Botulinum Toxin for Major Depressive Disorder

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Q. What is botulinum toxin?

A. Botulinum toxin (BTX) is a neurotoxin produced by the bacterium *Clostridium botulinum*. Serotype A (BTX-A) is the form most commonly used in clinical applications. BTX was first approved by the U.S. Food and Drug Administration (FDA) under the brand name Botox in 1989 for the management of strabismus (crossed eyes) and blepharospasm (eyelid twitching), and went on to be used to treat other conditions characterized by muscular overactivity (Chen, 2012). BTX is most well known as a cosmetic treatment for temporary reduction of facial lines and wrinkles. BTX is injected into the affected muscles, and the effects typically last about three months. In 2010, the FDA approved intramuscular BTX injections for prophylactic treatment of chronic migraine headache (Chen, 2012). Glabellar injection (between the eyebrows) of BTX is currently being investigated in Phase III clinical trials as a treatment for depression.

Q. What is the potential mechanism of action underlying BTX?

A. The mechanism of action by which BTX can reduce symptoms of depression is unknown (Kruger & Wollmer, 2015). Some investigating BTX as a treatment for depression attribute its proposed mechanism to a "facial feedback" hypothesis which describes the bidirectional communication between the brain and facial muscles (Finzi & Rosenthal, 2016). Corrugator muscles, those involved in frowning, are viewed as part of a feedback loop connecting the face to the emotional centers of the brain (limbic system) that reinforces and maintains the negative emotions associated with depression (Kruger & Wollmer, 2015). BTX blocks the release of acetylcholine, a neurotransmitter critical to the activity of motor neurons in the neuromuscular junction, causing local muscle paralysis. According to the facial feedback hypothesis, by inhibiting frowning, BTX injections in corrugator muscle fibers interrupt feedback to the limbic system. Preliminary evidence demonstrates that participants receiving BTX injections in corrugator muscle fibers have less of a response in the amygdala to negative stimuli (Henlotter et al., 2009; Kim et al., 2014).

Q. Is BTX recommended as a treatment for major depressive disorder (MDD) in the Military Health System (MHS)?

A. No. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* does not include BTX as a treatment for MDD.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend BTX as a treatment for MDD?

A. No. Other authoritative reviews have not substantiated the use of BTX for MDD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No comparative effectiveness reviews including studies on BTX for depression were identified.
- Cochrane: No systematic reviews of BTX for depression were identified.

Q. Is there any recent research on botulinum toxin as a treatment for MDD?

A. A literature search conducted in October 2019 identified five randomized controlled trials (RCTs) evaluating the efficacy of BTX as a treatment for MDD. Two meta-analyses (Parsaik et al., 2016;

Magid et al., 2015) include three of these RCTs (Wollmer et al., 2012; Finzi & Rosenthal, 2014; Magid et al., 2014). These studies investigated BTX as an adjunctive treatment to antidepressant medications, were conducted with adult male and female patients with major depressive disorder (N = 134) based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), and randomized patients to receive either a single injection of BTX (different doses across studies) or placebo. The primary end point of these studies was reduction in self-reported depressive symptoms at six week follow-up. Meta-analyses found that BTX was superior to placebo in improving self-reported depression scores at six weeks. The few adverse events reported in these trials were known side effects of BTX, including local irritation at the injection site and headaches during the first week after injection.

Two more recent RCTs not included in meta-analyses were identified. One RCT on 28 patients with DSM-V MDD found that scores on the Beck Depression Inventory were significantly improved at six weeks in the BTX group compared to placebo (Zamanian, Ghanbari Jolfaei, Mehran, & Azizan, 2017). The second larger RCT sponsored by Allergan (maker of Botox) randomized 255 females with DSM-IV MDD into three groups: two different doses of BTX (30 U or 50 U as a single dose) or placebo (Brin et al., 2019). In this study, improvements in self-reported depressive symptoms (as measured with the Montgomery-Asberg Depression Rating Scale) were significant for the 30 U group at three and nine weeks, but not at six weeks. Significant differences were not found for the 50 U group.

A critical review of BTX for MDD includes four of the above studies (Wollmer et al., 2012; Finzi & Rosenthal, 2014; Magid et al., 2014; Zamanian et al., 2017) and describes some limitations of these trials (Stearns, Shad, & Guzman, 2018). A primary issue is whether adequate blinding can be implemented in trials on BTX, given its noticeable cosmetic effects. The authors of this review note that the high response rates and unusually low placebo rates found in these trials may be related to unblinding, and suggest use of a more convincing placebo, such as collagen filler.

Q. What conclusions can be drawn about the use of botulinum toxin as a treatment for MDD in the MHS?

A. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* does not include BTX as a treatment for MDD. Though several RCTs have found promising results for BTX as a potential treatment for MDD, most of the trials have been small, and the one large trial did not find BTX to be significantly more effective at the primary end point (six months) for the smaller dose, or at any time point for the larger dose. As the review by Stearns et al. notes, the possibility of unblinding from the cosmetic effects of BTX may introduce biases that explain the unusual and significantly low placebo rates and high treatment response rates. This evidence brief concludes that more trials are needed, with adequate sample sizes and appropriate placebos, in order to determine the efficacy of BTX as a therapeutic option for MDD, as well as identify adverse effects based on repeated and long-term use and clarify the optimal dosing, delivery, and treatment combination.

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