

Q. What is vagus nerve stimulation?

A. Originally approved for the treatment of epilepsy, vagus nerve stimulation (VNS) comprises indirect stimulation of neural networks via the vagus nerve, the tenth cranial nerve. VNS often involves an invasive procedure in which a pulse generator (similar to a pacemaker), implanted below the skin in the patient's chest, connects to electrodes on the left vagus nerve in the neck via an electrical lead (VA/DoD, 2016). Following implantation, the pulse generator is controlled by a computer, and is programmed to periodically send electrical impulses 24 hours a day (typically for 30 seconds every five minutes), usually for a ten-week period. Recently, novel noninvasive VNS devices have been developed, allowing for external stimulation of the vagus nerve (Bremner et al., 2020). VNS is a U.S. Food and Drug Administration (FDA)-approved intervention for treatment-resistant depression (FDA, 2005), and is being evaluated as a potential treatment for other mental health disorders, including obsessive compulsive disorder (OCD), schizophrenia, panic disorder (PD), and posttraumatic stress disorder (PTSD; Cimpianu, Strube, Falkai, Palm, & Hasan, 2016).

Q. What are the potential mechanisms of action underlying VNS for the treatment of PTSD?

A. The vagus nerve carries signals back and forth between the central nervous system and the digestive system and organs, and is involved in a wide range of functions. During VNS, a pulse generator sends electrical impulses through the vagus nerve to the brain, altering the excitability of nerve cells. The exact mechanisms by which VNS may alleviate PTSD symptoms are unknown. The vagus nerve sends inputs to several regions of the brain, including the locus coeruleus, the main source of norepinephrine in the brain. Stimulation-induced increases in norepinephrine from VNS may be responsible for improvements in cognitive processing, learning and memory, and mood (Hassert, Miyashita, & Williams, 2004; Roosevelt, Smith, Clough, Jensen, & Browning, 2006). In individuals with PTSD, increases in norepinephrine in limbic regions may result in improvements in extinction learning (Breit, Kupferberg, Rogler, & Hasler, 2018). In animal models of PTSD, VNS enhances extinction of conditioned fear and reduces anxiety (Noble, Souza, & McIntyre, 2019; Souza et al., 2019).

Q. Is VNS recommended as a treatment for PTSD in the Military Health System (MHS)?

A. **No.** The 2017 VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder states that there is insufficient evidence to recommend for or against VNS.

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 VNS as a treatment for PTSD?

A. **No.** Other authoritative reviews have not substantiated VNS for PTSD.

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 were identified that include VNS as a treatment for PTSD.
- Cochrane: No systematic reviews of VNS for PTSD were identified.

Q. Is there any recent research on VNS as a treatment for PTSD?

A. A March 2021 literature search identified one randomized controlled trial (RCT) and one systematic review that evaluated the efficacy of VNS as a treatment for PTSD. Cimpianu et al. (2016) conducted a systematic review of VNS use in psychiatry. Out of the 33 studies in the review, only one included PTSD patients. This was an open-label study of 11 patients with treatment-resistant anxiety disorders, only two of whom were diagnosed with PTSD (George et al., 2008).

In a recent RCT, Gurel et al. (2020) randomized 25 patients with PTSD to receive either transcutaneous cervical (noninvasive) VNS (tcVNS) or sham tcVNS. This trial examined the physiological effects of tcVNS in patients with PTSD resulting from traumatic and mental stress. Personalized traumatic stress scripts were developed for each participant based on their own written accounts. tcVNS stimulation was administered following exposure to personalized traumatic stress scripts and mentally stressful activities (public speech, mental arithmetic) over a three day period. Both active and sham tcVNS devices produced voltages that could be felt by the participants, but the sham tcVNS used a lower frequency signal which was unlikely to induce vagal stimulation. Participants randomized to receive active tcVNS exhibited decreased sympathetic function (as measured by some of the physiological outcome measures, including heart rate) compared to participants receiving sham stimulation. PTSD symptoms were not included as an outcome of this study.

Q. What conclusions can be drawn about the use of VNS as a treatment for PTSD in the MHS?

A. Currently, there is insufficient evidence to recommend the use of VNS as a treatment for PTSD. Much of the evidence supporting the treatment mechanisms behind VNS for PTSD comes from animal studies. Though FDA-approved for treatment-resistant depression, the *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* strongly recommends against the use of VNS for the treatment of MDD due to the lack of evidence of efficacy, safety concerns (there are numerous side effects), and associated costs. The use of VNS has been limited by the cost and invasive nature of the surgical implantation of the device, and non-compliance rates have been high in VNS studies (Gurel et al., 2020). Novel noninvasive VNS technology may encourage future RCTs evaluating the efficacy of VNS for the reduction of PTSD symptoms.

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