21%, respectively), more studies are warranted before definitively concluding that monotherapy is as effective as augmentation.

There was no statistical difference in adverse events between the placebo and BTA groups (p = 0.44). In a sub analysis, there was a statistically significant relationship between baseline CSS-GFL scores and percent change in patient-rated scores (p = 0.03) and percent change in expert-rated scores (p = 0.03), with a higher baseline CSS-GFL scores being associated with less improvement in mood. However, there was no significant association between baseline CSS-GFL scores and patient-rated response rates (p = 0.13) or patient-rated remission rates (p = 0.14). A similar insignificant relationship was found with expert-rated response rates (p = 0.36) and remission rates (p = 0.78).

Fig. 2 Improvement in BDI score. The figure shows absolute reduction in the BDI scores (14.3 vs. 5.1 ± standard error of the mean) from the baseline to the primary end point 6 weeks thereafter in the combined sample (n = 134) for the BTA (n = 59) and the placebo group (n = 75), respectively.
the spontaneous course leads to marked improvement or remis-
sion is low. Moreover, it is known that placebo responses are low
in such patients [31]. In addition, our sample size was relatively
small (n = 134). Although this generated statistically significant
data with a large effect size, a larger sample size would have
yielded more definitive results.

Strikingly few men were included in all 3 original studies. Also in
the pooled sample the number of male participants was too low
(n = 14) to determine the efficacy of the treatment in men. Con-
sequently, there is a need for a study specifically investigating
antidepressant effects of BTA in men.

Further studies are warranted to determine how BTA may be
integrated into treatment algorithms for depression, be it as a
sole or adjunctive treatment, in relapse prevention, in treat-
ment-resistance or in antidepressant intolerance. In this con-
text, psychomotor endophenotypes of depression (e.g., agitated
depression) may also be predictors of response and allow for a
stratified or personalized application of BTA [32]. Future research
should also address if BTA can be used in the treatment of bipo-
lar depression or other affective disorders. Moreover, other facial
muscles like the depressor anguli oris (corners of mouth) or the
mentalis (chin), which are also involved in depressed facial
expression, may be treated in the future. A major challenge for
future trials may be to find an adequate control condition. This
may be an active comparator or even no treatment at all, which
would at least circumvent nocebo effects that may be associated
with undergoing an invasive procedure only to discover that one
has received sham injections.

Should future studies replicate the safety and efficacy data from
this pooled analysis, glabellar BTA injection may emerge as a
novel therapeutic option for the treatment of depression.

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tions were affiliated with pharmaceutical agencies.

Conflict of Interest

MAW received honoraria for talks from Merz, Eli Lilly and
Novartis. THCK received honoraria for talks from Servier,
Lundbeck, Eli Lilly and Dr. Schwebe. THCK received a grant from
Trommsdorf. These activities were all unrelated to the study.
MAW received a grant from the Asklepios Hamburg GmbH
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after conclusion and publication of the original study, MAW and
THCK became members of the advisory board of Allergan. This
activity ended in April 2014 for MAW and in September 2014 for
THCK. In November 2012, i.e., after conclusion and as a result of
the original study, MM became a consultant with Allergan. JSR’s
spouse (MM) became a consultant for Allergan in 2012. EF has
received a patent to treat depression with BTA. HR, BHK, SJ and
NER declare no conflict of interest.

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