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Depression – An emerging indication for botulinum toxin treatment

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ABSTRACT

The treatment of glabellar frown lines with botulinum toxin injection is one of the most prevalent procedures in esthetic medicine. It is possible that the popularity of this intervention is not only owing to its cosmetic effect but also to modulatory effects on mood and affectivity.

Recently, a series of studies including three randomized controlled trials have consistently shown that such effects can be used in the treatment of depression. Predominantly female patients suffering from partly chronic and treatment resistant unipolar depression experienced a quick, strong and sustained improvement in depressive symptoms after a single glabellar treatment with botulinum toxin A as a sole or adjunctive therapy.

If these findings are further corroborated in additional studies, the ever-growing spectrum of applications for botulinum toxin may spread into the field of psychiatry, showing that the superficial paralysis of facial muscles may, probably via proprioceptive feedback mechanisms, have profound effects on the emotional brain.

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1. Introduction

With several million applications per year injections of botulinum toxin as a treatment of glabellar frown lines, this is probably the most frequent intervention in esthetic medicine (Winter and Spiegel, 2009). Glabellar frown lines are produced by the contraction of the corrugator muscles that occurs under exposure to bright light, during concentration and above all in order to express negative emotions like anger, fear, or sadness. Thus, the motivation to undergo glabellar botulinum toxin treatment and remove frown lines may not be only the whish for a more youthful facial appearance but also for a more relaxed and positive facial expression. Hence, it has been shown that the facial expression is shifted away from negative towards positive emotions by glabellar botulinum toxin treatment (Heckmann et al., 2003). However, it is not only emotional expression that is changed by the treatment, but also emotional experience: This procedure may lead to an enhancement of emotional wellbeing beyond the mere cosmetic benefit (Sommer et al., 2003). It is also associated with reduced levels of irritable, depressed, and anxious mood (Lewis and Bowler, 2009). Moreover the perception of visual emotional stimuli is altered and also the comprehension of sentences with negative emotional connotations is delayed (Davis et al., 2010; Havas et al., 2010). Accordingly, the treatment reduces the activation of the left amygdale during imitation of an angry facial expression (Hennenlotter et al., 2009).

2. The first case series

Physicians in esthetic medicine who treat patients with botulinum toxin are familiar with psychological effects of this treatment (Sommer et al., 2003). The dermatologist and plastic surgeon Eric Finzi was the first to specifically test the hypothesis that glabellar injections of botulinum toxin may be useful in the treatment of depression, a psychiatric disorder in which negative emotions abound. In a case series Finzi and Wasserman treated ten middle-aged women with moderate to severe partly chronic and treatment-resistant depression with a single open label application of botulinum toxin A (BTA) injections in the glabellar region according to a standard protocol also used for cosmetic treatment of frown lines (Finzi and Wasserman, 2006). As measured on the Beck Depression Inventory (BDI) II before (mean = 29) and eight weeks after the treatment (mean = 5.3) nine patients responded to the treatment with eight of them going to remission of depression. The only one who showed only partial response was a patient suffering

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from severe bipolar depression. Half of the participants received BTA as a sole and the other half as an adjunctive treatment of depression.

3. The first randomized controlled trial

In the first randomized controlled trial (RCT), Wollmer and colleagues showed that a single glabellar treatment with BTA can lead to a quick, strong and sustained improvement in the symptoms of depression (Wollmer et al., 2012). Their study included 30 patients, mostly women with an average age of about 50 years, who suffered from mild to moderate, partly chronic, and treatment resistant unipolar depression currently under stable treatment with one or two antidepressants. These patients were able to produce moderate to severe frown lines and where randomized to receive blinded injection of either BTA or saline according to the same scheme also applied in the case series by Finzi and Wasserman. Men received a total of 39 units onabotulinumtoxinA instead of the 29 units applied in women to account for the higher muscle mass. In comparison with the placebo group that remained more or less stable throughout the study, the BTA group showed a significant improvement in the symptoms of depression as early as two weeks after the injection both on the Hamilton Depression Rating Scale (HAM-D) and in the BDI. This effect was strong at the primary end point after six weeks (47%; $d = 1.28$) and increased further until the end of the study after sixteen weeks ($d = 1.87$). The improvement in the depression scales was accompanied by an improvement also in Clinical Global Impressions. Partial response (>25% reduction in HAM-D score; 87%) and response (>50% reduction in HAM-D score; 60%) rates were significantly higher in the BTA group than in the placebo group and 33% of the BTA treated patients attained remission. Those participants with higher levels of psychomotor agitation at the baseline (HAM-D item 9 > 2) had a particularly high probability to respond (100%, Wollmer et al., 2014).

4. Further randomized controlled trials

In a second, larger ($n = 74$) RCT Finzi and Rosenthal confirmed the antidepressant effect of BTA. The participants in this trial were slightly more depressed with otherwise similar baseline characteristics compared to the study by Wollmer et al. (Finzi and Rosenthal, 2014). According to the same protocol of the previous trials, patients were randomized to receive either BTA ($n = 33$) or saline ($n = 41$) injections and were examined after three and six weeks using the BDI-II and Montgomery-Asberg Depresssion Rating Scale depression rating scales. Highly significant improvement in depression occurred after three weeks and was more pronounced after six weeks, which was the primary end point of the study with similar improvement and response rates observed in the study by Wollmer et al. (Wollmer et al., 2012). In addition Finzi and Rosenthal also observed a significantly higher remission rate in the BTA group compared to placebo. Of note, BTA was effective both as a sole (remission rate 21%) and as an adjunctive (remission rate 36%) treatment and the antidepressant effect did not seem to require the presence of glabellar frown lines at baseline (remission in 5 of 13 participants without frown).

In a third RCT ($n = 30$) by Magid et al. the previous findings were further corroborated and extended (Magid et al., 2014). This study had a crossover design, in which those patients who initially where randomized to the BTA ($n = 11$) arm received a second injection of saline and those who were in the placebo arm ($n = 19$) were switched to BTA after 12 weeks. Since the muscle relaxing effect of the first BTA injection had not worn off after 12 weeks and the observed improvement in depression remained stable, the study actually had a delayed start design, in which one group received BTA treatment immediately and the other with a delay of 12 weeks. With an overall follow up period of 24 week this study allowed for a rather long-term observation of those patients who were in the BTA first group. From the visit after 15 weeks to the final visit after 24 weeks, depression scores and frown line severity showed a divergent development with further improvement in the former and a return to baseline of the latter. Thus, the clinical improvement in depression outlasted the cosmetic BTA effect. The group that received BTA as the second injection after 12 weeks also showed an improvement in depression after that second injection. Another phase II RCT on the use of BTA as a treatment of major depression (NCT02116361) with an estimated enrollment of 140 female patients will probably be completed early in 2016.

5. Other studies

Hexsel et al. conducted an open label study on the effects of glabellar BTA injections on self-esteem and depression (Hexsel et al., 2013). In a group of 25 depressed subjects the BDI score dropped from an average of 27 to an average of 13, which corresponds to the effects observed in the RCTs described above. Recently, Boudreau et al. studied the effect of BTA on mild depressive symptoms in patients ($n = 32$) with chronic migraine (Boudreau et al., 2015). BTA was applied according to the scheme developed for the treatment of chronic migraine. The authors reported improvement not only in the number of headache free days but also in the severity of depressive symptoms as measured by the BDI-II after 12 and 24 weeks. However, it can't be excluded the one occurred as function of the other.

An overview of all clinical trials on the use of BTA in the treatment of depression is given in Table 1.

6. Mechanism of action

Although there is consistent evidence suggestive of that glabellar injection of BTA can reduce the symptoms of depression, the mechanism of action by which improvement in mood is accomplished is still unknown. There are several possibilities how BTA alleviates depression: cosmetic effects achieved by glabellar muscle relaxation may result in a better body image, enhanced self esteem, and elevated mood (Molina et al., 2015). However, several findings make it unlikely that this is the main mechanism of action: In the first RCT the method under investigation, i.e. the injection of BTA was not disclosed in the advertisement for the recruitment of participants but only at screening, in order to avoid participants that were particularly attracted by the perspective to receive a BTA treatment with the known cosmetic effects. In the RCT treatment outcome did not correlate with the appreciation of the cosmetic change (Wollmer et al., 2012). Improvement in BDI scores did not correlate with changes in self esteem scores as measured by the Rosemberg scale (Hexsel et al., 2013) Moreover, presence of frown lines at the baseline was not a prerequisite for response in a RCT that did not have frown lines as an inclusion criterion (Finzi and Rosenthal, 2014). One patient with a structurally fixed severe frown line did not experience any cosmetic change but went into remission. Another subject even reported that she specifically disliked the cosmetic change but still attained remission of her depression (Wollmer et al., 2012). Moreover, the antidepressant effect outlasted the cosmetic change in a RCT with a follow-up period of 24 weeks (Magid et al., 2014).

It is possible that a change in facial expression from the negative emotions associated with depression towards more positive emotions may confer a more positive social feedback during the interaction with the own mirror image or a social interaction partner.

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