**A Comprehensive Review of Vagus Nerve Stimulation for Depression**

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**Abstract**

**Objectives:** Vagus nerve stimulation (VNS) is reemerging as an exciting form of brain stimulation, due in part to the development of its noninvasive counterpart transcutaneous auricular VNS. As the field grows, it is important to understand where VNS emerged from, including its history and the studies that were conducted over the past four decades. Here, we offer a comprehensive review of the history of VNS in the treatment of major depression.

**Materials and methods:** Using PubMed, we reviewed the history of VNS and aggregated the literature into a narrative review of four key VNS epochs: 1) early invention and development of VNS, 2) path to Food and Drug Administration (FDA) approval for depression, 3) refinement of VNS treatment parameters, and 4) neuroimaging of VNS.

**Results:** VNS was described in the literature in the early 1900s; however, gained traction in the 1980s as Zabara and colleagues developed an implantable neurocybernetic prosthesis to treat epilepsy. As epilepsy trials proceed in the 1990s, promising mood effects emerged and were studied, ultimately leading to the approval of VNS for depression in 2005. Since then, there have been advances in understanding the mechanism of action. Imaging techniques like functional magnetic resonance imaging and positron emission tomography further aid in understanding direct brain effects of VNS.

**Conclusions:** The mood effects of VNS were discovered from clinical trials investigating the use of VNS for reducing seizures in epileptic patients. Since then, VNS has gone on to be FDA approved for depression. The field of VNS is growing, and as noninvasive VNS quickly advances, it is important to consider a historical perspective to develop future brain stimulation therapies.

**Keywords:** Depression; major depressive disorder; tVNS; taVNS; vagus nerve stimulation.

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