



# How Mental Health is Shortchanged by Lack of Reimbursement for Vagus Nerve Stimulation

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In 2007, the Centers for Medicare and Medicaid Services (CMS) denied reimbursement for the use of VNS Therapy® (LivaNova PLC, London, UK) in treatment-resistant depression, despite overwhelmingly positive clinical data. Positive data continues to accumulate in favor of the novel medical device, but the CMS has not yet reversed its decision. In this article, which was published in *Brain Stimulation* on December 30, 2015, we explore the potential for VNS Therapy to meet the needs of patients who have not improved with the standard of care, and how the lynchpin to providing patient access lies in reimbursing them for the device.

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## How Mental Health Is Shortchanged by Lack of Reimbursement for Vagus Nerve Stimulation

With a continuing weekly newsfeed on the destructive consequences of inadequate mental healthcare and with growing data on how depression negatively impacts the ability to perform daily tasks and engage in social interactions, why does a proven therapeutic intervention for chronic depression still remain far out of reach for so many patients?

More than one-third of the patients who can tolerate first-line antidepressant pharmacotherapies do not achieve remission or response to treatment; they may be defined as having treatment-resistant depression (TRD) [1]. While the variety of available drugs and treatment courses demonstrate efficacy in some patients, the current treatment paradigm continues to fail millions of people worldwide each year, which emphasizes the need for new, accessible classes of therapies with greater promise.

As healthcare industry analysts from Wall Street, we have the unique perspective of focusing on the developing landscape of therapies available to patients. We make a living analyzing concrete scientific results, healthcare policy, and the cost-benefit of therapies to patients and health economics as a whole. Here we discuss the obstructed availability of a novel antidepressant, which has objectively demonstrated efficacy in the TRD population, and its cost-effectiveness.

In 2005, a vagus nerve stimulation (VNS) device called VNS Therapy® was approved for TRD by the United States' Food and Drug Administration (FDA) [2]. The device, while novel in the treatment of mood disorders, had already been approved in 1997 for the treatment of epilepsy. A decade of newer research shows that VNS offers a unique and indispensable antidepressant mechanism of action to patients who have not previously responded to traditional pharmaceuticals or electroconvulsive therapy (ECT). Developed by Cyberonics, Inc., VNS Therapy uses an electrical pulse generator implanted in the chest that periodically stimulates the left vagus nerve in the mid cervical region [3], which sends signals through the nucleus tractus solitarius and to various regions of the brain [4].

However, as TRD patients and their doctors know, FDA approval is not always the final hurdle in facilitating patient access to emerging medical technologies. In 2007, the United States' Centers for Medicare and Medicaid Services (CMS) essentially nullified FDA approval by denying reimbursement for the device to TRD patients, effectively blocking access for those under either Medicare or Medicaid, regardless of history of failed treatment. This decision hits those with TRD especially hard, as they are highly likely to rely on affordable or state-subsidized healthcare. For example, persistently depressed men in the United States were 3.64 times more likely to be unemployed if they are in the labor force, and 3.28

times more likely not to participate in the labor force than men who are depression-free [5].

The CMS overstepped its own jurisdiction, which is to determine whether reimbursement is necessary and reasonable following the FDA's approval of safety and efficacy. The CMS decision instead relied on its own assessment of the available studies of efficacy, thus performing a *de facto* override of the function of the FDA. In its National Coverage Decision (NCD) on VNS Therapy for TRD, it argued that the data in the available short-term studies were insufficient to show that the device benefitted patients [6].

Ironically, the NCD has restricted the growth of additional long-term efficacy data; additionally, it failed to consider the ethical ramifications of long-term sham controls. We are acutely aware that the CMS decision may hinder global receptivity to the therapeutic device, and perpetuate the dearth of promising treatments for TRD.

The data with which CMS made its decision in 2007 may have been premature. Evidence of VNS efficacy has since continued to accumulate, along with the results of a 5-year study that included surprisingly unequivocal data. A TRD population treated with VNS Therapy and treatment as usual (VNS + TAU) was compared to a TRD population that only received treatment as usual (TAU). TAU entails pharmacological treatment and the possible addition of electroconvulsive therapy (ECT). The data show 20–30 percentage-point separations from placebo in response and remission rates on the Montgomery-Åsberg Depression Rating Scale (MADRS), with compelling statistical significance. The median duration of response was also significant, at 40 months with VNS Therapy versus 19 without the device [7].

Preliminary results were presented in 2014 at the annual meeting of the American Society for Clinical Psychopharmacology (ASCP). Its lead author Dr. Scott Aaronson said at the meeting [8], "It's very rare in psychiatry to see 5-year data about anything, so this is very unusual, and the results are very positive." The findings echoed those of a 2013 meta-analysis of 6 VNS Therapy trials [9] that measured participants at up to 2 years. Remission and response rates grew over the period among the VNS-treated population, and those who had achieved either at 24 weeks were more likely maintain it over time.

The 5-year study's positive news has yet to bring access to VNS to more TRD patients. In 2014, the Appeals Board of the US Department of Health and Human Services rejected an appeal sought by two Medicare beneficiaries [10], stating that the NCD in question was valid given the information available on the device at the time. They additionally ruled that new evidence (including results from the Berry et al. 2-year study but not the Aaronson et al. 5-year study) did not contradict the NCD, despite favorable statistical and

clinical significance. There is no record of the CMS or the Appeals Board reviewing the 5-year data. But as doctors search for better ways to treat TRD patients, data supporting the use of VNS such as the 5-year study will become increasingly difficult to dismiss.

The CMS explicitly states that its coverage decisions are not based on cost, unlike many government health agencies that use a cost-effectiveness threshold. However, it must nonetheless operate within a budget that is allocated by Congress [11]. We, as healthcare industry analysts, wonder whether the upfront cost of the device played a part in the NCD outcome.

The NCD sets a precedent for private insurance companies and governmental reimbursement agencies abroad, which can include cost in their evaluations [12]. If cost did play a role in the NCD, then we would argue that the high cost of the implant (excluding the cost of programming it and including the cost of surgical incision), which is US\$26,152 [13], is misleading. Consider that the generic version of the atypical antipsychotic aripiprazole, approved to augment antidepressants in major depressive disorder (MDD), may cost up to over US\$900 for a month's supply in the United States [14]. This drastically accumulates to dwarf the cost of VNS Therapy over the course of its minimum battery life of three years [3]. Unfortunately, the CMS decision has already been reflected by several major private insurers' rejections of VNS for TRD. In addition, foreign national health agencies may follow the US example and similarly suppress availability of VNS treatment.

After detailed review, we found that the cost-benefit analysis of the proven VNS therapy overwhelmingly favors such treatment. A retroactive study of Medicare patients found that TRD beneficiaries with VNS implants (who were treated before the NCD) had an average of US\$8749 per year in medical expenses post-implantation, which is far better than the cost of US\$13,618 per year for TRD beneficiaries who do not use VNS [15]. Added to the cost of the implant amortized over the maximum life of the replaceable battery, the total comes to US\$12,018, which remains lower than the cost of not treating patients with VNS. In one case report [16] a patient treated with VNS was able to halve the frequency of maintenance ECT sessions, further demonstrating the possibility of cost savings. The patient reported "feeling as well as he had felt at any time he could remember."

Not only does VNS have the potential to lower the long-term cost of treatment for patients, thus the fiscal burden on the CMS and private insurers, but also it provides much-needed relief and increases functionality in patients. This allows them to achieve more gainful employment, which is an important and highly valuable return on investment in VNS therapy, even if indirect.

The CMS's mistake in refusing coverage of VNS highlights an unmet need for new therapies to reduce the severity of depression. While antidepressants demonstrate some efficacy, antipsychotics often prescribed as a stronger treatment to address chronic and treatment-resistant depression present a serious risk of deleterious side effects. Those adverse effects include an expected drop of 17.7 IQ points not attributable to the symptoms treated [17].

By contrast, cognitive deficits have not been reported with the use of VNS Therapy. The reduction in IQ with antipsychotics is dramatic enough that it is comparable the cognitive impairment from neurodegenerative disease or brain injury, which may even qualify the patient for Social Security disability benefits in the United States [18].

The side effects of currently available pharmaceutical antidepressants are less severe than those of antipsychotics, but pharmaceuticals overall are prone to failure or tachyphylaxis. SSRIs demonstrated in one study a 14.1% rate of tachyphylaxis [19]. Another study found 25% of patients experienced tachyphylaxis during maintenance treatment of their MDD over the course of three years [20]. In a surprising meta-analysis of all FDA-filed clinical studies for four

new-generation antidepressants, each drug-placebo difference was found to be relatively small [21]. The CMS should have considered the partial efficacy and numerous side effects in the standard of care.

The agency should have also considered the ethical issues of using a sham control in studies of implantable devices before criticizing the lack of such studies. The use of implanted sham devices in studies is already controversial because they pose risks in surgery and add no potential benefit, and using shams in VNS trials for long durations would be even more egregious [22,23]. The CMS rested its criticisms on the only available sham-control study, which observed masked active or sham over a 10-week period and showed benefit, albeit limited, to patients with active VNS Therapy [24]. Unfortunately, the agency regarded the activation of the device in sham-control patients after 10 weeks as a study design flaw rather than as a standard ethical consideration. This is not the first time we as healthcare industry analysts have seen a promising surgical implant blocked due to the lack of long-term sham controls.

It was also important to consider that the patients included in the VNS trials had not improved or had relapsed after using pharmacotherapies or ECT. If prior pharmacotherapies did not improve the long-term outlook for these patients through placebo effect, as is the case, then it seems unlikely that the long-term improvement observed with VNS is attributable to a strong placebo effect.

Meanwhile, suicide remains the second leading cause of death for American youth between the ages of 15 and 24, and it ranks among the top ten leading causes of death in the United States overall [25]. Of people alive today, 1.5 million Americans and more than 20 million worldwide (extrapolated) with major depression or bipolar disorder are likely to commit suicide [26-29]; lack of long-term medication for sufferers of depression correlates with a higher likelihood to do so [30]. It is imperative that all treatment avenues for TRD be afforded the opportunity to demonstrate merit and, for cases such as VNS where merit is demonstrated, that these avenues be appropriately available to patients. To deny affordability of treatment to this population is to deny access to that treatment.

For all these reasons, the CMS decision simply falls short – it shortchanges patients, doctors, and scientific progress. The compelling data published after the 2007 NCD, including Aaronson et al.'s comparative 5-year results, shows VNS Therapy can help fill in the gap left by existing pharmacological treatments. From our perspective, VNS is clinically – and financially – a viable treatment that is worth paying for.

Conflicts of interest: None.

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