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 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 as a treatment for MDD?

A: The mechanism of action by which BTX can reduce symptoms of depression is unknown (Kruger & Wollmer, 2015; Li et al., 2021). 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; Li et al., 2021). 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; Li et al., 2021). 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 MDD in the Military Health System (MHS)?

A: No. The 2022 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 on the use of BTX for MDD have been identified.

Other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DoD CPGs. Notable among these is Cochrane, an international network that conducts high-quality reviews of healthcare interventions.

Q: What conclusions can be drawn about the use of BTX as a treatment for MDD in the MHS?

A: The 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. A review by Stearns et al. notes that possible unblinding from the cosmetic effects of BTX may introduce biases that explain the unusual and significantly low placebo rates and high treatment response rates. More trials are needed, with adequate sample sizes and appropriate placebos, to determine the efficacy of BTX as a therapeutic option for MDD. In addition, further research could help identify adverse effects based on repeated and long-term use and clarify the optimal dosing, delivery, and treatment combination.

References

Chen, S. (2012). Clinical uses of botulinum neurotoxins: Current indications, limitations, and future developments. *Toxins, 4*(10), 913-939. https://doi.org/10.3390/toxins4100913

Department of Veterans Affairs/Department of Defense. (2022). *VA/DoD clinical practice guideline for management of major depressive disorder (version 4.0)*. https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf

Finzi, E., & Rosenthal, N. E. (2013). Treatment of depression with onabotulinumtoxin A: A randomized, double-blind, placebo-controlled trial. *Journal of Psychiatric Research, 52*, 1-6. https://doi.org/10.1016/j.jpsychires.2013.11.006

Hennenlotter, A., Dresel, C., Castrop, F., Ceballos-Baumann, A. 0., Wohlschlager, A. M., & Haslinger, B. (2009). The link between facial feedback and neural activity within central circuitries of emotion: New insights from botulinum toxin-induced denervation of frown muscles. *Cerebral Cortex, 19*(3), 537- 542. https://doi.org/ 10.1093/cercor/bhn104

Kim, M. J., Neta, M., Davis, F. C., Auberry, E. J., Dinescu, D., Heatherton, T. F., Stotland, M.A., & Whalen, P. J. (2014). Botulinum toxin-induced facial muscle paralysis affects amygdala responses to the perception of emotional expressions: Preliminary findings from an A-B-A design. *Biology of Mood & Anxiety Disorders, 4*, 11. https://doi.org/10.1186/2045-5380-4-11

Kruger, T. H. & Wollmer, M. A. (2015). Depression: An emerging indication for botulinum toxin treatment. *Toxicon, 107(Pt. A)*, 154- 157. https://doi.org/10.1016/j.toxicon.2015.09.035

Li, Y., Liu, T., & Luo, W. (2021). Botulinum neurotoxin therapy for depression: Therapeutic mechanisms and future perspective. *Frontiers in Psychiatry, 12*, 584416. https://doi.org/10.3389/fpsyt.2021.584416

Stearns, T.P., Shad, M.U., & Guzman, G.C. (2018). Glabellar botulinum toxin injections in major depressive disorder: A critical review. *Primary Care Companion for CNS Disorders, 20*(5). https://doi.org/10.4088/PCC.18r02298