



Vagus Nerve Stimulation: The Secret to Nervana

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in association with



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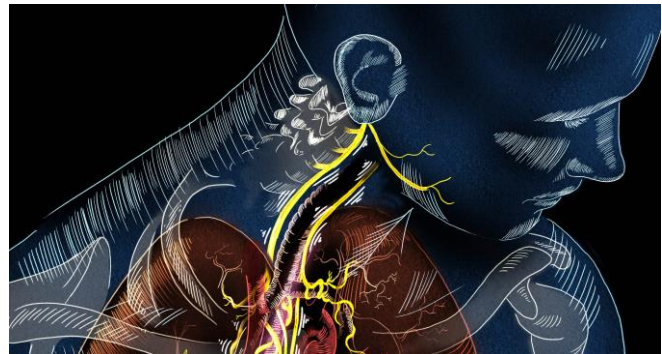
Playing air guitar to Rascal Flatts' *Life is a Highway* at full blast is such a high-energy activity. Which is why many people have a hard time grasping that they can come away from the experience with the same feelings of calm, focus and tranquility they get from mind-quieting pursuits like yoga and meditation. But that's precisely what happens when you use the Nervana headphones and generator.

Indeed, it doesn't much matter what you do during a Nervana session. Just put on the Nervana Headphones, select a song, crank the volume and set the Nervana Generator. Then sit back and relax. Or clean the house. The enveloping sense of well-being emerges just the same.

That's because, physiologically speaking, Nervana does essentially the same thing as relaxation-oriented activities: it stimulates the vagus nerve, which plays a leading role in maintaining calm in the body. The far-reaching nerve is the primary actor in the parasympathetic, or "rest-and-digest," system. It counters the "fight-or-flight," or sympathetic system by preparing the body for more relaxing, pleasant activities with "feel-good" neurotransmitters and hormones, like serotonin, dopamine, oxytocin and endorphins.

Lots of natural, everyday activities set the vagus nerve in motion. When you smell something tasty and your mouth begins to water, for example, it's because the vagus nerve is firing up the digestive system for dinner. It also prepares the body for sleep at night by ratcheting down your organs' activity levels. It even activates every time you exhale to help slow the heart after it's finished pumping oxygen through the body.

Of course, the sympathetic and parasympathetic systems are better balanced in some people than others. Which helps explain, for example, why some people feel the need to take melatonin to help them sleep, or Xanax for anxiety.



Nervana employs a technique called vagus nerve stimulation (VNS), which is designed to activate the nerve fibers with electronic signals. Implanted VNS devices have been used for decades to treat seizures and depression. As well, VNS is now being used to treat obesity and pain. And researchers have been experimenting with VNS to help those suffering from myriad other ailments, including asthma, digestive disorders, autism and even heart failure.

Not long ago, virtually all VNS devices were implanted into the chest cavity, like pacemakers, with electrodes attached to the vagus nerve, deep in the neck. Within the last decade, non-invasive transcutaneous devices (t-VNS) like Nervana have come available to stimulate the vagus nerve with electrodes placed on the skin near where the nerve is closest to the surface. In Europe, t-VNS devices are approved for treating epilepsy and chronic pain.

VNS is widely regarded by the medical community as safe. Reported side effects are minor, and don't typically have anything to do with actuating the nerve itself. For example, some patients with devices implanted in the chest report hoarseness, coughing and difficulty swallowing. And in Europe, some patients with non-invasive t-VNS devices experience itching and discomfort during treatment.

Nervana is a t-VNS device that transmits electrical signals to the vagus nerve through the ear canal. But it is designed for wellness. Which carries several important distinctions from medical VNS devices:

- There are no prescribed levels. You can set the Nervana Generator to the highest level that's comfortable for you.
- There is no prescribed duration. You're free to enjoy Nervana at your own pace. Nervana does suggest 15 to 30-minute sessions twice a day, which is a fraction of the four-hour-a-day prescription for reducing epileptic seizures.
- Most important – and what really sets Nervana apart from other t-VNS devices – is that it's designed from the ground up to be comfortable to use at effective levels. Nervana expertly mutes any feelings of discomfort by blending the stimulation signals in with music.

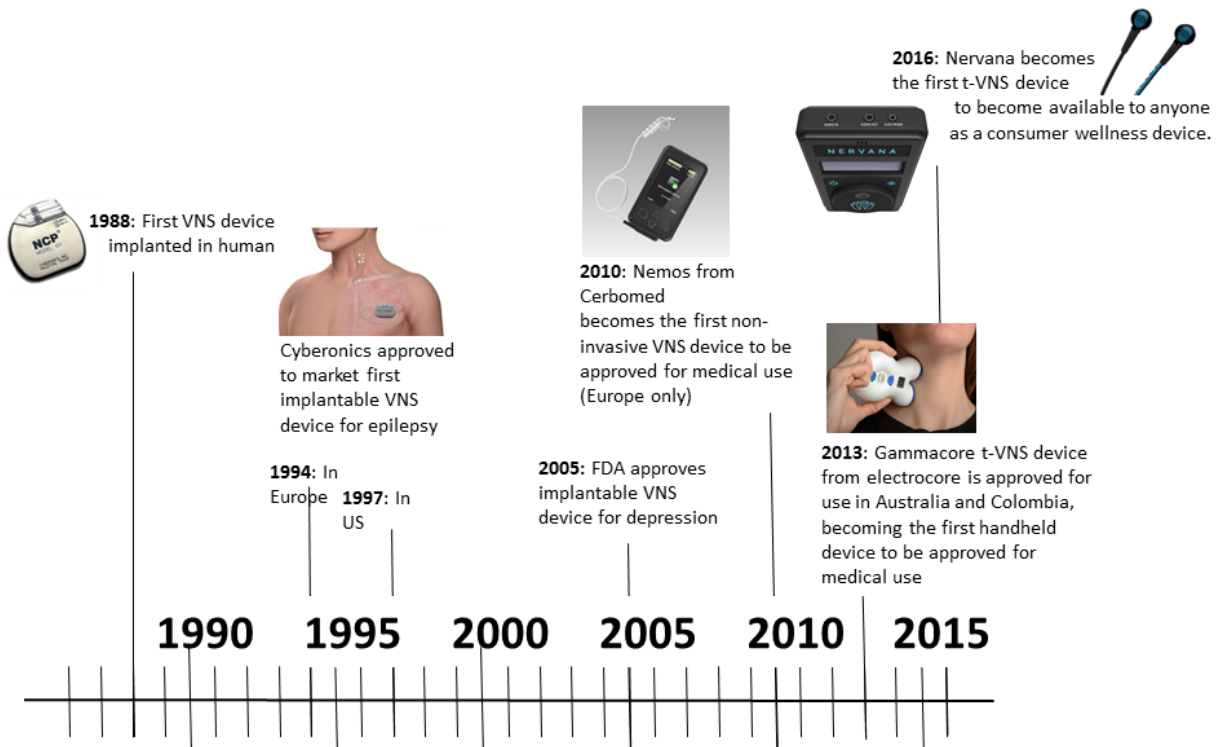
The purpose of this research brief is to retell the history of VNS, how it came to become a viable medical treatment delivered via an implantable device, and the evolution of medical treatment using t-VNS devices. The brief will also discuss some of the hurdles that have kept t-VNS from proliferating more widely. And finally, the brief will examine how the Nervana t-VNS system has scaled those hurdles to offer what could prove to be the most effective and reliable VNS device on the market today.



Vagus Nerve Stimulation: The Early Days

Vagus nerve stimulation has captured the imagination of the medical community for 150 years, since the time researchers first discovered a relationship between the nerve and blood flow. Today, we now know that the vagus nerve is responsible for far more than just signaling the heart to throttle back. Indeed, the nerve influences nearly every organ in the body. Which means that VNS has the potential to positively impact health and wellbeing in many ways.

In 1985, American neuroscientist Jake Zabara's canine studies showed that VNS helped reduce seizure activity, and that the benefits improve over time. That study was instrumental in the decision to start human trials. Zabara co-founded Cyberonics Inc. in late 1987, and trials began the following year.



Source: FeibusTech. Images courtesy Cyberonics, Cerbomed, Gammacore and Nervana

VNS for Medical Treatment

In 1994, after years of clinical trials, Cyberonics (now LivaNova) received approval to market its device, a flat, silver-dollar sized implant with electrodes that attach to the vagus nerve, for treating epilepsy in Europe. The US FDA approved the device in 1997. And in 2005, the FDA approved VNS implants for the treatment of severe depression.

Nemos, a t-VNS device from Cerbomed, in 2010 became the first non-invasive VNS device to be approved for medical use. It's available for treating epilepsy in Europe. And three years later, a New Jersey company called ElectroCore saw its non-invasive VNS device approved for use as a treatment for cluster headaches and migraines in Australia and Colombia. The device, called GammaCore, is a smartphone-sized unit that patients hold against their necks during stimulation. GammaCore is also being studied as a possible treatment for obesity and other gastrointestinal disorders.

Other VNS devices now approved or being assessed for medical use include:

- Maestro, an invasive VNS device from EnteroMedics, for obesity.
- Vivistim, from MicroTransponder, is an implantable VNS device for stroke victims. The company is also testing Serenity, which pairs an implantable with a tone-producing headset for tinnitus.
- An implant from SetPoint Medical, for rheumatoid arthritis and other inflammatory diseases.
- CardioFit from BioControl, for congestive heart failure.

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Nervana and t-VNS

Safety and Efficacy of t-VNS

There is substantial evidence, stemming from research that led to the approval in Europe and the US of implanted devices for epilepsy and, later, depression, that demonstrate the effectiveness of invasive VNS. Further, the risks and side effects are predominantly associated with surgically implanting an invasive device rather than the nerve stimulation itself. Infection, hoarseness and discomfort are the most common adverse effects – and they're typically not serious or permanent.

Increasingly, the evidence is growing that t-VNS devices can be just as effective as invasive VNS units – but without the disruption or potential complications that come with surgery. In 2007, German researchers demonstrated that t-VNS does indeed trigger brain activity that's similar in pattern to invasive VNS. Further, the researchers noticed significant mood enhancement in participants.

Safety hasn't ever emerged as a concern with t-VNS devices. And, given that they can be just as effective as invasive implants, it's surprising that VNS hasn't moved more quickly to the convenience and portability of non-invasive alternatives.

At the heart of the issue is that, unlike invasive implants, t-VNS devices aren't attached directly to the vagus nerve. Which means it's more challenging to:

- Make and maintain a comfortable, steady connection with the skin. Electrodes typically are made using rigid metals rather than soft, cushiony materials used for earbud tips.
- Deliver signals to just the right location. And to complicate matters, some people have vagus nerve fibers in some spots but not in others. So even if the electronic signals are precisely targeted, they still may not be effective for many people.
- Make stimulation tolerable. For the vast majority of people, electronic signals from a t-VNS device aren't strong enough to cause a rash or other irritation. And they're too weak to travel beyond the targeted spots, just a few millimeters under the skin. Still, many people find the sensation of stimulation to be uncomfortable.

Can you OD on VNS?

When many people first consider vagus nerve stimulation, they ask if they can get addicted to the serene, contented sensation. And they wonder if they can hurt themselves by doing VNS too much, as with cocaine, heroin, Percocet and other dangerous drugs.

VNS and addictive drugs do in fact both trigger the brain's pleasure center to release feel-good neurotransmitters. But that's where the similarities end. VNS doesn't possess any of the traits that make drugs addictive. And if there is a way to overdose on VNS, no one seems to have found it yet. In the 30 years since clinical trials began, there has not been one reported instance of overdose.

Drugs trigger a sharp spike in neurotransmitters, followed by an equally precipitous drop that leaves users feeling down and depressed. And in search of more drugs. VNS, on the other hand, results in a much gentler release of neurotransmitters that slowly elevates the mood, followed by a smooth, gradual return. The pattern is much closer to the effect from anti-depressants like Prozac, which are not generally considered to be addictive.

Addictive drugs are dangerous not because they make you feel good. Rather, they're dangerous because they have toxic – and potentially lethal – side effects. Cocaine, for example, constricts your coronary arteries, increasing the risk of a heart attack. And heroin throttles down the breathing reflex.

The toxic effects, in turn, trigger the liver to spring into action and flush the drugs from the system. The user gets depressed, and takes more.

But next time, the drug's euphoric effect is muted, because the liver now recognizes the substance and quickly kicks into high gear to cleanse it from the system. As the liver gets better and better at flushing the drug, the user needs more and more to achieve the same effect. Which can lead to overdose. And liver failure.

Unlike with drugs and alcohol, there are no collateral systemic effects of VNS. The stimulation sends signals directly to the vagus nerve, which prompts the nerve to tell the brain's pleasure center to release more neurotransmitters. And that's it. There's nothing for the liver to reject, so it's not muting the effect. Which means there's no "let down" after a VNS session so there is no rebound craving.

To treat serious conditions, healthcare prescriptions for VNS treatment do sometimes call for extensive stimulation. Cerbomed, for example, recommends daily stimulation of three to four hours a day for seizure treatment with its transcutaneous device. And some programs involving implanted devices call for all-day stimulation.

But there isn't any evidence to suggest that a longer, more intense stimulation session will take your good feelings up to 11. For one thing, studies show that nerves stop sending signals when they're overstimulated.

As well, the body has safeguards in place to prevent harmful effects of overstimulation. The sympathetic nervous system, for example, would step in before the parasympathetic system slowed a normal, healthy adult's heart rate below life-sustaining levels.

As with most activities, you should consult your physician before trying VNS.

- Mike Feibus

Achieving Nervana

With its ground-breaking new device, Nervana has overcome all three hurdles associated with delivering VNS signals through the skin.

First, Nervana's expertly-shaped earbud tips are built using a proprietary blend of conductive and non-conductive materials to establish a reliable electrical connection to the skin, without sacrificing comfort. The spot tips come in five sizes to ensure that virtually anyone will be able to use Nervana effectively.

Next, a piece of the earbuds called the coupler, which is also proprietary, consistently pinpoints the electrodes on the inner ear. Through extensive testing, Nervana's founders identified what they believe are the outer-ear sites likely to deliver stimulation for the highest percentage of people.

Thus far, preliminary studies corroborate the assertion, suggesting the Nervana platform enhances mood for more than 80 percent of those observed. More extensive tests are underway, with results expected by year's end.

And third, Nervana weaves the stimulation signals into the beat of the music, which makes them far easier to tolerate. Psychologically speaking, the patent-pending technique works in two ways:

- *Distraction.* Studies show that distracting subjects with more enjoyable diversions makes painful and unpleasant activities more tolerable. With Nervana, music is that diversion.
- *Predictability.* Researchers have demonstrated that uncomfortable or painful events are more easily tolerated when their occurrence is predictable. By synchronizing the electronic signal with the music, Nervana users quickly sense when to expect stimulation signals.

Is t-VNS Painful?

In our lab testing at FeibusTech, the test subject reported that the stimulation feels foreign, but not painful or uncomfortable in any way. FeibusTech tested the Nervana system on two separate occasions, several weeks apart. Each time, our test subject became acclimated to the sensation after only a few moments. And at that point, proceeded to turn up the stimulation signal further to enhance the effect.

For perspective, the amperage from the Nervana system is roughly equivalent to that of a 9V battery.

After having tested the device in the FeibusTech lab, we find it difficult to believe that anyone would experience pain, discomfort or rash, the minor side effects reported in clinical studies of other t-VNS devices. We suspect that the fixed length of treatment in those studies combined with the pre-set amperage may have played a role.

After both sessions, our test subject described the sensation as being very pleasurable: "I can only describe it as intensely calm and relaxed, with an elevated ability to shut out distraction and just focus." The sensation was observed to last for about an hour.

- Mike Feibus

What started as a way to treat epileptics whose seizures were resistant to conventional medications, vagus nerve stimulation is now being looked at to ease a multitude of conditions, from pain to arthritis, and from premenstrual syndrome to obesity.

The drawback of early VNS devices is that they are implanted, which means they require patients to commit to surgery, and accept the risks that go along with that. Transcutaneous VNS devices are non-invasive, which means they require a far smaller commitment. The flip side is that, while they have the potential to be every bit as effective as invasive devices, as yet they haven't been due to technical hurdles.

The founders of Nervana set out to overcome those hurdles and realize the potential of t-VNS therapy. They developed a new system that makes and maintains an electrical connection with the outer ear, and targets areas under the skin that give them the greatest possibility of delivering signals to the nerve. And to help more people tolerate therapy, the Nervana t-VNS system melds the signals with music.

Nervana is also distinctive in that it's being sold as a wellness product rather than as a medical device. First and foremost, it means that you don't need a prescription to buy it. Anyone can pick one up online for \$299.

It's possible that Nervana might one day be effective at treating seizures and depression, just like clinically approved t-VNS devices. In fact, with the proprietary enhancements for increasing accuracy and improving tolerability, it's even possible that Nervana could do a better job than the alternatives.

But the company isn't producing the Nervana platform for that. And it isn't making any such claims. Indeed, it's only suggesting that the device can give users a pleasant mood boost with a technique that's far quicker and lower commitment than even meditation. You don't even need to count your breaths.

All that's required is the Nervana platform. And a few choice music tracks.

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