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Review Paper

Drug Free Implantable Vagus Nerve Stimulation Device (Epilepsy)

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ABSTRACT

Drug-free implantable vagus nerve stimulation (VNS) devices represent a promising neuromodulation technology for managing chronic and treatment-resistant disorders. These implantable systems deliver controlled electrical impulses to the vagus nerve, providing therapeutic effects without long-term drug use. VNS is an approved treatment for drug-resistant epilepsy and treatment-resistant depression, and recent innovations have extended its application to stroke rehabilitation, heart failure, and autoimmune disorders. This review summarizes the structure, mechanism, manufacturers, clinical applications, advantages, limitations, and future directions of drug-free implantable VNS devices. Continuous developments in bioelectronic medicine and closed-loop systems are expected to broaden their clinical utility and improve patient outcomes.

INTRODUCTION

- Vagus nerve stimulator (VNS) is an drug free implantable device.
- Acts like a ‘pacemaker for the brain’.
- Implantable Vagus nerve stimulation device is a pulse generator, implanted under the skin to stimulate the vagus nerve.
- The vagus nerve stimulation (VNS) device is a bioelectronic implant that helps control brain activity by sending mild electrical signals to the vagus nerve.

- It is mainly used to treat epilepsy (seizures) and depression when medicines don’t work.

WHEN IT WAS INVENTED & IT’S HISTORY

19th century:

The vagus nerve was first studied for its role in heart rate, digestion, and the autonomic nervous system. Researchers found that stimulating the vagus could slow the heart and affect respiration.

1930s–1950s:

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Experiments in animals showed that electrical stimulation of the vagus could influence brain activity, suggesting potential therapeutic use in neurological disorders.

Origins of Vagus Nerve Stimulation Therapy

1980s:

Researchers began exploring the vagus nerve as a therapeutic target for epilepsy.

In 1985, Jacob Zabara, a researcher in the U.S., demonstrated that intermittent vagus nerve stimulation reduced seizure activity in dogs.

Zabara founded Cyberonics, Inc. in 1987 to develop implantable VNS devices.

First Human Use and FDA Approval

1988–1990:

The first human clinical trials of VNS for refractory epilepsy were conducted. The results

showed reduced seizure frequency in some patients.

1994:

The VNS Therapy System (Cyberonics) received CE Mark approval in Europe for epilepsy.

1997:

The U.S. FDA approved VNS therapy as an adjunctive treatment for refractory epilepsy in adults and children over 12 years old.

2005:

The FDA approved VNS for treatment-resistant depression (TRD) after evidence showed mood improvement in some patients unresponsive to medication.

2010s:

Research expanded into heart failure, anxiety disorders, migraine, cluster headaches, and inflammatory diseases (e.g., rheumatoid arthritis).

Table No1: based on the discovery of vagus nerve stimulation device

YEAR	Milestone	Description
1985	Preclinical success	Zabara demonstrates seizure reduction in animals
1987	Cyberonics founded	Company formed to commercialize VNS
1990	First human implant	Early clinical trials begin
1997	FDA approval	VNS approved for refractory epilepsy
2005	FDA approval (depression)	VNS for treatment-resistant depression
2017	Non-invasive VNS	gammaCore approved for headache disorders
2020s	Closed-loop & bioelectronic medicine	Research into adaptive and systemic applications

WHAT IS VAGUS NERVE

The vagus nerve (also known as the 10 cranial nerve, or cranial nerve X) is the longest and one of



the most complex nerves in the autonomic nervous system.

The part of your nervous system that controls Involuntary actions like heart rate, digestion, and breathing, moods, seizure.

Connects brain to heart, lungs, stomach, intestines.

Anatomy and Pathway

Origin:

Begins in the brainstem, specifically in the medulla oblongata.

Pathway:

Travels down the neck, through the chest, and into the abdomen.

Connections:

It sends fibers to several organs:

- Heart
- Lungs
- Stomach and intestines
- Liver
- Spleen
- Voice box (larynx) and throat (pharynx)

Table No 2: Functions of Vagus Nerve

Functions	Example
Heart rate control	Slows heart rate when you relax
Breathing regulation	Coordinates breathing rhythm
Digestion	Stimulates stomach acid, intestinal movement, and enzyme release
Reduces stress	hormones, lowers blood pressure
Speech and swallowing	Controls muscles of voice and throat
Inflammation control	Regulates immune responses via the "inflammatory reflex"

Why It's Important in Medicine

- Epilepsy (reducing seizure frequency)
- Depression and anxiety
- Inflammatory diseases (like rheumatoid arthritis)
- Heart conditions
- Headaches and migraines

WHAT IS VAGUS NERVE STIMULATION DEVICE

A vagus nerve stimulation (VNS) device is a medical device designed to stimulate the vagus

nerve — a long cranial nerve that runs from the brainstem through the neck and into the chest and abdomen. The vagus nerve helps regulate many vital functions, including heart rate, digestion, and mood.

- Small electronic device implanted under the skin of chest.
- Sends regular electrical impulses to the vagus nerve.
- Helps reduce abnormal brain activity and balance functions.



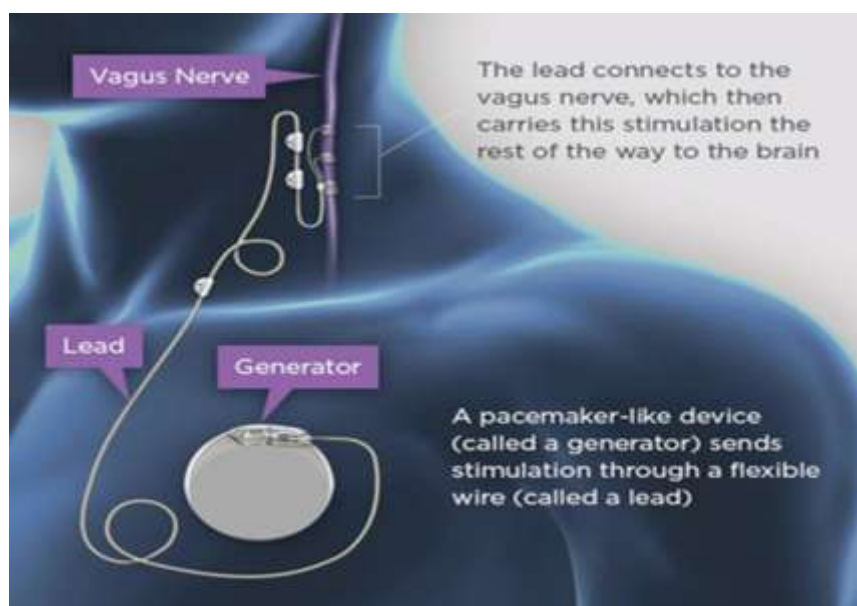


Figure No 1: Diagrammatic representation of VNS (reference in 13)

Types of VNS Devices

1. Implantable VNS (traditional):
 - i. Surgically implanted under the skin.
 - ii. Battery-powered pulse generator.
 - iii. Controlled by a doctor with an external programmer.
2. Non-invasive (transcutaneous) VNS:
 - i. Handheld or ear-worn devices that stimulate the vagus nerve through the skin.
 - ii. No surgery needed
 - iii. Examples: gammaCore, NEMOS, etc.

IMPLANTABLE VNS

A vagus nerve stimulation (VNS) device is a medical device designed to stimulate the vagus nerve — a long cranial nerve that runs from the brainstem through the neck and into the chest and abdomen. The vagus nerve helps regulate many vital functions, including heart rate, digestion, and mood.

PARTS OF VAGUS NERVE STIMULATION DEVICE

1. Pulse Generator

2. Leads(Wires)
3. Programmer System

PULSE GENERATOR (Implantable Stimulator)

- A small, battery-powered device (like a pacemaker).
- Implanted under the skin in the upper chest.
- Generates electrical pulses. (battery+ computer)
- A small, round device—about the size of a silver dollar (2–3 cm in diameter).
- Contains a battery and an electronic circuit that generates electrical pulses.

Main Components & Materials of an Implantable Pulse Generator

Titanium or Biocompatible Metal Casing

- The outer shell of the generator is usually made from titanium (a metal that is biocompatible, corrosion-resistant, and non-reactive with body tissues).
- The casing protects the internal electronics from body fluids and mechanical damage.

Electronic Circuitry (Pulse Generation Unit)

- A microprocessor and custom circuitry inside generate precisely timed electrical pulses.
- The system allows doctors to program parameters such as
 - i. Pulse amplitude (intensity)
 - ii. Pulse width
 - iii. Frequency
 - iv. On/off timing cycles



Figure No 2: diagram represent pulse generator (reference in 14)

Battery (Power Source)

- A lithium-based battery, typically lithium-carbon monofluoride (Li-CFx) or lithium-manganese dioxide (Li-MnO₂), is used for long life and stability.
- The battery life is usually 5 to 10 years, depending on stimulation settings and frequency.

Telemetry Coil / Communication System

- Embedded coil allows wireless communication between the implanted device and an external programmer.
- Clinicians use this to adjust settings or check device status without surgery.

Connector Port

- The top part of the generator includes a connector where the lead wire attaches.
- The lead carries the stimulation pulses from the generator to the electrodes wrapped around the vagus nerve.

LEADS (electrode wires)

In a vagus nerve stimulation (VNS) system, the lead wire is the insulated cable that connects the pulse generator (implanted in the chest) to the electrodes wrapped around the vagus nerve in the neck.

It's a highly specialized medical component made from biocompatible, flexible, and electrically conductive materials, designed to work safely inside the human body for many years.

- Thin wire that connects the generator to the left vagus nerve in the neck.
- Wrapped around the nerve to deliver impulses.
- Connect generator to vagus nerve in the neck. (cuff on nerve)

Components & Materials of a VNS Lead Wire

Part Typical Material Function / Properties

Conductors (core wires) Platinum-Iridium alloy (Pt-Ir) or sometimes MP35N (nickel-cobalt-chromium alloy) Carries electrical pulses from generator to electrodes; excellent conductivity, corrosion resistance, and fatigue strength.

Insulation (outer coating) Silicone elastomer or polyurethane Provides electrical insulation;

biocompatible, flexible, and resistant to body fluids.

Electrodes (at nerve end) Platinum–Iridium contacts with silicone cuff Deliver stimulation to the vagus nerve; soft cuff wraps gently around the nerve to avoid damage.

Connector (generator end) Titanium and medical-grade polymer Connects securely to the pulse generator header; ensures a hermetic, low-resistance connection.

Helical (coiled) structure — (Design feature) The wire is coiled like a spring to allow stretching and bending with body movement, minimizing stress and breakage.

- The platinum–iridium alloy (often 90% Pt / 10% Ir) is the industry standard for implantable leads due to its

- High conductivity
- Corrosion resistance
- Biocompatibility
- Mechanical strength
- The silicone insulation ensures flexibility and long-term durability inside soft tissues.
- The helical (spiral) shape allows the lead to move naturally with neck motion without breaking or damaging the vagus nerve.

DIMENSIONS

- Lead length: ~43 cm (varies by patient anatomy)
- Diameter: ~2–3 mm
- Two or three electrodes at the distal end for stimulation and sensing.



Figure no 3: Diagram represent lead wire of the VNS device (refe =15)

PROGRAMMING SYSTEM: (electrode)

The programming system of a vagus nerve stimulation (VNS) device is the external equipment that allows a clinician to set, adjust, and monitor how the implanted pulse generator delivers electrical stimulation to the vagus nerve.

- Doctors use a computer and magnetic wand to adjust the strength, duration, and frequency of impulses.
- External device for doctors to adjust settings. (doctor set signals)

Table No 3: Components of The VNS Programming System

COMPONENT	DESCRIPTION/FUNCTION
Programmer (Tablet or Laptop)	Specialized computer or tablet (provided by the VNS manufacturer, e.g., LivaNova's Model 3000 or 4000 Programmer). Runs dedicated VNS Therapy software for setting and reading device parameters.
Programming Wand (Telemetry Head)	A handheld wireless communication device (usually using RF or inductive telemetry) placed over the implanted generator site. It transmits data between the programmer and the implanted device.
External Power Supply	Powers the programming system during clinic sessions.
Software Interface	Displays patient information, device status, battery level, and allows parameter adjustments.

How the Programming Process Works

Patient Visit:

- The clinician places the wand over the patient's implant site (usually the upper left chest).
- The wand communicates wirelessly with the implanted pulse generator.

Device Interrogation:

- The programmer reads current device settings and diagnostic data (e.g., battery life, lead impedance, stimulation history).

Parameter Adjustment:

- The clinician can modify parameters such as:
- Output current (mA): strength of the stimulation
- Pulse width (μ s): duration of each pulse
- Frequency (Hz): how many pulses per second
- On time / Off time: duration of stimulation and rest cycles
- Magnet mode: settings for when a patient uses the external magnet to trigger or stop stimulation

- Auto-stimulation: if enabled, adjusts output based on heart rate detection (in models like AspireSR or SenTiva)

Programming Confirmation:

- New parameters are transmitted to the implant through the wand.
- The device responds with a confirmation, and the patient's new stimulation settings take effect immediately.

Example Programming Parameters (Typical Ranges)

<i>Parameter</i>	<i>Typical Range</i>
Output Current	0.25 – 3.5 mA
Pulse Width	130 – 500 μ s
Frequency	20 – 30 Hz
On Time	30 se
Off Time	5 min





Figure No 4:Diagram represent programming system of VNS device (refe =16)



Figure No 5: Diagram represents how the doctor adjust the VNS devise frequency as per the patient. (refe =17)

Transcutaneous (Non-Invasive) VNS Devices

These do not require surgery.

They stimulate the vagus nerve through the skin — either at the ear (auricular branch) or the neck.

A. Auricular (Ear-based) VNS

Stimulates the auricular branch of the vagus nerve in the ear.

- i. Examples: NEMOS® (cerbomed / tVNS Technologies, Germany)
 - a. Gamma Core Sapphire™ (electro Core, USA – though it targets the neck, not ear)
 - b. Parasym™ (UK – for cluster headaches and migraines)
 - c. Vitulus, Vagus Fit, etc. (consumer wellness versions)

transcutaneous auricular Vagus Nerve Stimulation
The only integrated device and accessories for clinical research on taVNS

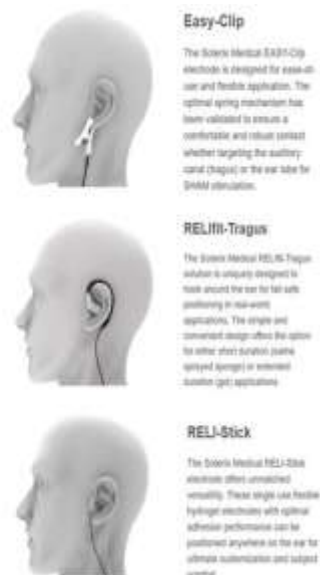


Figure No 6: image of auricular VNS devise(refe =18)



Figure No 7: Picture of TAVNS device (refe =19)

B. Cervical (Neck-based) tVNS

Stimulates the cervical branch of the vagus nerve through the neck skin.

Example:

- a. gammaCore™ (electroCore)

FDA-cleared for:

- Acute migraine treatment
- Cluster headache prevention and treatment
- Paroxysmal hemicrania and hemicrania continua



Figure No 8: diagram of NIVNS device (refe =20)



Figure No 9: diagram of CtVNS device (refe =21)

IMPLANTATION PROCEDURE

Before the procedure

Before surgery, you have a physical exam. Your surgeon may have you start taking antibiotics before surgery to prevent infection.

During the procedure

Surgery to implant the vagus nerve stimulation device often is done on an outpatient basis. You go home that day. During surgery, you'll likely get medicine, called general anesthesia, to put you into a sleep like state.

The surgery itself doesn't involve the brain. The surgeon makes two cuts, called incisions. One is on the chest or in the armpit area. The other is on the left side of the neck.

The surgeon puts the pulse generator in the upper left side of the chest. The pulse generator is about the size of a stopwatch. It runs on battery power.

A lead wire connects to the pulse generator. The surgeon guides the lead wire under the skin from the chest up to the neck. Then the surgeon connects the wire to the left vagus nerve through the second cut.

The device and its battery last for years before it needs to be replaced. A surgeon also can remove it, if needed.

After the procedure

If you had the device implanted to treat epilepsy or depression, your healthcare team turns on the pulse generator during a medical visit a few weeks after surgery. Then the team programs how long and how often the device sends electrical impulses to the vagus nerve.

Vagus nerve stimulation most often starts at a low level. Your healthcare team can raise it depending on your symptoms and side effects.

The device turns on and off in cycles, such as 30 seconds on, five minutes off. You may feel some tingling or slight pain in your neck. Your voice may be hoarse when the device is on.

Newer models that treat epilepsy can sense a sudden increase in your heart rate and react by sending a signal to the nerve. A sudden increase in heart rate may mean you're about to have a seizure. You can use a hand-held magnet to start the impulse at other times. For instance, you can turn it on if you feel you're about to have a seizure.

For a device that's put in after a stroke, a specialist most often turns it on during rehabilitation. You also can turn it on at home using a magnet. You might turn it on to help with certain tasks such as cooking.

You need to make follow-up visits to your healthcare professional to make sure that the pulse generator is working and hasn't moved out of place. Check with your healthcare team before having medical tests, such as an MRI. The test might affect the device.

MECHANISIM & WORKING OF VNS

Vagus Nerve Stimulation (VNS) – Mechanism of Action

The vagus nerve stimulation device is a small, battery-powered implant placed under the skin in the chest. It sends mild electrical pulses to the vagus nerve in the neck at regular intervals.

Step-by-step Mechanism:

Electrical pulse generation:

The implanted device (like a pacemaker) produces small, controlled electrical signals.

Signal transmission to vagus nerve:

A thin wire connects the device to the left vagus nerve in the neck. The signals travel through this wire to the nerve.

Activation of brain areas:

The vagus nerve carries the signals to important parts of the brain — such as the thalamus, amygdala, and brainstem — that control mood, seizure activity, and body functions.

Balancing brain chemicals:

The stimulation helps release or regulate neurotransmitters like norepinephrine, serotonin, and GABA, which calm overactive nerve cells.

Reduced abnormal brain activity:

This reduces the irregular electrical activity in the brain that causes epileptic seizures or mood disorders.

Automatic and adjustable:

The device works automatically, but doctors can adjust the strength and timing of the signals using a computer.

Some patients can also trigger extra stimulation using a magnet if they feel a seizure coming.



EXPLANATION

1. Device implantation

- a. A small pulse generator (like a pacemaker) is surgically implanted under the skin of the chest.
- b. A thin wire (lead) runs from the generator to the left vagus nerve in the neck.
- c. The left side is chosen because it has fewer effects on the heart compared to the right side.

2. Electrical pulse generation

- a. The device produces mild, regular electrical impulses at preset intervals.
- b. These impulses are low in intensity and safe for the nerve.

3. Stimulation of the vagus nerve

- a. The electrical pulses travel through the wire and stimulate the vagus nerve fibers.
- b. The vagus nerve acts as a bridge between the body and the brain, carrying signals to the brainstem.

4. Transmission of signals to the brain

Once the vagus nerve is stimulated, the impulses move up to the brainstem, mainly to an area called the nucleus tractus solitarius (NTS).

From there, signals are sent to different regions of the brain such as:

- Locus coeruleus (controls alertness and norepinephrine release)
- Thalamus (relay center of the brain)

- Amygdala and hippocampus (control mood and emotion)
- Cerebral cortex (controls brain activity)

5. Neurochemical modulation

VNS influences neurotransmitters like:

- Serotonin (5-HT) – improves mood and reduces depression
- Norepinephrine (NE) – increases alertness and helps stabilize brain signals
- GABA – calms overactive neurons
 - This chemical balance reduces abnormal brain firing responsible for epileptic seizures
 - Signals travel to brain regions controlling seizures, mood, pain.
 - Helps reduce seizures, improve mood, and control inflammation.

TREATMENT

Epilepsy

Anti-seizure medicines don't fully manage seizures for about one-third of people with epilepsy. For some of them, vagus nerve stimulation may help manage their seizures.

The FDA has approved vagus nerve stimulation for people with epilepsy who

- Are 4 years old and older.
- Have focal epilepsy. In focal epilepsy, one area of the brain causes the seizures.
- Can't fully manage their seizures with medicines.
- Healthcare professionals also may use vagus nerve stimulation for people with generalized epilepsy.



Table No 4: shows VNS device epilepsy trials

Authors	Study/ sample size	Parameters (active group)	Implanted/ transcutaneous	Primary outcome	Study conclusions
Penry and Dean [19]	4 patients with seizure disorder	PW: 47–50 Hz On/off: varied I: 1–3 mA	Implanted	Long-term safety and efficacy	All patients tolerated the procedure with minimal long-term side effects. Seizures were reduced in 3/4 of patients
Uthman et al. [123]	14 patients with medically refractory partial seizures	PW: 250 μ s Freq: 50 Hz On/off: 60 s/60 min I: 1 mA	Implanted	Mean reduction in seizure frequency	Mean reduction in seizure frequency was 46.6% after 14–35 months; 14 of 35 patients showed at least 50% reduction in seizure frequency
Amar et al. [37]	18 patients with medically refractory epilepsy and at least six complex partial or secondarily generalized seizures per month	High-level group: PW: 500 μ s Freq: 30 Hz On/off: 30 s/5 min I: up to 3.5 mA Low-level group: PW: 130 μ s Freq: 1 Hz On/off: 30 s/3 h I: up to 3.5 mA	Implanted	Comparison of high stimulation VNS vs. low-stimulation on seizure frequency	High-stimulation VNS patients had significantly greater reduction in seizure frequency at 3- and 18-month follow-up
Scherrmann et al. [38]	95 adult patients with drug-resistant seizures who had received implants	PW: 500 μ s Freq: 20 Hz On/off: 7 s/30 s I: 0.25–3 mA	Implanted	Median percentage of reduction in seizure frequency compared to antiepileptic drug alone	Median percentage of reduction in seizure frequency as compared to baseline was 30%, and seizure outcome was positively correlated with VNS duration
Klinkenberg et al. [40]	41 children with either partial or generalized epilepsy	PW: 0.5ms Freq: 30 Hz On/off: 30 s/5 min I: 0.25 mA	Implanted	Comparison of high stimulation VNS vs. low-stimulation on seizure frequency and severity in children	VNS well tolerated in children, but no significant difference seen in frequency or severity between low and high stimulation groups

Depression

Vagus nerve stimulation may help people with depression. It may be used when medicines,

psychological counselling and electroconvulsive therapy haven't worked well.

The FDA has approved vagus nerve stimulation for the treatment of depression in adults who:



- Have long-lasting, hard-to-treat depression, known as treatment-resistant depression.
- Haven't improved after trying four or more medicines, electroconvulsive therapy or both.
- Keep using their other depression treatments with vagus nerve stimulation.

Stroke recovery

For people who are recovering from a stroke, the FDA has approved vagus nerve stimulation for use in rehabilitation. Vagus nerve stimulation with

rehabilitation may help people recover the use of their hands and arms after an ischemic stroke.

ONGOING REASCHER ON

- Migraine
- cluster headache
- Rheumatoid arthritis
- Crohn's disease
- Heart failure
- Anxiety
- Obesity

Table No 5: work of VNS as per patient condition

Disease DISEASE CONDITION	PURPOSE OF VNS
Epilepsy	Reduce frequency and severity of seizures.
Depression	Improves mood in treatment resistance cases.
Stroke rehabilitation	Helps restoring movement in affected limbs.
Heart failure	Helps regulate heart rate and improve cardiac output.
Rheumatoid arthritis/ Autoimmune diseases	Reduces inflammation via the "inflammatory reflex"
Obesity(experimental)	Controls hunger by modulating stomach signals.

USED TO MANUFACTURE VNS DEVISE

Table No 6: companies used to manufacture VNS device

Company names	Devise name/ system	Main use/ Indication
LivaNova plc	<i>VNS Therapy r System</i>	Drug-resistant epilepsy, Depression.
Micro Transponder Inc.	<i>Vivistim Paired VNS system</i>	Stroke rehabilitation (improves arm function)
Setpoint Medical	<i>Bioelectronic VNS system</i>	Autoimmune diseases like rheumatoid arthritis.
BioControl Medical	<i>CardioFit</i>	Heart failure
EnteroMedics (Reshape lifesciences)	<i>VBLOC Therapy</i>	Obesity treatment



Figure No10: Devices of Different companies.(refe -22)

Side effects

Common side effects of vagus nerve stimulation include:

- Coughing.
- Hoarseness.
- Change in voice.
- Neck pain or throat pain or tickling.
- Shortness of breath/trouble breathing (dyspnea).
- Trouble speaking (dysphonia).
- Trouble swallowing (dysphagia).
- Headache.

Advantages of VNS Device

- Effective in treatment-resistant epilepsy
Reduces frequency and severity of seizures in patients who do not respond to anti-epileptic drugs.
- Useful for treatment-resistant depression

Provides clinical improvement in mood and depressive symptoms when medications and psychotherapy fail.

- Non-pharmacological treatment
Avoids long-term drug-related side effects and interactions.
- Continuous, automatic therapy
Delivers stimulation regularly without requiring patient intervention.
- Adjustable stimulation parameters
Intensity, frequency, and timing can be optimized based on patient respons
- Emergency control of seizures
Patients can swipe a magnet over the device to activate extra stimulation during aura or seizure onset.
- Long-term benefits
Gradual improvement over months and sustained therapeutic response in many patients.
- Minimal brain invasion

No direct surgery on the brain; device is implanted in the chest with lead attached to vagus nerve.

CONCLUSION

Inevitably, more data will help shape our understanding of how these novel treatments can be made more effective. As in other areas of VNS research, future areas for improvement are in our understanding of how parameters interact with disease state. VNS has an infinite number of parameter combinations, as clinicians can adjust frequency, pulse width, duty cycle, and duration of stimulation. Understanding how these parameter combinations affect treatment outcomes is of utmost importance. Additionally, non invasive VNS has opened the door for further study of the effects of VNS. This includes translation of the wealth of evidence in animal models to human clinical research, as well as further study of how VNS may be an effective treatment for other medical and neuropsychiatric disorders. Discovery of reliable biomarkers will be crucial in aiding the development of personalized VNS treatments, a revolution that is already occurring in other areas of brain stimulation.

In conclusion, the history of VNS spans four decades but has already accomplished a great deal. To date, VNS has gained approvals from the FDA for medication-refractory epilepsy, treatment-resistant depression, obesity, post-stroke motor rehabilitation, and migraine and cluster headache. The development of novel non invasive forms of VNS promises to further advance the field's evolution.

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