Web audio at CurrentPsychiatry.com
Dr. Magid: Improved mood doesn't correlate with improvement in wrinkle scores

Current PSYCHIATRY

Botulinum toxin for depression? An idea that's raising some eyebrows

Botulinum toxin injected into forehead muscles has been shown to relieve depressive symptoms

Psychiatry is experiencing a major paradigm shift.[1] No longer is depression a disease of norepinephrine and serotonin deficiency. Today, we are exploring inflammation, methylation, epigenetics, and neuroplasticity as major players; we are using innovative treatment interventions such as ketamine, magnets, psilocin, anti-inflammatories, and even botulinum toxin.

In 2006, dermatologist Eric Finzi, MD, PhD, reported a case series of 10 depressed patients who were given a single course of botulinum toxin A (BTA, onabotulinumtoxinA) injections in the forehead.[2] After 2 months, 9 out of the 10 patients were no longer depressed. The 10th patient, who reported improvement in symptoms but not remission, was the only patient with bipolar depression.

As a psychiatrist (M.M.) and a dermatologist (J.R.), we conducted a randomized controlled trial[3] to challenge the difficult-to-swallow notion that a cosmetic intervention could help severely depressed patients. After reporting our positive findings and hearing numerous encouraging patient testimonials, we present a favorable review on the treatment of depression using BTA. We also present the top 10 questions we are asked at lectures about this novel treatment.

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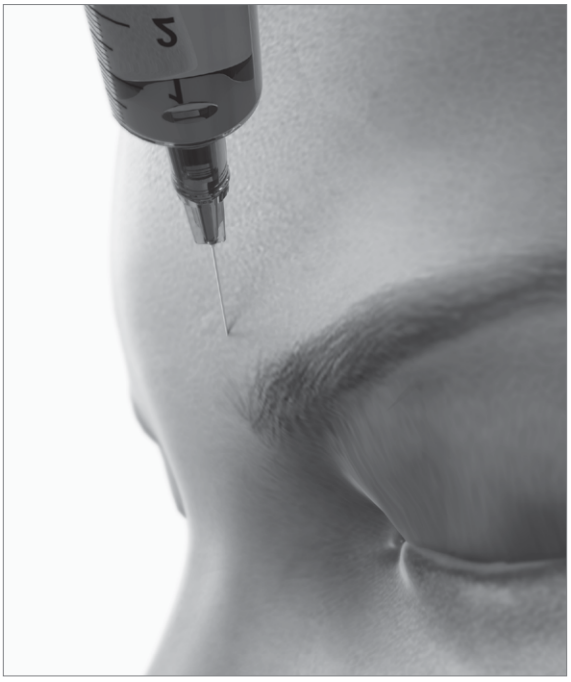
Disclosures
In July 2011, Dr. Magid received a young investigator award from the Brain and Behavior Research Foundation for her study on treating depression using botulinum toxin (Grant number 17648). In November 2012, after completion and as a result of the study on treating depression using botulinum toxin, Dr. Magid became a consultant with Allergan to discuss study findings. In September 2015, Dr. Magid became a speaker for IPSEN Innovation. Dr. Reichenberg is married to Dr. Magid. Dr. Reichenberg has no other conflicts of interest to disclose.



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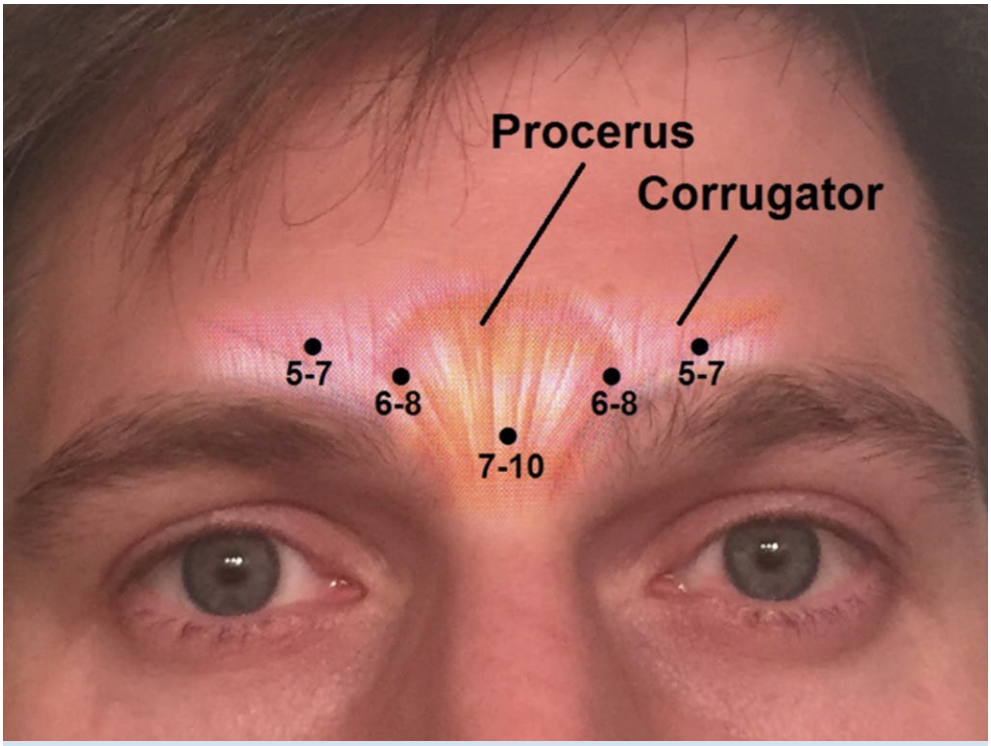
Botulinum toxin for depression

Figure

Target injection sites for botulinum toxin A for depression



Five injections are given into the glabellar region, which comprises the procerus muscle that is sandwiched between 2 corrugator muscles. In most studies, women received 29 units: 7 into the procerus; 6 bilaterally into the overlap of the procerus and corrugator muscles; and 5 bilaterally into the middle of the corrugator muscles. Men received 39 units, 2 units more in each site because of higher muscle mass. (Note: In 1 study, men received 10 units into the procerus, making 40 units total.)

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BTA prevents contraction of muscles in the glabellar region, thus preventing the appearance of a furrowed brow

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A deadly toxin used to treat medical conditions

Botulinum toxin is one of the deadliest substance known to man.[4] It was named after the gram-positive bacterium *Clostridium botulinum*, which causes so-called floppy baby syndrome in infants who eat contaminated honey. Botulinum toxin prevents nerves from releasing acetylcholine, which causes muscle paralysis.

In the wrong hands, botulinum toxin can be exploited for chemical warfare.[4] However, doctors are using it to treat >50 medical conditions, including migraine, cervical dystonia, strabismus, overactive bladder, urinary incontinence, excessive sweating, muscle spasm, and now depression.[5,6] In 2014, BTA was the top cosmetic treatment in the United States, with >3 million procedures performed, generating more than 1 billion dollars in revenue.[7]

The most common site injected with BTA for cosmetic treatments is the glabellar region, which is the area directly above and in between the eyebrows (ie, the lower forehead). The glabella comprises 2 main muscles: the central procerus flanked by a pair of corrugators (***Figure***). When expressing fear, anger, sadness, or anguish, these muscles contract, causing the appearance of 2 vertical wrinkles, referred to as the "11s." The wrinkles also can form the shape of an upside-down "U," known as the omega sign.[8] BTA prevents contraction of these muscles and therefore prevents the appearance of a furrowed brow. During cosmetic procedures, approximately 20 to 50 units of BTA are spread out over 5 glabellar injection sites.[9] A similar technique is being used in studies of BTA for depression[2,3,10,11] (***Figure***).

BTA for depression is new to the mental health world but, before psychiatrists

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caught on, dermatologists were aware that BTA could improve quality of life,[12] reduce negative emotions,[13] and increase feelings of well-being.[14]

The evidence

To date, there have been 2 case series,[2,15] 3 randomized control trials (RCTs),[3,10,11] 1 pooled analysis,[16,17] and 1 meta-analysis[18] looking at botulinum for depression (***Table 1, page 52***).[2,10,11,15-17] In each trial, a single treatment of BTA (ie, 1 doctor's visit; 29 to 40 units of BTA distributed into 5 glabellar injections sites), was the intervention studied.[2]

The first case series, by Finzi and Wasserman[2] is described above. A second case series, published in 2013, describes 50 female patients, one-half depressed and one-half non-depressed, all of whom received 20 units of BTA into the glabella.[15] At 12 weeks, depression scores in the depressed group had decreased by 54% (14.9 point drop on Beck Depression Inventory [BDI], $P < .001$) and self-esteem scores had increased significantly. In non-depressed participants, depression scores and self-esteem scores remained constant throughout the 12 weeks.

A pooled analysis reported results of 3 RCTs[16,17] consisting of a total of 134 depressed patients, males and females age 18 to 65 who received BTA (n = 59) or placebo (n = 74) into the glabellar region. At the end of 6 weeks, BDI scores in the depressed group had decreased by 47.4% (14.3 points) compared with a 16.2% decrease (5.1 points) in the placebo group. This corresponds to a 52.5% vs 8.0% response rate and a 42.4% vs 8.0% remission rate, respectively (***Table,***[1,2,10,11,15-17] ***page 52***). There was no difference between the 2 groups in sex, age, depression severity, and number of antidepressants being taken. Females received 29 units and males received 10 to 11 units more to account for higher muscle mass (***Figure, page 46***).

Depression as measured by the physician-administered Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale showed similar reduction in overall scores (–45.7% vs –14.6%), response rates (54.2% vs 10.7%) and remission rates (30.5% vs 6.7%) with BTA.

Although these improvements in depression scores do not reach those seen with electroconvulsive therapy,[19,20] they are comparable to placebo-controlled studies of antidepressants.[21,22]

Doesn't this technique work because people who look better, feel better?

Aesthetic improvement alone is unlikely to explain the entire story. A recent study showed that improvement in wrinkle score did not correlate with improvement in mood.[23] Furthermore, some patients in RCTs did not like the cosmetic effects of BTA but still reported feeling less depressed after treatment.[10]

How might it work?

Several theories about the mechanism of action have been proposed:

- **The facial feedback hypothesis** dates to Charles Darwin in 1872: Facial movements influence emotional states. Numerous studies have confirmed this. Strack et al[24] found that patients asked to smile while reading comics found them to be funnier. Ekman et al[25] found that imitating angry facial expressions made body temperature and heart rate rise. Dialectical behavioral therapy expert Marsha Linehan recognized the importance of modifying facial expressions (from grimacing to smiling) and posture (from clenched fists to open hands) when feeling distressed, because it is hard to feel "willful" when your "mind is going one way and your body is going another."[26] Accordingly, for a person who continuously "looks" depressed or distressed, reducing the anguished facial expression using botulinum toxin might diminish the entwined negative emotions.
- **A more pleasant facial expression improves social interactions,** which leads to improvement in self-esteem and mood. Social biologists argue that (1) we are attracted to those who have more pleasant facial expressions and (2) we steer clear of those who appear angry or depressed (a

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A recent study showed that improvement in wrinkle score did not correlate with improvement in mood

Botulinum toxin for depression

Clinical Point

It is possible that, after BTA, a person's social connectivity is improved because of a more positive reciprocal firing of mirror neurons

Table 1

Studies on treating major depressive disorder using botulinum toxin A

Study	Design	Were patients taking an antidepressant?	Length of trial	Week for reporting results
Finzi and Wasserman 2006[2]	Case series; 10 depressed females age 18 to 65, all receiving BTA	No: 5 Yes: 5	8 weeks	Week 6
Wollmer et al, 2012[10]	RCT; 30 depressed males and females age 25 to 64, 15 receiving BTA and 15 receiving placebo	No: 1 Yes: 29	16 weeks	Week 6
Hexsel et al, 2013[15]	Case series; 50 females age 25 to 60, 25 depressed and 25 non-depressed, all receiving BTA	Yes: 25 No: 25 All depressed patients were taking an antidepressant	12 weeks	Week 12
Finzi et al, 2014[11]	RCT; 74 depressed males and females, 33 receiving BTA and 41 receiving placebo	No: 43 Yes: 31	6 weeks	Week 6
Magid et al, 2014[16]	Crossover RCT; 30 depressed males and females, 11 receiving BTA and 19 receiving placebo. Groups switched treatment halfway through study	No: 4 Yes: 26	24 weeks	Week 6, Week 18 (crossover at week 12)
Magid et al, 2015[17]	Pooled analysis; 134 depressed males and females, 59 receiving BTA and 75 receiving placebo	No: 48 Yes: 86	Variable	Week 6

BDI-II: Beck Depression Inventory-II; BTA: botulinum toxin A; HAMD-17: Hamilton Depression Rating Scale-17; RCT: randomized controlled trial

negative facial expression, such as a growling dog, is perceived as a threat). Therefore, anyone who looks depressed might have less rewarding interpersonal interactions, which can contribute to a poor mood.

On a similar note, mirror neurons are regions in the brain that are activated by witnessing another person's emotional cues. When our mirror neurons light up, we can feel an observed experience, which is why we often feel nervous around anxious people, or cringe when we see others get hurt, or why we might prefer engaging with people who appear happier. It is possible that, after BTA injection, a person's social connectivity is improved because of a more positive reciprocal firing of mirror neurons.

- **BTA leads to direct and indirect neurochemical changes in the brain** that can reduce depression. Functional MRI studies have shown that after glabellar BTA injections, the amygdala was less responsive to negative stimuli.[27,28] For example, patients who were treated with BTA and then shown pictures of angry people had an attenuated amygdala response to the photos.

This is an important finding, especially for patients who have been traumatized. After a traumatic event, the amygdala "remembers" what happened, which is good, in some ways (it prevents us from getting into a similar dangerous situation), but bad in others (the traumatized amygdala may falsely perceive a non-threatening stimuli as

Comments
Depressed patients treated with BTA experienced a 90% BDI-II response rate and a 73.6% reduction in BDI-II scores
Depressed patients treated with BTA vs placebo experienced a –47% vs –9% change in score (P = .002), a 60% vs 13% response rate (P = .02), and a 33% vs 13% remission rate (P > .05) as measured by HAMD-17
Depressed patients treated with BTA experienced a 54.4% reduction in BDI scores in (P < .001). Self-esteem scores also significantly improved. Non-depressed patients' self-esteem and depression scores did not significantly change
Depressed patients treated with BTA vs placebo experienced a –55% vs –21% change in score (P < .001), a 61% vs 12% response rate (P < .0001), and a 48% vs 12% remission rate (P < .001) as measured BDI-II
Depressed patients treated with BTA vs placebo experienced a –42% vs –15% change in score (P < .0001), a 45% vs 5% response rate (P = .0067), and a 27% vs 5% remission rate (P = .09) as measured BDI. Depressed patients treated with BTA continued to improve throughout the 24 weeks, even when cosmetic effects of BTA wore off When placebo patients were switched to BTA, they also showed a statistically significant improvement
Depressed patients treated with BTA vs placebo experienced a –47% vs –16% change in score (P < .0001), a 53% vs 8% response rate (P < .0001), and a 42% vs 8% remission rate (P < .0001)

threatening). A hypervigilant amygdala can lead to an out-of-proportion fear response, depression, and anxiety. Therefore, quelling an overactive amygdala with BTA could improve emotional dysregulation and post-traumatic disorders.

Many of our patients reported that, after BTA injection, "traumatic events didn't feel as traumatizing," as one said. The emotional pain and rumination that often follow a life stressor "does not overstay its welcome" and patients are able to "move on" more quickly.

It is unknown why the amygdala is quieted after BTA; researchers hypothesize that BTA suppresses facial feedback signals from the forehead branch of the trigeminal nerve to the brain. Another hypothesis is that BTA is directly transported by the trigeminal nerve into the brain and exerts central pharmacological effects on the amygdala.[29] This theory has only been studied in rat models.[30]

When does it start working? How long does it last?

From what we know, BTA for depression could start working as early as 2 weeks and could last as long as 6 months. In one RCT, the earliest follow-up was 2 weeks,[10] at which time the depressed patients had responded to botulinum toxin ($P \leq .05$). In the other 2 controlled trials, the earliest follow-up was 3 weeks, at which time a more robust response was seen ($P < .001$). Aesthetically, BTA usually lasts 3 months. It is unclear how long the antidepressant effects last but, in the longest trial,[3] depression symptoms continued to improve at 6 months, after cosmetic effects had worn off.

These findings raise a series of questions:

- Do mood effects outlast cosmetic effects? If so, why?
- Does botulinum toxin start to work sooner than 2 weeks?
- Will adherence improve if a patient has to be treated only every 6 months?

In our clinical experience, depressed patients who responded to BTA injection report a slow resurfacing of depressive symptoms 4 to 6 months after treatment, at which point they usually return for "maintenance treatment" (same dosing, same injection configuration).

Will psychiatrists administer the treatment?

Any physician or physician extender can, when properly trained, inject BTA. The question is: Do psychiatrists want to?

Administrating botulinum toxin requires more labor and preparation than prescribing a drug (***Table 2***,[31] ***page 54***) and requires placing hands on patients. Depending on the type of psychiatric practice, this may be a "deal-breaker" for some providers, such as those in a psychoanalytic practice who might worry about boundaries.

As a basis for comparison, despite several indications for BTA for headache and

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Depressed patients who responded to BTA injection report a slow resurfacing of depressive symptoms 4 to 6 months after treatment

Botulinum toxin for depression

Clinical Point

Patients with anxious or agitated depression might be ideal candidates for BTA injection

Table 2

Starting a botulinum toxin for depression practice can be daunting

Obtain certification on proper injection technique; get training on how to reconstitute BTA powder into the active form
Set up an account with a reputable supplier for BTA delivery
Set up an account to obtain ancillary supplies, including syringes, alcohol pads, gauzes, gloves, and ice packs
Buy a medical-grade refrigerator with a lock to store the BTA product; create a protocol to ensure that the refrigerator stays at the appropriate temperature
Obtain a sharps box to dispose of used needles that meets health and safety regulation standards; create a system to ensure the box is emptied appropriately when full
Create patient consent forms and new note templates for BTA visits
Create different appointment slots for BTA procedures; you could need more or less time than a typical patient visit, depending on your skill. Schedule patients close enough together to ensure you use all BTA before it loses effectiveness and needs to be discarded (FDA recommends using within 24 hours of reconstitution[31])
Addition of a new procedure might affect your malpractice insurance; check with your carrier on rate adjustments
Medical procedures may require you to update your billing system or hire extra medical staff to help assist and coordinate care, or both

BTA: botulinum toxin A

neurologic conditions, few neurologists have added botulinum toxin to their practice. Dermatologists who are comfortable seeing psychiatric patients or family practitioners, who are already set up for injection procedures, could become custodians of this intervention.

Which patients are candidates for the treatment?

Patients with anxious or agitated depression might be ideal candidates for BTA injection. A recent study looked at predictors of response: Patients with a high agitation score (as measured on item 9 of the HAM-D) were more likely to respond, with a sensitivity of 100%, a specificity of 56%, and an overall precision of 78%.[32] So far, no other predictors of response have been clearly identified. Higher baseline wrinkle scores do not predict better response.[23] Sex and age do not have any predictive value. The treatment appears to be equally effective in males and females; because only a handful of males have been treated (n = 14), however, these patients need to be studied further.

Is botulinum toxin better as monotherapy or augmentation strategy?

So far, it appears to be equally effective as monotherapy or augmentation strategy,[16] but more studies are needed.

How expensive is it?

Estimates of patient cost include the cost of the product and the professional fee for injection. As a point of reference, for cosmetic purposes, depending on practice location, dermatologists charge $11 to $20 per unit of BTA. Therefore, 1 treatment of BTA for depression (29 to 40 units) can cost a patient $319 to $800.

When treating a patient with BTA for medical indications, such as tension headache, insurance often reimburses the physician for the BTA at cost (paid with a J code: J0585) and pay an injection fee (a procedure code) of $150 to $200. A recent analysis of cost-effectiveness estimated that BTA for depression would cost a patient $1,200 to $1,600 annually.[33] Compared with the price of branded medications (eg, $500 to $2,000 annually)[33] plus weekly psychotherapy (eg, $2,000 to $5,000 annually), BTA may be a cost-effective option for patients who do not respond to conventional treatments. Of course, for patients who tolerate and respond to generic medications or have a therapist who charges on a sliding scale, BTA is not the most cost-effective option.

What about injecting other areas of the face?

We've thought about it but haven't tried it.

There are several muscles around the mouth that allow us to smile and frown. BTA injections in the depressor anguli oris, a muscle around the mouth that is largely responsible for frowning, could treat depression. However, if the mechanism of action is via amygdala desensitization through the trigeminal nerve, treating mouth frown muscles might not work.

Is it safe?

BTA in the glabella has an exceptionally good safety profile.[9,31,34] Adverse reactions, which include eyelid droop, pain, bruising, and redness at the injection site, are minor and temporary.[9] In addition, BTA has few drug–drug interactions. The biggest complaint for most patients is discomfort upon injection, which often is described as feeling like "an ant bite."

In the pooled analysis of RCTs, apart from local irritation immediately after injection, temporary headache was the only relevant, and possibly treatment-related, adverse event. Headache occurred in 13.6% (n = 8) of the BTA group and 9.3% (n = 7) of the placebo group (P = .44). Compared with antidepressants such as citalopram, where approximately 38.6% of patients report a moderate or severe side-effect burden,[21] BTA is well tolerated.

Are other studies underway?

Larger studies are being conducted,[35] mainly to confirm what pilot studies have shown. It would be interesting to discover other predictors of response and if different dosing and injection configurations could strengthen the response rate and extend the duration of effect.

Because of the cosmetic effects of BTA, further studies are needed to address the problem of blinding. In earlier studies, raters were blinded during appointments because patients wore surgical caps that covered their glabellar region.[3,10] Patients did not know their treatment intervention, but 52% to 90% of patients guessed correctly.[3,10,11] Although unblinding is a common problem in "blinded" trials in which some researchers have reported >75% of participants and raters guessed the intervention correctly,[36] it is a particularly sensitive area in studies that involve a change in appearance because it is almost impossible to prevent someone from looking in a mirror.

Summing up

Botulinum toxin for depression is not ready for prime time. The FDA has not approved its use for psychiatric indications, and Medicare and commercial insurance do not reimburse for this procedure as a treatment for depression. Patients who request BTA for depression must be informed that this use is off-label.

For now, we recommend psychotherapy or medication management, or both, for most patients with major depression. In addition, until larger studies are done, we recommend that patients who are interested in BTA for depression use it as an add-on to conventional treatment. However, if larger studies replicate the findings of the smaller studies we have described, botulinum toxin could become a novel therapeutic agent in the fight against depression.

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Clinical Point

Apart from local irritation, temporary headache was the only relevant, and possibly the only treatment-related, adverse event of BTA

Botulinum toxin for depression

Clinical Point

We recommend that patients who are interested in BTA for depression use it as an add-on to conventional treatment

Related Resources

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- Botox for depression. www.botoxfordepression.com.
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Drug Brand Names

Botulinum toxin A • Botox
Citalopram • Celexa

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Bottom Line

In pilot studies, botulinum toxin A (BTA) has shown efficacy in improving symptoms of depression. Although considered safe, BTA is not FDA-approved for psychiatric indications, and Medicare and commercial insurance do not reimburse for this procedure for depression. Larger studies are underway to determine if this novel treatment can be introduced into practice.