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Review article

# Botulinum toxin for the management of depression: An updated review of the evidence and meta-analysis

Jara Schulze [a], Insa Neumann [b], Michelle Magid [c], Eric Finzi [d], Christopher Sinke [a], M. Axel Wollmer [b], Tillmann H.C. Krüger [a,e,*]

[a] Hannover Medical School, Division of Clinical Psychology and Sexual Medicine, Department of Psychiatry, Social Psychiatry and Psychotherapy, Carl-Neuberg-Strasse 1, 30625, Hannover, Germany
[b] Asklepios Clinic North - Ochsenzoll, Asklepios Campus Hamburg, Medical Faculty, Semmelweis University, Langenhorner Chaussee 560, 22419, Hamburg, Germany
[c] Department of Psychiatry, Dell Medical School, University of Texas at Austin, 1601 Trinity St., Bldg. B, Stop Z0600, Austin, TX, 78712, USA
[d] Department of Psychiatry and Behavioral Sciences, George Washington School of Medicine, 2120 L Street, NW, Suite 600, Washington, DC, 20037, USA
[e] Center for Systems Neuroscience, Bünteweg 2, 30559 Hannover, Germany

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ABSTRACT

Botulinum toxin (BTX) treatment of glabellar frown lines is one of the most common procedures in aesthetic medicine. In addition to its cosmetic effect, the neurotoxin has been shown to have a positive influence on mood and affect. Several randomized clinical trials (RCTs) have examined the effect of botulinum toxin on the treatment of depression. Combining the results of the five RCTs in a random effects meta-analysis revealed that patients treated with BTX showed a more intense improvement of depressive symptoms in comparison to subjects that received placebo injections ($d$ = 0.98). Despite methodological limitations, the results of this study emphasize the effectiveness of BTX in the treatment of depression and therefore pave the way for its use in the field of psychiatry.

## 1. Introduction

The use of botulinum toxin (BTX) in aesthetic medicine has risen steadily since its introduction over 30 years ago. The neurotoxin is approved for the treatment of wrinkles in the facial glabellar region in over 50 countries (Guo et al., 2015) and globally is the most popular non-surgical cosmetic intervention (Sundaram et al., 2016). As a neurotoxin, it paralyzes muscles and is used cosmetically to reduce wrinkles. Frown lines in the glabellar region are produced by the contraction of the corrugator supercilii muscles and the procerus muscle. Besides narrowing of the eyes to bright sun light or concentration, these muscles also play a pivotal role in the expression of negative emotions. An injection of BTX in the glabellar region is thought not only to influence the expression of emotions, but also the *perception* of emotions (Sommer et al., 2003). Several studies indicate that the neurotoxin has an effect on the experience of emotions (Baumeister et al., 2016; Bulnes et al., 2019; Davis et al., 2010; Havas et al., 2010). In healthy individuals BTX injections in facial areas induce a blunting of the perception of emotional stimuli, indicated by lower recognition rates of facial expressions (Baumeister et al., 2016; Lewis, 2018). These results are supported neurobiologically by the effect of BTX on the reduction of amygdala activation during the imitation and exposition of negative stimuli (Hennenlotter et al., 2009; Kim et al., 2014). The negative effect of BTX on emotion processing can be used in conditions with a bias towards negative emotions, like major depressive disorder (Bourke et al., 2010).

In 2017, more than 264 million people worldwide suffered from a depressive disorder (James et al., 2018), making it one of the major causes of disability (Ferrari et al., 2013). Despite the broad range of approved psychotherapeutic or pharmacological treatment options, many patients do not respond to any of the common attempts. Up to 20% of sequentially treated patients stayed symptomatic for two years or longer (Keitner et al., 2006). Treatment-resistant depressive disorders are associated with sustained high burden and costs (Üstün and Kessler, 2002). Thus new treatment approaches are needed from a medical, social, and economic standpoint. This review and meta-analysis will therefore compile the evidence of BTX as a treatment option for depressive disorders.

* Corresponding author. Hannover Medical School, Division of Clinical Psychology and Sexual Medicine, Department of Psychiatry, Social Psychiatry and Psychotherapy, Carl-Neuberg-Strasse 1, 30625, Hannover, Germany.
*E-mail address:* krueger.tillmann@mh-hannover.de (T.H.C. Krüger).

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### 1.1. Previous research

A case series by Finzi and Wasserman (2006) was the first to describe the potential effect of BTX injected into the glabellar region on depressive disorders. According to a protocol for cosmetic treatment of frown lines, Finzi injected BTX into five sites in the glabellar muscles of ten women, either as a sole or as an adjunctive treatment of their depressive symptoms. Eight weeks after one treatment, nine out of ten initially clinically depressed patients no longer met the criteria for the diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and Beck Depression Inventory (BDI-II).

The first randomized controlled trial to test the impact of BTX on depression was conducted in 2012 by Wollmer and colleagues. Thirty men and women were included in the study and randomized to receive either a single administration of BTX or saline, injected according to the protocol of Finzi and Wasserman (2006). Prior to study inclusion, the participants had to fulfill the diagnosis of a major depressive disorder, according to DSM-IV. Additionally, the Hamilton Depression Scale (HAM-D) had to indicate a mild to moderate depression, and the participants needed to be treated with at least one psychotropic drug. Because of the gender specific differences in muscle mass, men received 39 units of onabotulinumtoxinA, and women, 29 units. Throughout the observation period, the BTX group showed an improvement of depressive symptoms on the BDI and the HAM-D at two weeks, at the primary end point (six weeks) (47%; $d = 1.28$) and at the last follow up at sixteen weeks ($d = 1.87$). The scores of the placebo group remained stable over time. The improvement of depressive symptoms also correlated with an increase in Clinical Global Impressions (CGI) scores. Response (>50% reduction in HAM-D score, 60%), partial response (>25% reduction in HAM-D score, 87%) and remission (33%) rates were significantly higher in participants that received BTX in comparison to the placebo. The adverse events evaluation revealed that 40% in the BTX group and 26.7% in the placebo group showed short-term irritation around injection side and subsiding headache. These side effects are also known from previous trials using botulinum toxin (Tremaine and McCullough, 2010).

A second RCT was conducted by Finzi and Rosenthal (2014). Seventy-four men and women were randomly allocated to either receive onabotulinumtoxinA (n = 33) or saline (n = 41). Participants were not required to have an adjunctive antidepressant treatment, unlike the study of Wollmer et al. (2012). But if participants were on an adjunctive treatment, mode and dose had to be stable for at least four weeks before entering the study. Depressive symptoms, assessed by BDI-II and Montgomery-Åsberg Depression Rating Scale (MADRS) were decreased in the BTX group three weeks after injection and were even lower at the primary end point at six weeks. Remission rates were similar for participants that used BTX as a sole therapy and for those that applied it as an adjunctive treatment (sole remission rate: 21%; adjunctive remission rate: 36%). Two participants in the placebo group and one in the BTX group reported a short headache as side effect.

A third RCT by Magid et al. (2014) investigated the effect of BTX on depressive symptoms, assessed by the HAM-D at the primary end point six weeks after treatment. The study had a crossover design; thus the groups changed conditions after twelve weeks. Participants that were initially randomized to the BTX group changed to the placebo condition and subjects of the placebo group were injected BTX at week 12. Thirty participants were treated with 29 units (women) or 39 units (men) of onabotulinumtoxinA or saline. Independent of the time of BTX injection (first or second) the treatment resulted in a reduction of depressive symptoms, as assessed by HAM-D at six weeks. This improvement was still visible at 24 weeks for the group that received BTX first. No side effects were reported in either group.

In a fourth RCT, Zamanian et al. (2017) injected BTX or saline in the glabellar region of 28 participants. As primary outcome the authors investigated BDI scores three and six weeks after treatment. After six weeks, the groups showed significant differences of BDI scores, whereas 40% in the BTX group and 12% in the placebo group showed an improvement in depressive symptoms. No adverse events occurred.

The largest RCT was conducted by Brin et al. (2020). A total of 255 females were enrolled in the study. The women showed a HAM-D score >18 at baseline and were randomly assigned to one of four different groups. Brin and colleagues set up a design with two different dosages for both BTX and saline and collected HAM-D/MADRS scores 3, 6, 9, and 18 weeks after injection. In one condition, participants were injected with 30 units of onabotulinumtoxinA or saline (n = 123), whereas in the other condition, participants received 50 units of onabotulinumtoxinA or saline (n = 132). For the 30 unit BTX group, a trend of improvement in MADRS scores was shown at the primary end point, six weeks after baseline ($p = 0.053$). At weeks three, nine and eighteen, symptoms were significantly improved compared to the placebo group. Participants that received either 50 units BTX or saline showed improvement in depression symptoms over time as assessed by the MADRS; however, the BTX arm did not separate out from placebo on the MADRS scale until week 18. The authors explain this finding by a potentially altered placebo response with the increase of dosage. The participants that received 50 units BTX or saline received an elevated total number of injections, which the authors hold responsible for the finding. In both groups, the only side effects occurring in over 10% of the cases, were short-term headaches.

The data of the RCTs of Wollmer et al. (2012), Finzi and Rosenthal (2014) and Magid et al. (2014) were assessed in a collaborative project of the authors (Magid et al., 2015), an individual patient data (IPD) meta-analysis, and systematic review. The data of N = 134 participants were pooled and revealed supremacy of BTX over placebo injections. 45.7% of the BTX recipients showed an improvement of depressive symptoms, assessed by HAM-D or MADRS six week after injection of BTX, whereas only 14.6% of the subjects in the placebo group improved. The response rate for BTX was 54.2% (vs. 10.7%) and the remission rate 30.5% (vs. 6.7%).

Parsaik et al. (2016) also conducted a systematic review and meta-analysis on the studies of Wollmer et al. (2012), Finzi and Rosenthal (2014) and Magid et al. (2014). In accordance with the meta-analysis of Magid et al. (2015) the authors described a difference in the improvement of depressive symptoms of participants that received BTX versus placebo. Despite the lower scores of subjects with BTX, the authors point to the modest heterogeneity between the studies (Cochran $Q$ test $p > 0.04$, $I^2 = 70\%$). After the exclusion of the Magid et al. (2014) study, the heterogeneity was reduced (Cochran $Q$ test $p =$ n. s., $I^2 = 0\%$) and the change in depressive severity was still observable. The authors explain the heightened heterogeneity with the crossover design of the study, which might have had an influence on the estimation of the reported effect sizes.

The newest meta-analysis by Coles et al. (2019a) included two case studies, one open-label study and four RCTs (Finzi and Wasserman, 2006; Hexsel et al., 2013; Chugh et al., 2018; Wollmer et al., 2012; Finzi and Rosenthal, 2014; Magid et al., 2014; Zamanian et al., 2017). A random effects model revealed that groups treated with BTX showed less depressive symptoms compared to placebo ($d = 0.83$) and in contrast to baseline scores ($d = 1.57$). Nevertheless, the authors noted some caveats. In 50% of the studies described, effect sizes seemed to be uncommonly large in comparison to typical effect sizes from antidepressants ($d = 0.31$) (Turner et al., 2008). In addition, they mentioned possible publication bias and conflict of interest of the authors. Finally, the authors remarked that the blinding procedures of the studies were imperfect.

### 1.2. Assumed underlying mechanisms

Despite increased evidence for a crucial effect of BTX on depressive symptoms, the underlying mechanisms are still unknown. The general mode of action of BTX is thought to be secondary to the inhibition of release of acetylcholine (ACh). In the peripheral nervous system ACh

triggers muscle contractions. Specifically, the intramuscular injection causes the neurotoxin to enter the adjoining nerve terminal to cleave the protein SNAP-25. Consequently the vesicles of the synapse are no longer able to dock onto the nerve ending and to release ACh into the synaptic cleft (Tremaine and McCullough, 2010). In addition to the paralytic effect at the injection side, BTX is also thought to influence the central nervous system (CNS). Two different explanations have been given: an indirect pathway initiated by the paralysis, or direct retrograde and transsynaptic transmission. In animal models BTX was reported to be found distant from the injection site in structures of the CNS (Lawrence et al., 2012; Matak et al., 2012; Papagiannopoulou et al., 2016; Restani et al., 2011), and an axonal transport is also debated for humans (Caleo and Schiavo, 2009; Marchand-Pauvert et al., 2013). ACh in the CNS is described to be increased in patients with depression (Higley and Picciotto, 2014) and therefore the effect of BTX on ACh within central structures could lead towards a normalization of ACh-levels in depressed individuals.

However, a recent review on central effects of BTX concludes that the effect of BTX on the CNS is more likely to occur via the indirect pathway (Weise et al., 2019). The authors suggest that the denervation and changes of the afferent input modulate and reorganize parts of the CNS. The following ideas on the mechanisms of the antidepressant effect of BTX are therefore all based on the assumption of an indirect pathway.

One approach to explain the underlying mechanisms of the effect of BTX on depressive symptoms is through the impact of the cosmetic changes on self-awareness. In a study of cosmetic injections, people that received BTX reported higher levels of satisfaction, a more positive self-perception and more self-confidence (Molina et al., 2015), in comparison to pretreatment. Additionally, the quality of life in users of BTX was described to be higher in comparison to a global sample (Scharschmidt et al., 2018). However, the aesthetic change and the accompanying cosmetic effects are unlikely to be the main mechanism of the mood lifting in people with depression. In the first RCT of Wollmer et al. (2012), symptom improvement did not correlate with appreciation of the cosmetic change. The authors even reported on a participant that disliked the aesthetic change and still improved in depression severity.

The effect of BTX on depression could also be mediated by social feedback. Here the mechanism could work as follows: BTX in the glabellar region blocks the expression of negative emotions, which effects the way others react towards oneself and thus influences self-awareness. In this context, Cartaud and colleagues described that angry facial expressions increased the desired space around oneself (Cartaud et al., 2018). It is further reported that prosocial behavior decreases towards people with angry facial expressions (Mussel et al., 2013). However women who received BTX stated that the usage did not change their social interactions with others (Singh et al., 2015) and in a different study BTX users even indicated feeling more rejected by others after the application (Sharif, 2013). To investigate further into the role of social feedback as a mediator for mood improvement after the injection of BTX, a study is currently underway (SNCTP000002474); results are yet to be determined.

Finally, the predominantly discussed explanation behind the effect of BTX on depression is the facial feedback hypothesis (FFH) (Strack et al., 1988). The FFH states that emotional experience and emotional expression influence each other via feedback loops. Patients with a depressive disorder show overactivity of corrugator muscles, which are essential for the expression of negative emotions (Schwartz et al., 1976). It is assumed that the paralysis of these muscles interrupts a proprioceptive feedback loop from the face to the brain and thus decreases the reinforcement and maintenance of negative emotions in depression (Finzi and Rosenthal, 2016). The basis of the FFH lies in the emotion theory of William James. Back in the late 19th century, James stated "Refuse to express a passion, and it dies" (James, 1884) (p.197). With his assumption of emotional experience being strongly connected to physiologic states, researchers of the following decades further explored this topic. Nowadays, the representatives of the FFH assume that the contraction of facial muscles can modulate the emotional experience. Smiling and frowning therefore produce proprioceptive feedback from the face to the brain that can influence the experience of happiness or anger, and thus impact depressive symptoms (Finzi and Rosenthal, 2016). The FFH has been investigated in many experimental studies and has been recently reviewed by Coles et al. (2019b). Their results confirmed effects of facial manipulations on emotional experience and emotional judgement. They further described that BTX in comparison to less invasive techniques (e.g., active muscle manipulation) had the largest effect sizes. However, the authors also showed that the overall effect sizes of FFH studies were small, and that experiments suffered from methodological difficulties with blinding, which may result in an awareness of subjects of the experimental manipulation. In addition, the effect sizes of the facial feedback interventions were based more on affective judgement than emotional experience.

The antidepressant effect of facial BTX has been shown not only in humans but also in a rodent model of depression (Li et al., 2019). A single injection of facial BTX caused a persistent improvement in depression-like behavior in mice. The authors state their results might be partially connected to an increase of 5-hydroxytryptamine, which is discussed to be decreased in depression. Mice have the ability to facially express emotions (Dolensek et al., 2020); therefore the FFH can also be considered for interpretation of the antidepressant effect of BTX in mice.

### 1.3. Meta-analysis

To add empirical evidence to the investigation of the effects of BTX on depressive disorders we conducted a meta-analysis to analyze all pre-existing research. The current research extends previous research by drawing from a pooled sample size of N = 417 compared to less than 200 participants in the other meta-analyses.

Clinical trials analyzed included men and/or women with a clinical depression. The outcomes of interest in the analysis were: a) a group (BTX vs. placebo) by time (baseline vs. six week post intervention) interaction effect, b) the main effect of group (BTX/placebo) at the primary end point (six week post intervention) and c) the difference of depressive symptoms between baseline and the primary end point (six weeks post intervention) of BTX treatment.

## 2. Methods

### 2.1. Study selection and data sources

To be included into the analysis the studies had to fulfill the following pre-defined criteria: 1) The participants had to show a clinical depression, 2) BTX had to be injected into the glabellar region as sole or adjunct treatment of depression, 3) The study had to report depression scores as an outcome variable, 4) The study had to be a RCT. The selection process is described in detail in a PRISMA flowchart (Fig. 1). Studies were only included when published and no research was excluded due to a specific language. For the identification of potential literature the subsequent databases were examined in June 2020 with the according search terms:

**PubMed:** ("BTX" OR "botox" OR "BoNT" OR "botulinum") AND ("depression" OR "depressive" OR "depressed" OR "emotion")

**Web of Science:** ("BTX" OR "botox" OR "BoNT" OR "botulinum") AND ("depression" OR "depressive" OR "depressed" OR "emotion")

**U.S. National Library of Medicine, Clinicaltrials.gov:** "botulinum toxin" AND "depression".

**ProQuest for Dissertations & Theses Global:** ("BTX" OR "botox" OR "BoNT" OR "botulinum") AND ("depression" OR "depressive" OR "depressed" OR "emotion")

After eliminating duplicates a total of 531 records persisted for further screening. In independent procedures two researchers (JS and IN) screened titles and abstracts of the potential records. With a satisfying compliance 475 records were excluded. The two researchers

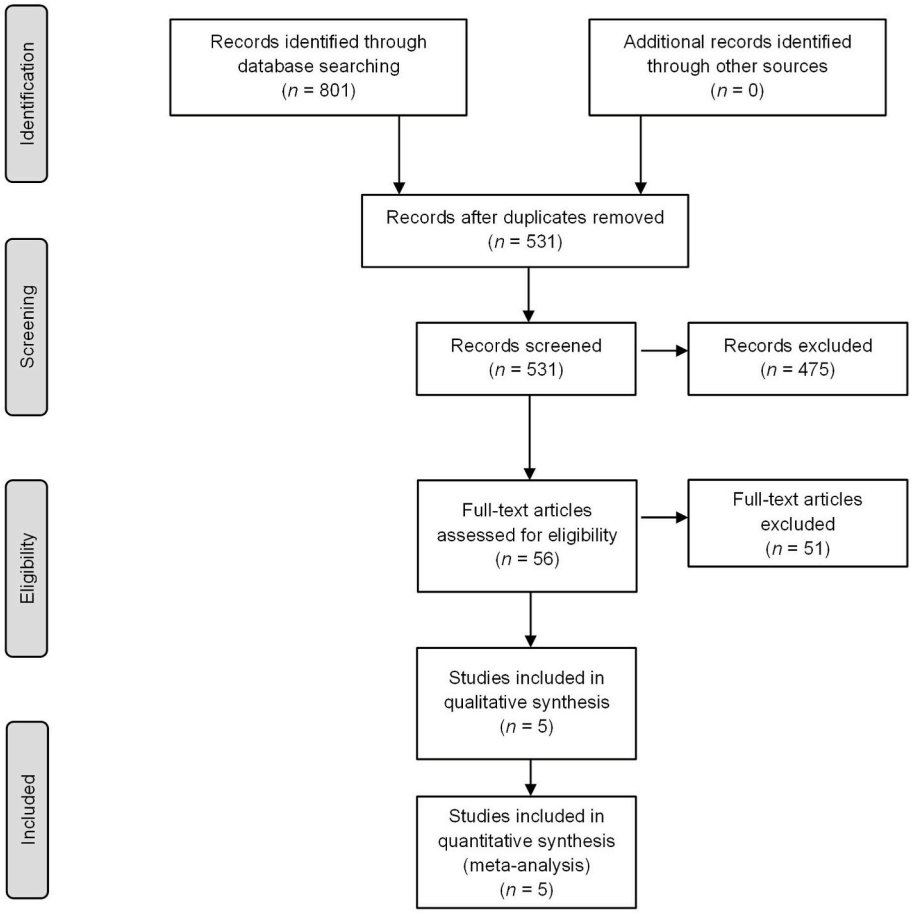


**Fig. 1.** PRISMA flowchart for selection process.

further examined the full-texts of 56 records, only five met all predefined inclusion criteria.

### 2.2. Statistical analysis

The statistical analysis was conducted using Comprehensive Meta-Analysis (Borenstein et al., 2013). As the continuous scales varied between studies, the standardized mean difference (cohens d') was chosen as effect size measure to evaluate the effect of BTX on depressive symptoms (Cooper et al., 2019). For the calculation of the standardized mean difference over time, correlation measures were needed. As this information is often not provided in original reports, we assumed a correlation of 0.50, an accepted value used in previous meta-analyses (Coles et al., 2019a).

**Table 1**
Randomized controlled trials on botulinum toxin treatment for depression.

| Study | Trial* | Participants | Intervention+ | Comparison | Primary outcome | Week |
|---|---|---|---|---|---|---|
| Wollmer et al. (2012) | NCT00934687 | N = 30 (23 women/7 men) | 29/39 U onabotulinumtoxinA or saline placebo | Between<br>Within | HAM-D17<br>HAM-D17 | 6<br>0 to 6 |
| Finzi and Rosenthal, (2014) | NCT01556971 | N = 74 (69 women/5 men) | 29/40 U onabotulinumtoxinA or saline placebo | Between<br>Within | MADRS<br>MADRS | 6<br>0 to 6 |
| Magid et al. (2014) | NCT01392963 | N = 30 (28 women/2 men) | 29/39 U onabotulinumtoxinA or saline placebo | Between<br>Within | HAM-D21<br>HAM-D21 | 6<br>0 to 6 |
| Zamanian et al. (2017) | TCTR20170409001 | N = 28 | onabotulinumtoxinA | Between<br>Within | BDI<br>BDI | 6<br>0 to 6 |
| Brin et al. (2020) | NCT02116361 | N = 123 (women only) | 30 U onabotulinumtoxinA or saline placebo | Between<br>Within | MADRS<br>MADRS | 6<br>0 to 6 |
| | | N = 132 (women only) | 50 U onabotulinumtoxinA or saline placebo | Between<br>Within | MADRS<br>MADRS | 6<br>0 to 6 |

Notes: *registration number in trial register + doses separated by "/" refer to women and men, respectively.
**Abbreviations:** U, units; HAM-D17, Hamilton Depression Rating Scale-17; MADRS, Montgomery-Asberg Depression Rating Scale; HAM-D21, Hamilton Depression Rating Scale-21; BDI, Beck Depression Inventory.

For the pooling of the effect sizes a random effects model was chosen. This method is the most appropriate in meta-analyses that combine studies with varying scales and thus contain differing true effects (Cooper et al., 2019). Random effect models include a weight for each primary study that is calculated as a function of within- and between study variances (Cooper et al., 2019). When studies reported outcomes of several depression scales, we included only the primary depression outcome.

Except for one, all five studies applied roughly the same dosage of BTX and saline to their participants (see Table 1). However, Brin et al. (2020) established two independent sub-trials, one with 30 and one with 50 units of BTX. Each sub-trial had its own saline placebo group, adjusted to the respective number and sites of injection. Hence, these two sub-trials were treated as separate primary studies for the meta-analysis. The results of an analysis, which includes solely those studies with a similar dose, are provided in the supplementary material.

The heterogeneity of the assessed effect sizes was examined by $\tau^2$ and $I^2$ and the 95%CI of $I^2$. $\tau^2$ and $I^2$ were considered to assess the magnitude of heterogeneity and the 95% CI of $I^2$ as a measure of uncertainty. This information allows interpretation of the heterogeneity in meta-analyses (Borenstein et al., 2010). Finally, to correct for bias, the funnel plot was inspected visually and the Egger's regression was used for quantification. The regression computes a regression line of the standard normal deviate on precision. If no bias is detectable the intercept of the line will be not significantly different from zero (Cooper et al., 2019).

## 3. Results

This meta-analysis was conducted to assess a) the interaction between time (baseline/six weeks post intervention) and group (BTX/placebo) in a combined analysis, b) the difference between BTX and a placebo injection after treatment, and c) the change of depressive symptoms with the treatment of BTX over time (baseline/six weeks post intervention).

The combined analysis of time and group revealed that compared over time (baseline to six weeks post intervention) participants who received BTX showed a highly significant improvement of depressive symptoms compared to subjects who received placebo ($d = 0.98$; 95% CI (0.47; 1.49); $z = 3.78$; $p > 0.001$; $\tau^2 = 0.30$; $I^2 = 81.31$; 95% CI of $I^2$ (59.51; 91.45)). The Egger's regression identified a bias (intercept = 5.40; SE = 0.91; 95% CI (2.86; 7.94); t-value = 5.91; p < 0.01) (see Fig. 2).

The results for the investigation of the difference between BTX and placebo six weeks after treatment showed that subjects who received BTX were significantly less depressed than participants who received placebo ($d = 0.63$; 95% CI (0.27; 0.98); $z = 3.47$; $p > 0.01$; $\tau^2 = 0.12$; $I^2 = 63.61$; 95% CI of $I^2$ (10.71; 85.32)). The Egger's regression detected a bias (intercept = 3.88; SE = 1.03; 95% CI (1.01; 6.75); t-value = 3.75; p < 0.05) (Fig. 3).

The combined results from the five studies indicate that six weeks after treatment participants who received BTX showed decreased depressive symptoms when compared to baseline ($d = 1.47$; 95% CI (1.27; 1.67); $z = 11.62$; $p > 0.001$; $\tau^2 = 0.03$; $I^2 = 28.63$; 95% CI of $I^2$ (0; 71.10)). Egger's regression did not reveal a bias (intercept = 1.96; SE = 0.93; 95% CI (−0.62; 4.53); t-value = 2.11; p = 0.10) (see Fig. 4).

## 4. Discussion

Starting from the first case series in 2006, the five RCTs testing the effect of BTX on depressive symptoms indicated that BTX might be a promising new treatment option for depressive disorders. The results of the primary studies and three independent meta-analyses confirmed that BTX can reduce depression when compared to placebo. The safety evaluation revealed subsiding headaches in both BTX and placebo groups; this was also observed in cosmetic usage. Different possible underlying mechanisms are discussed, including aesthetic changes and social feedback, retrograde transport, and the facial feedback theory. The latter is the most likely theory to explain the effects of BTX on depressive symptoms, and is supported by recent work in animal models. The facial feedback theory assumes an interaction between facial emotional expression and emotional experience via feedback loops. As depression is characterized by strong negative emotions, it is

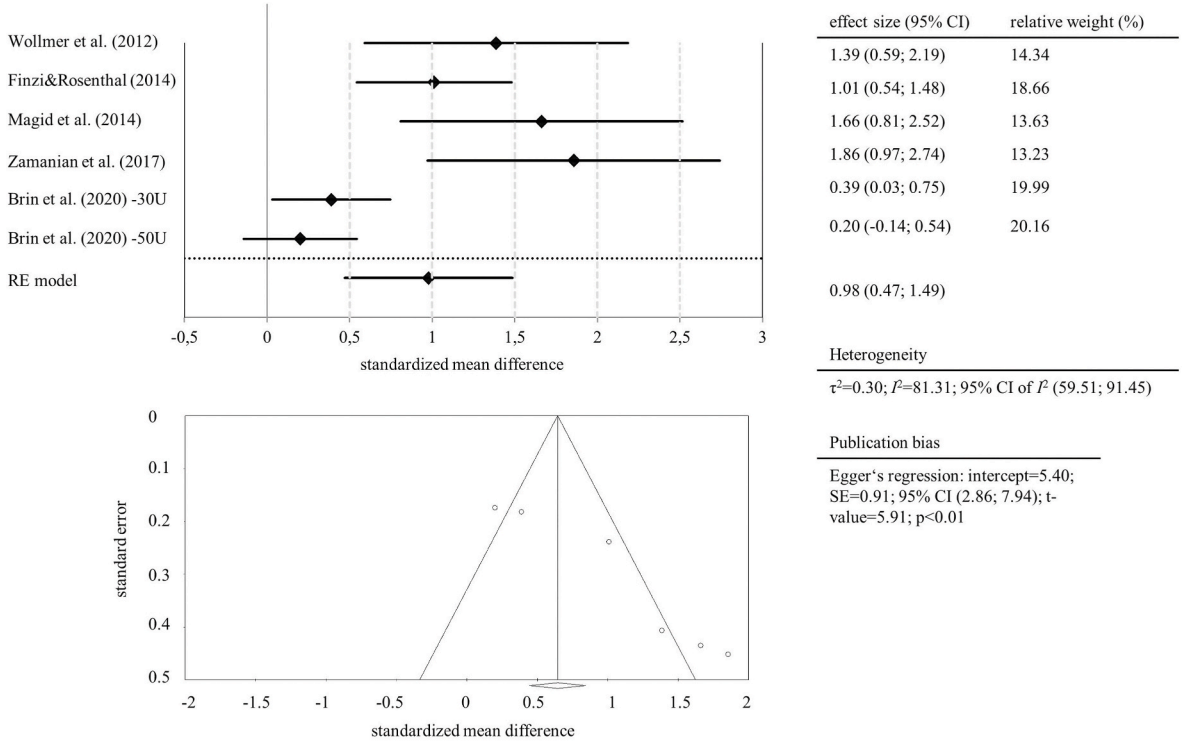


**Fig. 2.** Forest plot and funnel plot for the interaction model of BTX vs. placebo (T0 vs. T1).

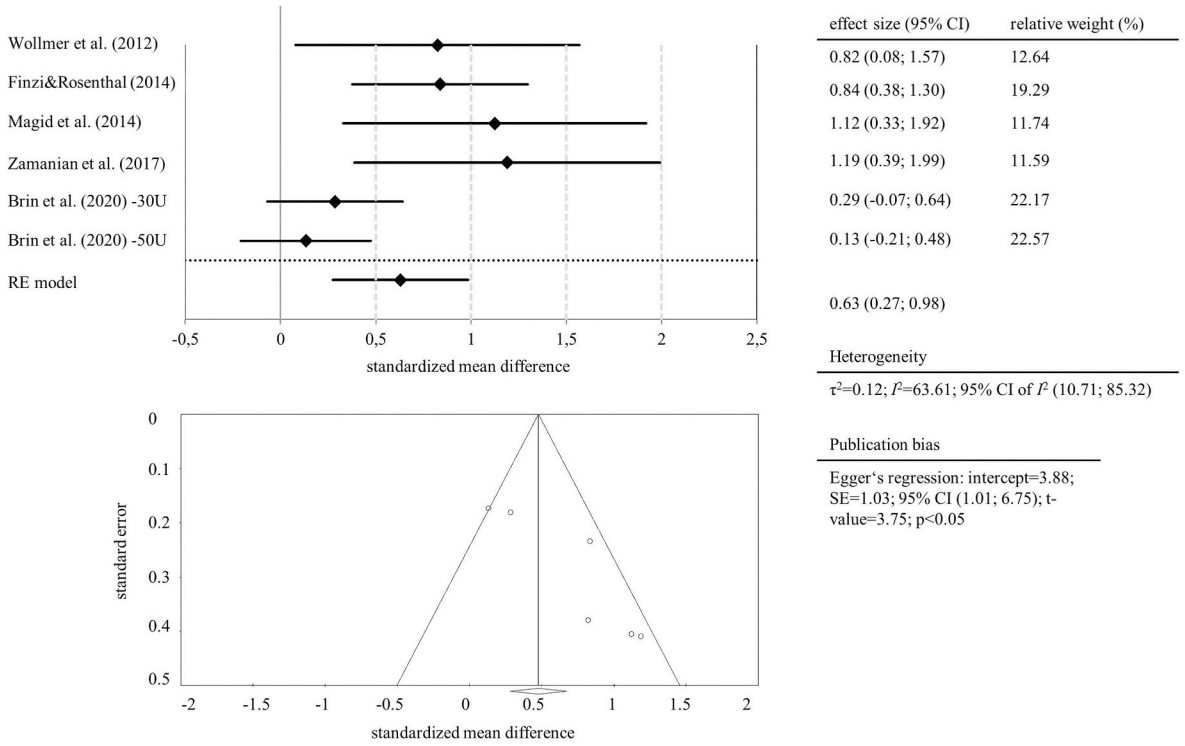


**Fig. 3.** Forest plot and funnel plot for the model of BTX vs. placebo at the primary endpoint (T1).

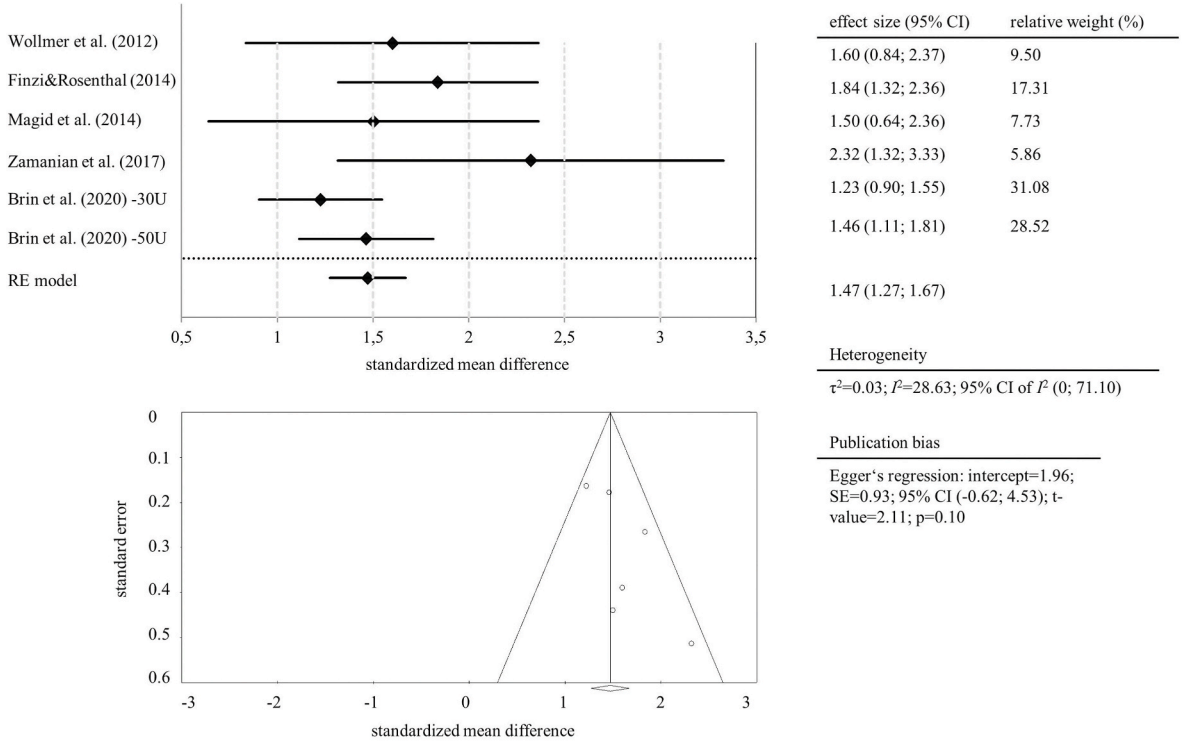


**Fig. 4.** Forest plot and funnel plot for the model of BTX over time (T0 vs. T1).

assumed that the paralysis of the overactive muscles expressing negative emotions interrupts the feedback loop to the brain that normally generates and maintains negative emotions. Underlining its antidepressant effect, recent studies of safety surveillance data revealed a decreased incidence of depressive symptoms in patients treated with BTX for a variety of indications other than depression. This strongly argues against the possibility that the antidepressant effect of BTX may essentially be explained by expectations in this regard (Makunts et al., 2018, 2020).

We conducted a random effects meta-analysis with all five pre-existing RCTs. The analysis suggests that when comparing time and treatment in one model, depressive symptoms were reduced more after the BTX treatment in comparison to placebo ($d$ = 0.98). Further

comparison of BTX and placebo at the primary end point and the pre-post comparison of BTX also revealed significant effect sizes ($d = 0.63$ and $d = 1.47$). The funnel plots and Egger's regression of the interaction comparison (BTX vs. placebo (T0 vs. T0)) and the comparison at the primary endpoint (BTX vs. placebo at T1) suggested a bias. We are convinced that this bias is not introduced by unpublished studies with divergent results, but is rather mediated by the variability in the behavior of the placebo groups, which probably relates to heterogeneity in the cohorts and centers between the studies and to the difficulty with blinding the participants for group allocation. Accordingly, the bias depends on the inclusion of the placebo group and does not occur in the T0 vs. T1 comparison within the BTX groups alone.

Overall, the effect sizes of all three comparisons were slightly smaller than in the previous meta-analysis (Coles et al., 2019a) (BTX vs. placebo (baseline vs. follow ups): $d = 1.28$; BTX vs. placebo at six week follow up: $d = 0.83$, BTX baseline vs. six week follow up: $d = 1.57$), which might be due to the higher number of studies included.

The computed effect sizes of the different comparisons exceed those of state-of-the-art antidepressant medication, which average around $d = 0.31$ (Turner et al., 2008). The inflation of the overall effect size might be once again due to problems with blinding in the primary studies. Real double-blinding is not feasible due to the paralytic effect of BTX. This problem has been addressed by the meta-analysis of Coles et al. (2019a), who suggested a different way of blinding for future research, by injecting BTX into parts of the head that are not thought to be involved in emotion processing. Implementing the concern of inappropriate blinding from a different point of view, a study on the effects of BTX in patients with borderline personality disorder used an open label BTX vs. acupuncture control group setup to account for blinding concerns (NCT02728778). Further the larger effect sizes of our study in comparison to the average pharmacological antidepressant effect size might be influenced by the dosage form. Placebo research revealed higher responses to subcutaneous injections than to oral compounds due to the induced feeling of a "more powerful" treatment (Chae et al., 2018; de Craen et al., 2000). Since common antidepressant medication is primarily applied orally (Das et al., 2019), it should therefore kept in mind that our large effect sizes might be inflated by the kind of administration the underlying studies used.

The heterogeneity of the effect sizes of the primary studies ranges, depending on the comparison, from moderate to high. This should be accounted for in the interpretation of the results. The heterogeneity might have been influenced by the type of symptom assessment. Because we chose to include only the primary outcome of each study, results of self- and external assessment methods were cumulated, although these do not necessarily show high correlations (Keller et al., 1997). Another source of heterogeneity is suspected to emerge from the different inclusion criteria of the primary studies. While some studies included participants with a moderate depression score, some comprised only those with a severe depression symptomatology. Future research should therefore investigate a possible moderating effect of symptom severity on the effect of BTX on depressive symptoms. This was not possible in this meta-analysis due to the small number of primary studies (Borenstein et al., 2010).

## 5. Conclusion and implications

An evaluation of the literature, as well as a meta-analytic approach suggests a superiority of BTX over placebo in the treatment of depressive symptoms and thus on a formal level a 1a level of evidence was reached. However, future investigations should try to address the methodological problems discussed above.

Treatment of depression with glabellar BTX has several advantages: Because the paralytic effects of a single injection last up to three months, treatment adherence is simplified. Additionally, the infrequent injections are less costly compared to long-term psychotherapy, or prolonged treatment with commonly used antidepressants. This appears to be of high importance since the occurrence of depressive disorders is not limited to first world countries and the state-of-art treatment is particularly challenging in countries with a limited mental health care system. The safety and tolerability of BTX is also exceptional: the only adverse event that occurred throughout studies (and groups) was a short-term subsiding headache.

In summary, BTX seems like a treatment option with an empirical effectiveness, high adherence, a positive safety profile, and moderate costs. This makes it an appealing option even for countries with fragile economies and health systems. Since glabellar BTX is not yet registered for the treatment of depressive disorders, its use is considered off-label. Depressed patients who exhibit glabellar frown lines can still receive BTX treatment for their depression, but currently, it must be done under the cosmetic indication in order for it to be considered on-label. Further studies may result in an on-label indication in the near future.

## Declaration of competing interest

Author Kruger has received honoraria for talks and/or advisory board activities from Allergan, Lilly, Lundbeck, Otsuka, Schwabe, Servier, and Trommsdorf. Authors Kruger, Wollmer, and Magid were members of an advisory board of Allergan. Author Magid has received honoraria for talks and/or advisory board activities from Ipsen, Allergan, and Janssen. Author Finzi has been granted patents on the use of BTX to treat depression. All other authors have no conflict of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.01.016.

## Contributors

**Jara Schulze:** Conceptualization, data curation, formal analysis, methodology, writing original draft and review and editing; **Insa Neumann:** Data curation, review and editing; **Michelle Magid:** Supervision, review and editing; **Eric Finzi:** Supervision, review and editing, **Christopher Sinke:** Supervision, review and editing; **M. Axel Wollmer:** Supervision, review and editing; **Tillmann Krueger:** Conceptualization, supervision, review and editing.

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