The Use of Botulinum Toxin for Treatment of Depression

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Abstract

A series of clinical studies have shown that botulinum toxin can treat major depression. Subjects suffering from unipolar depression may experience a quick, strong, and sustained improvement in the symptoms of depression after a single glabellar treatment with botulinum toxin.

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Preliminary data suggest that botulinum toxin therapy may also be effective in the treatment of other mental disorders characterized by an excess of negative emotions, such as borderline personality disorder.

The mood-lifting effect of botulinum toxin therapy is probably mediated by the interruption of a proprioceptive feedback loop from the facial musculature to the emotional brain.

Keywords
Embodiment · Emotional proprioception · Facial feedback hypothesis

1 Background

More than 300 million people in the world suffer from depression, which is the leading global cause of disability (WHO). In spite of standard treatments with antidepressant medications and psychotherapy, a considerable proportion of patients do not respond and suffer from chronic depression. Thus, there is a need for new treatment approaches.

Injection of botulinum toxin into the glabellar region (i.e., the muscles above and between the eyebrows) may be such a new approach. Glabellar frown lines are produced by the contraction of the corrugator muscles (*musculi corrugatores superciliorum*), which are key muscles in the expression of negative emotions like anger, fear, or sadness. Charles Darwin called these muscles "grief muscles." Their activity also accounts for facial features of emotional distress like the "*omega melancholicum*" or Veraguth's folds (Greden et al. 1985; Fig. 1).

Injection of botulinum toxin in the glabellar region is probably the most popular intervention in esthetic medicine (https://www.isaps.org/wp-content/uploads/2017/10/GlobalStatistics2016-1.pdf). The wish for an emotionally more positive/less

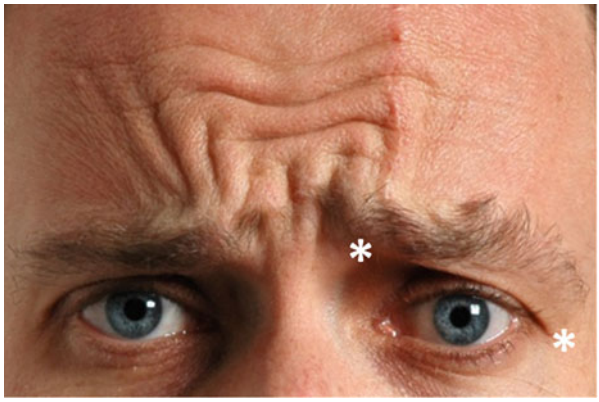

Fig. 1 The corrugator muscles are key muscles for the expression of negative emotions. Combined contraction of the corrugator muscles (FACS action unit 4) with the medial proportion of the frontalis muscle (FACS action unit 1) produces a wrinkle configuration described as "*omega melancholicum*," as it resembles the Greek letter Ω. It also results in the formation of Veraguth's folds from the lateral angle of the eye to the medial end of the eyebrow (∗)

negative facial appearance may be as important as the wish for a more beautiful and youthful look, when it comes to explaining why so many people seek removal of glabellar frown lines by the injection of botulinum toxin. The treatment can actually change facial expression in a way that makes it appear less negative or more positive, respectively (Heckmann et al. 2003).

The treatment can also influence emotional experience: It seems to enhance emotional well-being beyond a mere cosmetic benefit (Sommer et al. 2003). Moreover, it reduces irritability, as well as depressed and anxious mood (Lewis and Bowler 2009). Facial botulinum toxin treatment as it is applied in cosmetic medicine can influence the perception of visual emotional stimuli and delay the comprehension of sentences with negative emotional connotations (Davis et al. 2010; Havas et al. 2010; Baumeister et al. 2016). These behavioral effects are backed up with observations from functional studies showing that the treatment can reduce amygdala activation during viewing or imitation of an angry facial expression (Hennenlotter et al. 2009; Kim et al. 2014). Physicians in esthetic medicine are familiar with the enhanced well-being in patients they treat with botulinum toxin, and it is possible that the described effects may contribute to patients' desire for continued treatments.

2 Botulinum Toxin Therapy of Depression

There is cumulating evidence that glabellar botulinum toxin injections may have an antidepressant effect (for review, see also Kruger and Wollmer 2015; Wollmer et al. 2018). The first report of this effect was a case series published in 2006: Ten middle-aged women with moderate to severe, partly chronic, and treatment-resistant depression received a single open-label application of glabellar botulinum toxin injections. Botulinum toxin was injected according to a protocol for the cosmetic treatment of frown lines, as a sole or as an adjunctive treatment of depression (Finzi and Wasserman 2006). The treatment led to a marked improvement in the self-rated depression scores on the Beck Depression Inventory (BDI) II from before to 8 weeks after the treatment, with a high response and remission rate.

The first randomized controlled trial (RCT) of botulinum toxin therapy (BTT) for depression was published in 2012 and showed that a single treatment can lead to a quick, strong, and sustained improvement in depressive symptoms (Wollmer et al. 2012). The study included 30 middle-aged, mostly female patients, suffering from mild to moderate, partly chronic and treatment-resistant unipolar depression on stable treatment with antidepressant medication. Ability to produce moderate to severe frown lines was an inclusion criterion. The participants were randomized to a blinded treatment with either BTT or saline placebo injections. To account for the higher muscle mass, men received a higher dose of onabotulinumtoxinA than women. While the placebo group remained more or less stably depressed throughout the study, the BTT group showed a significant improvement in the symptoms of depression as early as 2 weeks after the injection, which was measurable on both the Hamilton Depression Rating Scale (HAM-D) expert rating and the BDI self-rating scales. At the primary end point 6 weeks after the baseline, the improvement had a large effect size ($d = 1.28$) and increased even further until the end of the study

16 weeks after treatment ($d = 1.87$). An improvement in Clinical Global Impressions reflected the improvement in the depression scales. Partial response (>25% reduction in HAM-D score; 87%) and response (>50% reduction in HAM-D score; 60%) rates were significantly higher in the BTT group than in the placebo group, and 33% of the botulinum toxin-treated patients attained remission. Psychomotor agitation was a predictor of response in this study (Wollmer et al. 2014).

A second RCT with a larger sample ($n = 74$) confirmed the antidepressant effect of BTT. The participants of this trial had similar baseline characteristics like those in the previous study with slightly higher depression scores (Finzi and Rosenthal 2014). After 3 weeks there was a highly significant improvement in depression measured by the BDI-II and Montgomery-Åsberg Depression Rating Scale (MADRS) depression rating scales that became even more pronounced at the primary end point 6 weeks after baseline. Improvement and response rates were comparable to those observed in the previous study, and the remission rate was significantly higher in the BTT group compared to placebo. In this trial, BTT was equally effective as a sole or adjunctive treatment. Presence of glabellar frown lines at the baseline was not an inclusion criterion and was shown not to be required for either response or remission.

A third RCT with 30 patients further corroborated and extended the previous findings (Magid et al. 2014). The crossover design of this study provided switching of the patients who were initially in the placebo arm to BTT after 12 weeks and vice versa. Given the long-lasting effect of botulinum toxin, this corresponds to a delayed start design, in which one group received BTT immediately and the other one with a delay of 12 weeks. The overall follow-up period was 24 weeks, and both groups improved significantly after botulinum toxin treatment. Remarkably, the clinical improvement in depression outlasted the muscle-relaxing effect: In the original BTT group, depression scores showed further improvement from the visit after 16 weeks to the final visit after 24, while frown line severity returned to baseline.

An individual patient data meta-analysis by the authors of the original studies and an independent conventional systematic review and meta-analysis summarize the results of these three first RCTs (Fig. 2; Magid et al. 2015; Parsaik et al. 2016). Both meta-analyses confirmed a marked reduction in the symptoms of major depression and high response and remission rates by BTT with low numbers needed to treat (2.2–2.3 and 2.9–4.9, respectively). With these meta-analyses, there is a high level of evidence for the efficacy of BTT, especially as an adjunctive treatment for women with mild to moderate unipolar depression. The treatment was very well tolerated in all three studies with no significant difference in the incidence of side effects between the BTT and the placebo groups.

Meanwhile, a fourth RCT with 28 patients with major depression further confirmed the efficacy of the treatment, with a statistically significant reduction in BDI score at week 6 in the BTT compared to the placebo group (Zamanian et al. 2017).

The Botox® manufacturer Allergan has recently completed a multicenter phase II RCT. The trial tested one-time treatment with two doses of Botox® (30 or 50 U) against saline placebo in 258 moderately to severely depressed women. In the 24-week trial, change in MADRS score from baseline to 6 weeks in the Botox®

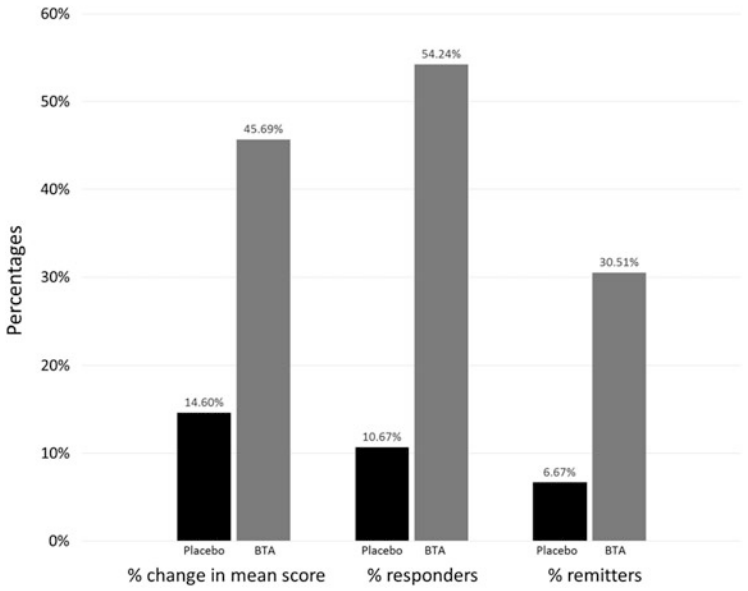

Fig. 2 In a pooled analysis of three previous randomized controlled trials on BTT in depression, there was a 45% reduction in depression scores. In 54% of the BTT recipients, there was a reduction by at least 50% (responders), and 30% of the BTT-treated patients' depression scores fell below the clinical threshold (remitters; Magid et al. 2015)

vs. the respective placebo groups was defined as the primary end point. Only the 30 U Botox® dose was superior to placebo, but the difference was not statistically significant at the primary end point. The results of the study are not yet published as a scientific report but are posted at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT02116361?term=botulinum&cond=depression&rank=4). Based on the results of the study, Allergan has announced to proceed with a phase III trial.

Ongoing trials investigate glabellar botulinum toxin injections as a treatment for depression in Parkinson's disease and in geriatric depression (NCT03069911, NCT03833063). Another trial compares the antidepressant effect of glabellar injections with the effect of injections into the lateral parts of the orbicularis muscles of the eyes, which is associated with the Duchenne smile (a "genuine" smile, which involves crinkling of the eyes) and the expression of positive emotions (NCT03484754).

Another case series with 42 patients suffering from severe treatment-resistant unipolar depression confirmed improvement in the symptoms of depression within 3 weeks after BTT (Chugh et al. 2018). Importantly, more than half of the patients of this case series were men and improved equally to the female participants, indicating that the antidepressant effect of the treatment is not dependent on patient gender.

A recent case series suggests that BTT may be effective in bipolar depression, too (Finzi et al. 2018).

3 Depression in Chronic Migraine

Based on the results of the two Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies, onabotulinumtoxinA has been registered as a treatment of chronic migraine (Dodick et al. 2010). Because depression is highly prevalent among chronic migraine patients, studies in these patients may provide additional information on the antidepressant effect of botulinum toxin injections. In the injection scheme for the treatment of chronic migraine, five units of onabotulinumtoxinA are provided for injection into the corrugator muscles on each side. This dose is below the doses used for the treatment of glabellar frown lines in esthetic medicine or in the treatment of depression. However, it will lead to at least partial relaxation of these muscles.

Several studies support the antidepressant effect of botulinum toxin injections:

One study, which investigated the effect of botulinum toxin on mild depressive symptoms in 32 chronic migraine patients, found an improvement in the severity of depressive symptoms as measured by the BDI-II after 12 and 24 weeks (Boudreau et al. 2015).

In a retrospective study on treatment of migraine with botulinum toxin in 359 patients, there was an improvement in depressive symptoms measured by the Patient Health Questionnaire (PHQ-9). The improvement in depressive symptoms was correlated with the reduction in headache (Maasumi et al. 2015).

In a study observing the long-term course of chronic migraine after several injection cycles with botulinum toxin in 27 patients, depressive symptoms measured by the BDI dropped stably and significantly throughout the yearlong study (Kollewe et al. 2016).

In a cohort of 60 patients with chronic migraine treated with botulinum toxin according to the PREEMPT protocol, BDI scores were significantly reduced 3 months after the treatment (Demiryurek et al. 2016).

A modified version of the PREEMPT injection scheme for the treatment of chronic migraine led to improvement in symptoms of depression and anxiety as measured by the HAM-D or Hamilton Anxiety Rating Scale (HAM-A) after 1 month. This prospective open-label study included 30 (in most cases) female patients with chronic daily headache (Zhang et al. 2017).

It is unclear if the effects on depression and headache in these studies were independent or if one occurred as function of the other.

However, other studies did not confirm improvement in psychiatric symptoms in migraine patients by botulinum toxin treatment.

In an open-label study, 190 patients were monitored for migraine symptoms and for negative emotional states measured by the Depression, Anxiety and Stress Scale (DASS-21) for almost a year. While migraine improved, there was no significant reduction in the DASS-21 scores. However, the interpretation of these findings is limited because a considerable proportion of patients was lost to follow-up (Aydinlar et al. 2017).

Psychiatric symptoms measured by the Zung self-rating anxiety and depression scale did not change significantly, while all headache-related parameters increasingly improved over 13 treatment cycles, according to the PREEMPT protocol in a study with 90 patients (Guerzoni et al. 2015, 2017).

4 Mechanisms of Action

While there is growing evidence for the efficacy of botulinum toxin injection as a treatment for depression, the mechanism of action by which it accomplishes the improvement in mood is still unknown. There are several possibilities how botulinum toxin may exert its mood-lifting effect:

Because of the obvious cosmetic change or the lack of, it is impossible to effectively blind patients for their treatment allocation in RCTs. Moreover, a facial injection has a high suggestive power and the targeted phenotype is subjective. Therefore, it is difficult to judge to what extent placebo and nocebo effects may inflate the differences between the botulinum toxin and placebo groups, respectively. However, some findings strongly argue against a predominant role of placebo effects: Patient's expectations and credibility regarding botulinum toxin therapy did not predict the outcome in one of the RCTs (Wollmer et al. 2012). In another RCT, patients' hit rate when guessing group allocation was only barely above chance level, and correct or incorrect guessing was not associated with outcome (Finzi and Rosenthal 2014). In a third RCT, the improvement in the symptoms of depression outlasted the cosmetic effect of the treatment (Magid et al. 2014). An Inverse-Frequency Analysis comprising millions of reports of the FDA Adverse Event Reporting System (FAERS) database showed that use of botulinum toxin as a cosmeceutical was associated with marked underreporting of depression and depressive symptoms as a side effect of the treatment with Log ORs of around 2.5 below the benchmark (Cohen et al. 2017). This is an indirect proof of the antidepressant effect of botulinum toxin treatment. Given the naturalistic application of botulinum toxin for cosmetic indications, it is unlikely that specific expectations of an antidepressant effect could induce placebo effects. Very recently, a study showed antidepressant-like effects of facial botulinum toxin injection in a mouse model of depression (Li et al. 2019). After stress induction by space restriction, mice showed prolonged immobility time in behavioral despair tests like the forced swim test and the tail suspension test. This may be looked upon as a correlate of learned helplessness associated with depression. A single facial injection of botulinum toxin improved this depression-like behavior and was associated with hippocampal increase in serotonin levels as well as activation of BDNF/ERK/CREB pathways. These findings argue against a predominant role of placebo effects but also raise questions regarding the possible mechanisms of action discussed below.

Cosmetic changes associated with glabellar muscle relaxation may improve body image, enhance self-esteem, and in the end elevate mood (Molina et al. 2015). Several findings speak against cosmetic improvement as the main mechanism of action: Recruiting for the first RCT tried to avoid attracting participants looking to receive a botulinum toxin treatment with its known cosmetic effects. The respective advertisements did not disclose that the study was about botulinum toxin injections. This information was given only at screening. In the same RCT, the appreciation of the cosmetic change did not correlate with treatment outcome (Wollmer et al. 2012). Also individual experiences of participants argued against the possibility that cosmetic changes mainly drove mood improvement: One patient with a structurally

fixed severe frown line did not experience the expected cosmetic improvement after botulinum toxin injection, was convinced to having received placebo, but still attained remission of her depression. Another subject reported to dislike the "Mephisto sign" (lateral elevation of the eyebrows because of medial weakening of the frontalis muscle), that occurred after injection of botulinum toxin, but still her depression went into remission. The improvement in BDI scores did not correlate with the changes in self-esteem scores on the Rosenberg scale in an open-label study (Hexsel et al. 2013). In the second RCT, half the subjects had no frown at rest and therefore obtained no cosmetic benefit. Patients who had previously used BTT were excluded from the studies. In addition, the presence of frown lines at the baseline was shown not to be required for response (Finzi and Rosenthal 2014). In the third RCT, the improvement in the symptoms of depression outlasted the cosmetic change (Magid et al. 2014).

It is possible that a change in facial appearance from emotionally negative toward emotionally positive is associated with a more positive social feedback when interacting with a social partner or even the own image in the mirror. However, living on their own or living with a partner or families does not seem to predict the antidepressant effect of botulinum toxin treatment (Wollmer et al. 2012, 2014). Therefore, it is not very likely that altered social feedback is the main mechanism of action. An ongoing study investigates altered social interactions as a possible mediator of mood improvement by botulinum toxin (SNCTP000002474).

The most probable and most plausible mechanism that could explain how botulinum toxin may reduce the symptoms of depression is that it interrupts a feedback loop of "emotional proprioception" from the face to the brain that reinforces and maintains the negative emotions that are prevalent in depression (Finzi and Rosenthal 2016). Glabellar injection of botulinum toxin abolishes the contraction of the corrugator muscles, which is a key element in the expression of negative emotions. Patients suffering from depression show a relative overactivity of the corrugator muscles that would be corrected by botulinum toxin injection (Schwartz et al. 1976).

Back in the nineteenth century, William James and Charles Darwin formulated the facial feedback hypothesis (FFH). According to the FFH, the facial expression of an emotion generates a proprioceptive feedback signal from the face to the brain that enhances the respective emotion. This feedback turns it from an initially faint and cool semicognitive experience into a powerful and warm sensation (Fig. 3; Adelmann and Zajonc 1989; Al Abdulmohsen and Kruger 2011). The FFH has been validated in classical experiments. They show that the arbitrary contraction of facial muscles can modulate emotional appraisal of or emotional reactions to presented visual stimuli (Ekman et al. 1983; Coles et al. 2019). Facial feedback effects tend to be rather small and inconsistent under experimental conditions, but among them experiments using botulinum toxin injections with the resulting long-lasting and complete muscle paralysis seem to have the strongest effects. It is possible that a facial expression can reinforce a preexisting, matching emotion or produce a corresponding emotion. Conversely, lack of or nonmatching facial expression may prevent, weaken, or abolish an emotion: "Refuse to express a passion, and it dies," as William James put it, reflects exactly the rationale of BTT in the treatment of depression.

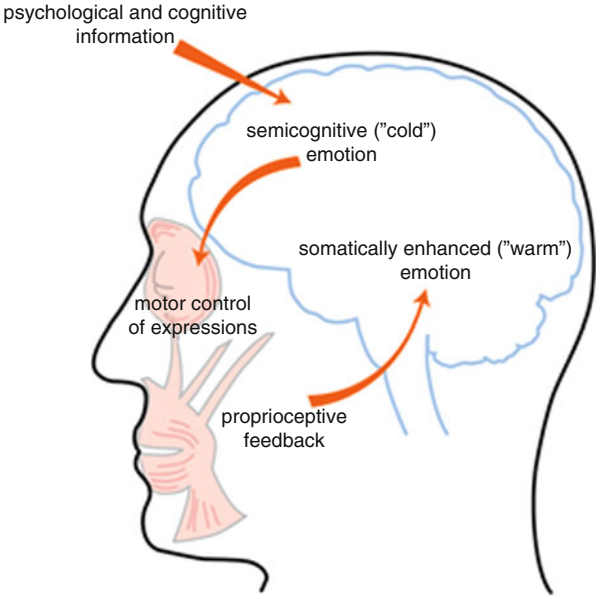

Fig. 3 The facial feedback hypothesis. Facial musculature activation expressing of emotional states generates proprioceptive feedback signals from the face to the emotional brain. This "emotional proprioception" reinforces the initially semicognitive, "cold" emotional state and turns it into a somatically enhanced, "warm" emotional experience. The antidepressant effect of glabellar botulinum toxin injections may be mediated by switching off proprioceptive feedback signals from this region that maintain negative emotions (Al Abdulmohsen and Kruger 2011)

The facial musculature is not equipped with typical proprioceptors like muscle spindles, and it is unknown how proprioceptive signals are picked up. Mechanical receptors in the skin or connective tissue may play a role (Cattaneo and Pavesi 2014). Along proprioceptive fibers that run with the facial and trigeminal nerve, signals are conducted to the mesencephalic trigeminal nucleus and locus coeruleus (Cobo et al. 2017). Via projections from there, they may modulate the activity of the prefrontal cortex and the amygdala (Matsuo et al. 2015; Finzi and Rosenthal 2016). In rats, facial injection of botulinum toxin can alter the metabolism of monoaminergic neurotransmitters in limbic brain regions (Ibragić et al. 2016).

There is some experimental evidence of axonal and even transsynaptic transport of locally injected botulinum toxin into the CNS, when injected in high doses (Caleo and Schiavo 2009). Central effects may be clinically relevant in humans, and it can't formally be excluded that they may be involved in the mood-lifting effects of botulinum toxin treatment (Marchand-Pauvert et al. 2013). Besides SNARE complex proteins, there are other central nervous substrates of botulinum toxin like the RAS-related C3 botulinum toxin substrate 1 (Rac1) that play a role in depression and other mental disorders (Golden et al. 2013). Theoretically, they might be involved in the antidepressant action of botulinum toxin.

5 BTT in the Clinical Management of Depression

BTT has several favorable aspects in the management of depression: A single treatment has a long-lasting effect averaging 3 months, which is practical for both physician and patient and may improve therapy adherence. With the long treatment

intervals, BTT is even an economic therapeutic option, if the costs are calculated per treatment day (Beer 2010). Finally, botulinum toxin injections to the glabellar region have an excellent safety and tolerability record (Brin et al. 2009). All these positive aspects render BTT an attractive treatment option for patients, physicians, and the public health system. This may particularly apply for regions with limited resources in mental health-care supply (Chugh et al. 2018). Glabellar injection of botulinum toxin is not yet registered as a treatment for depression or any other mental disorder. However, it is registered for the treatment of frown lines. Thus, it is possible to treat psychiatric patients featuring such lines on label for this indication, but with the aim to induce improvement in the affective symptoms as a side effect.

The goal of BTT for psychiatric indications is not to obtain an optimum esthetic result. It rather aims to prevent the expression of negative emotions and the resulting proprioceptive facial feedback that may reinforce and maintain them. The glabellar muscles, i.e., the procerus and the corrugator muscles, are key muscles for the expression of negative emotions, which universally comprises a contraction of the eyebrows (facial action unit 4 in the Facial Action Coding System, FACS; Ekman and Friesen 1978). The paralysis of these muscles is the most parsimonious way to prevent the expression and, at the same time, the experience of negative emotions via interruption of the corresponding proprioceptive feedback loop. This paralysis should be complete, as a residual activity may be enough to keep up the feedback loop. Therefore, the doses applied for psychiatric indications may be above those used to obtain the "natural look" desired in cosmetic treatments (Carruthers et al. 2007). The injection scheme used in the first studies on BTT for depression provides 29 units of onabotulinumtoxinA at a concentration of 40 or 100 U/ml 0.9% saline. They are distributed to five injection points (7 U *m. procerus*; 6 U *m. corrugator supercilii* medial, bilaterally; 5 U *m. corrugator supercilii* lateral, bilaterally; Fig. 4) for women. To account for their usually higher muscle mass, men received two more units at each injection point. These doses are sufficient to achieve a complete

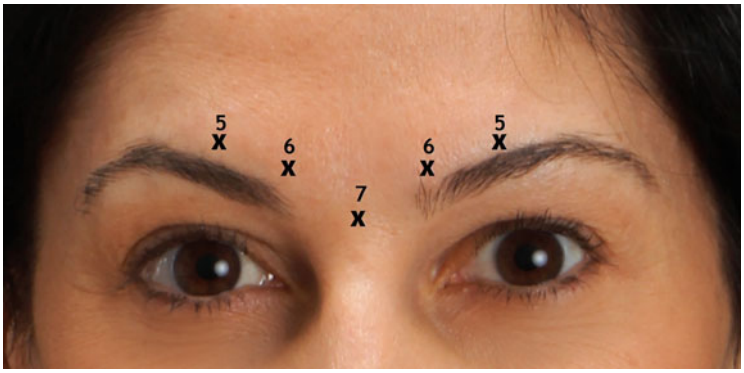

Fig. 4 The injection scheme used in the first studies on BTT for depression. For women, 29 units of onabotulinumtoxinA were distributed to five injection points (7 U *m. procerus*; 6 U *m. corrugator supercilii* medial, bilaterally; 5 U *m. corrugator supercilii* lateral, bilaterally). Men received two more units at each injection point, to account for their usually higher muscle mass

paralysis of the glabellar musculature in most cases. In clinical practice, the dose and its distribution may be adopted to the individual anatomic conditions. The facial action unit 1 that corresponds to the medial proportion of the *m. frontalis* is frequently activated together with the facial action unit 4. This activation pattern produces the "*omega melancholicum*," a wrinkle relief of the Greek letter omega. Patients with agitated depression frequently display this clinical sign (Greden et al. 1985; Fig. 1). The *m. frontalis* may be involved in the expression of negative emotions like sadness (only the medial proportion) or fear; yet, it is also involved in the expression of surprise, which can also be positive. Thus, extending the treatment to the *m. frontalis* to enhance the effect on specific negative emotions may be an option but may have a downside, too. A sad facial expression may involve chin dimpling ("popply chin") and depression of the corners of the mouth. They can occur habitually in depression. In this case, the injection of small doses of botulinum toxin into the *mm. depressores angulorum oris* (e.g., 2–3 U onabotulinumtoxinA, bilaterally) and the *m. mentalis* (e.g., 4–6 U onabotulinumtoxinA distributed to 1–3 injection points) may reinforce the mood-lifting effect of a glabellar treatment. Conversely, the injection of botulinum toxin into the *mm. orbiculares oculorum* to treat crowfeet may have detrimental effects on mood. These muscles are essential to the Duchenne smile, and their paralysis may not only weaken the expression of happiness but also interrupt the proprioceptive feedback that is involved in the experience of the happiness expressed by smiling.

To date botulinum toxin is not registered for any psychiatric indication. Thus, it is currently used on a compassionate basis for depressed patients who either did not improve sufficiently with established therapies or did not tolerate them. BTT may help many patients to attain substantial improvement or even remission of depression that was previously treatment resistant. The majority of patients need regular repetition of BTT to maintain an antidepressant effect, but some may stay well after a single treatment. So far, the majority of patients have been treated with onabotulinumtoxinA. However, first impressions from BTT with other botulinum toxins, especially incobotulinumtoxinA, are equally good.

6 Outlook

A phase III trial announced by Allergan will probably be pivotal for registration of botulinum toxin as an antidepressant drug. A great methodical challenge for future trials will be to control placebo effects. Comparator studies testing BTT against an established antidepressant may facilitate the estimation of the true effect sizes and help to overcome the obvious problems associated with blinding, expectations, and placebo/nocebo effects.

Very few men took part in the hitherto conducted clinical trials. In the first RCT, there seemed to be a gender effect in favor of women (Wollmer et al. 2012). However, in a recently published case series, BTT was equally effective for men (Chugh et al. 2018). Future RCTs will need to show if BTT is effective for depression in men.

RCTs on BTT in the treatment of severe, psychotic, or bipolar depression are still missing.

Future RCTs could also show if including other facial muscles involved in the expression of negative emotions, specifically sadness, like the *m. mentalis* or the *mm. depressores angulorum oris*, may enhance the effect of glabellar injections.

If BTT works by inhibiting negative emotions in general, then one would predict that BTT could be successfully used for a wide variety of disorders with an excess of negative emotions. Preliminary studies suggest this to be the case. A case series demonstrated that BTT may reduce the symptoms of borderline personality disorder (Kruger et al. 2016). Recently, BTT has been reported to induce and maintain remission of moderate to severe social anxiety disorder (Finzi and Rosenthal 2019).

Identifying predictors of response to BTT may allow for its stratified or even personalized application. A high level of agitation may be such a predictor (Wollmer et al. 2014). Moreover, BTT may be customized to patients' individual facial muscle activity patterns.

A great challenge for future research will be to uncover the neurobiological correlates and mechanisms of the mood-lifting effect of BTT.

Conceptually, BTT is fundamentally different from most established psychiatric treatment approaches: BTT tackles emotional processes in the CNS by their expression in the face, probably via interruption of a reinforcing proprioceptive feedback loop, reversing the therapeutic process from inside out (top down) to outside in (bottom up). BTT can be looked upon as a drug-mediated relaxation exercise that interrupts a behavior, i.e., negative facial expression, which maintains a negative emotional state. Unlike other psychiatric treatments, BTT is not syndrome-oriented or disorder-specific. It is rather a comprehensive approach as it targets a basic condition of mental suffering: the excess of negative emotionality.

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