

Q. What is vagus nerve stimulation?

A. Originally approved for the treatment of epilepsy, vagus nerve stimulation (VNS) is a U.S. Food and Drug Administration-approved intervention for treatment-resistant depression, indicated for “the adjunctive long-term treatment of chronic or recurrent depression for patients 18 or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments” (U.S. Food & Drug Administration, 2005). VNS involves indirect stimulation of neural networks via the vagus nerve, one of the cranial nerves. VNS often involves an invasive procedure where a pulse generator (similar to a pacemaker) is implanted below the skin in the patient’s chest, which 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 10-week period.

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

A. VNS was first considered as a treatment for major depressive disorder (MDD) based on clinical observations of improved mood and cognition in studies of VNS for epilepsy (Rush et al., 2000). It has been hypothesized that stimulation of the vagus nerve alters neurotransmitter levels and modulates activity of brain regions (Rush et al., 2005). VNS has been shown to alter concentrations of neurotransmitters in the cerebrospinal fluid of epilepsy patients (Carpenter et al., 2004), and has been shown to modulate the functional activity of regions of the brain in neuroimaging studies (Chae et al., 2003). However, the mechanisms of action of VNS are still unclear.

Q. Is VNS recommended as a front-line treatment for MDD in the Military Health System (MHS)?

A. No. The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder gives a “Strong Against” strength of recommendation for VNS for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting. This guideline is based on the lack of evidence of efficacy, safety concerns, and associated costs.

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 front-line treatment for MDD?

A. No. Other authoritative reviews have not substantiated VNS 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: A 2011 comparative effectiveness review of non-pharmacologic interventions for treatment-resistant depression (TRD) in adults found that there was no significant difference between VNS and sham comparisons on depressive severity and remission rates, but there was “Low” strength of evidence supporting this conclusion (Gaynes et al., 2011).
- Cochrane: No systematic reviews of VNS for depression were identified.

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

A. 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.

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References

- Carpenter, L. L., Moreno, F. A., Kling, M. A., Anderson, G. M., Regenold, W. T., Labiner, D. M., & Price, L. H. (2004). Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biological Psychiatry*, 56(6), 418–426.
- Chae, J. H., Nahas, Z., Lomarev, M., Denslow, S., Lorberbaum, J. P., Bohning, D. E., & George, M. S. (2003). A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *Journal of Psychiatric Research*, 37(6), 443–455.
- Department of Veterans Affairs/Department of Defense. (2016). *VA/DoD clinical practice guideline for management of major depressive disorder. Version 3.0*. Washington (DC): Department of Veterans Affairs/Department of Defense.
- Gaynes, B. N., Lux, L. J., Lloyd, S. W., Hansen, R. A., Gartlehner, G., ... Lohr, K. N. (2011). *Nonpharmacologic interventions for treatment-resistant depression in adults* (AHRQ Publication No. 11-EHC056-EF). Rockville, MD: Agency for Healthcare Research and Quality.
- Rush, A. J., George, M. S., Sackeim, H. A., Marangell, L. B., Husain, M. M., Giller, C., ... Goodman, R. (2000). Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biological Psychiatry*, 47(4), 276–286.
- Rush, A. J., Marangell, L. B., Sackeim, H. A., George, M. S., Brannan, S. K., Davis, S. M., ... Cooke, R. G. (2005). Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry*, 58(5), 347–354.
- U.S. Food and Drug Administration. Premarket Approval. VNS Therapy System. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S050>.

