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# Electrical stimulation in special clinical situations

Lenises de Paula van der Steld[1,*]

**ORCID ID**

Steld LP https://orcid.org/0000-0002-2083-9474

## ABSTRACT

**Introduction:** Neuromodulation is an approach used to treat diseases that are refractory to clinical treatments by employing electrical and chemical stimulation techniques, especially in cardiac, neurological, and psychiatric disorders. **Objective:** This study aims to provide an overview of the latest developments in neuromodulation therapies that use electrical stimulation. **Methods and results:** The present study describes the most common neuromodulation techniques. Neuroplasticity is used to adjust the ions and neural excitability in response to central and peripheral nervous system stimulation. The spinal cord, dorsal root, and gastric stimulations are effective treatments for neuropathies, chronic pain, muscle spasticity, epilepsy, depression, cluster headaches, heart failure, and gastroparesis symptoms. Deep brain stimulation and invasive cortical stimulation are medical procedures used selectively to treat Parkinson's disease, dystonia, obsessive-compulsive disorder, and chronic pain. Barostimulation therapy is beneficial in controlling refractory hypertension, reducing the risk of cardiovascular events, and improving overall quality of life. Repetitive Transcranial Magnetic Stimulation is a recommended treatment option for fibromyalgia, neuropathic pain, chronic headaches, treatment-resistant depression, generalized anxiety disorders, schizophrenia, and attention deficit disorder. While controlling obesity shows promise in regulating appetite and promoting satiety, more research is needed to understand the safety and efficacy of these therapies in various groups. **Conclusion:** Neuromodulation devices hold promise for treating diseases that do not respond to clinical treatments. Additional clinical trials and studies are required to understand it fully.

**KEYWORDS:** Neurotransmitter Agents; Computer Peripherals; Implantable Neurostimulators.

## INTRODUCTION

Recently, neuromodulators have become a promising way to treat various neurological conditions. As our knowledge of the brain and its complex functions grows, there is greater potential for new therapies that can directly regulate and adjust neural activity. While some studies focus on lower back pain and peripheral pain, healthcare professionals and researchers are working to use advanced technologies and innovative approaches to

**1.** Escola Bahiana de Medicina e Saúde Pública – Salvador (BA), Brazil.
***Correspondence author:** lenisesdepaula @gmail.com
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help patients with conditions like epilepsy, Parkinson's disease, resistant systemic arterial hypertension, congestive heart failure, and psychiatric disorders[1,2].

The cells in our body communicate with each other by the movement of ions such as sodium, potassium, calcium, and magnesium. This process takes place across the cell membrane and generates the action potential in both excitable cells, such as those in the heart and muscles, and non-excitable cells. It is an essential process for transmitting information throughout our tissues.

By applying electrical current to a cell, its behavior or response can be changed. Neuromodulation is used to study cell function and activate or inhibit neural and muscular pathways, among other purposes. Electrical stimulation affects the action potential. It involves various factors and mechanisms, such as the regulation of ion channels and neurotransmitter influence.

This study aims to provide an overview of the latest developments in neuromodulation therapies that use electrical stimulation.

# METHODS AND RESULTS

Neuromodulation or neuromodulator is defined as the alteration of nervous activity through electric or chemical stimulation in specific parts of the body. It offers various approaches aiming to target or interrupt dysfunctional cerebral or regional focus. In the 1980s, publications on "Brain pacemakers" or brain stimulation devices began to emerge. Many publications are available on neuromodulation, such as Helena Knotkova et al., who published a review in 2021 about various neuromodulation techniques for chronic pain treatment, including spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), and deep brain stimulation (DBS)[3].

The main complications observed in users of neuromodulators are infection, irritation/inflammation or pain at the implant site, erosion or migration of the system, electrode perforation, seroma, hematoma, concurrent muscle stimulation, battery wear, and programming difficulties.

Factors that can cause damage to the system or disable it include electrocautery, cardioversion/defibrillation, therapeutic ultrasound, MRI, microwave ablation, and radiofrequency ablation.

## Mechanisms of stimulations

The human nervous system has a feature called neuroplasticity, which involves changes in both structure and function in response to a stimulus. These changes include synaptic plasticity and functional modifications, such as the alteration of calcium ions, which can affect excitability. At the cellular level, stimulation causes a change in the electrical state of neurons, and neurotransmitters can modify pain and function in certain parts of the body[4].

## Neurostimulation techniques

Neuromodulation can involve the stimulation of either the central or peripheral nervous system. In this discussion, we will focus on the most extensively studied stimulation methods to date (Fig. 1).

Neuromodulation techniques are a reliable solution for patients who suffer from chronic pain and have not found success with traditional pain management methods. These techniques provide an alternative treatment option, with peripheral stimulations being the primary locations for their implementation (Fig. 2).

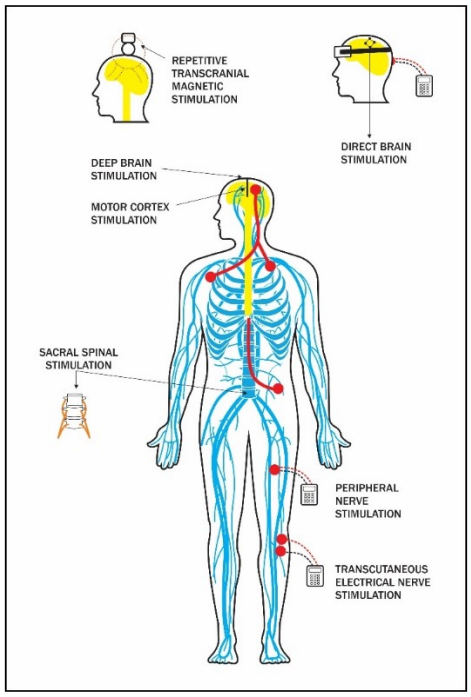


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**Figure 1.** Schematic drawing of various forms of neuromodulation

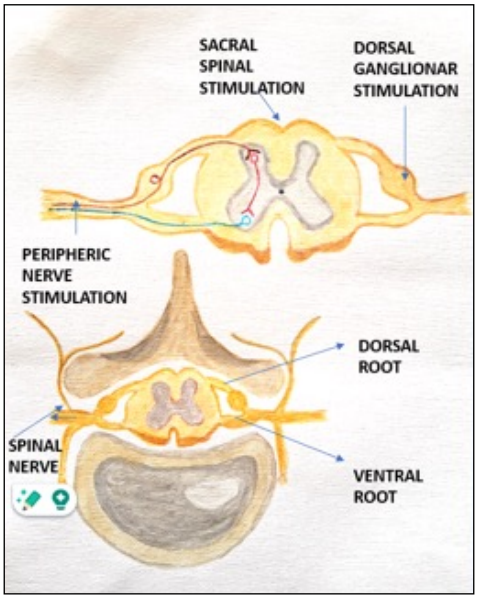


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**Figure 2.** Peripheral Stimulations

## Peripheral nerve stimulation

Peripheral nerve stimulation (PNS) is a technique that involves the application of electrical stimuli to specific peripheral nerves outside the central nervous system. This form of neuromodulation mainly targets nerves that transmit sensory and motor information between the brain and different parts of the body.

The PNS can be performed invasively or non-invasively, depending on the clinical application and patient's needs. The technique can be used for various purposes, such as treating chronic pain, peripheral neuropathies, and muscle spasticity, among other conditions.

When applied focally to a peripheral nerve, electrical stimulation can inhibit the transmission of pain signals, modify motor or sensory activity, and influence the functioning of the autonomic nervous system. Additionally, PNS can also have central effects, influencing neural circuits related to pain processing and modulation of other functions. This technique has shown promise as a therapeutic approach in several neurological and musculoskeletal conditions, providing symptom relief and improving patients' quality of life.

The PNS relieves pain, improves motor function, and promotes recovery after neurological injuries. It is indicated for the treatment of neuropathic pain distributed in one or two nerves. Selection tests of the nerves to be stimulated are necessary for precise sensor placement, and the use of pulsed radiofrequency is less common. In some urgent cases or situations with a high risk of multiple interventions, it can be used without prior selection of the peripheral nerve. Its use is intended for cases of conventional treatment failure, and the benefit is limited after one year of use[5,6,7].

## Spinal cord stimulation

Spinal cord stimulation (SCS) is a medical procedure that involves implanting a device, like a pacemaker, called a sacral neuromodulator, under the skin, usually in the gluteal or abdominal area. The electrodes are positioned around the sacral nerve roots or in the spinal cord, which then delivers electrical impulses to the spinal cord. These impulses interfere with the transmission of pain signals to the brain, thereby reducing or alleviating chronic pain in certain conditions. Additionally, it regulates the activity of neural circuits that control the neurogenic bladder, fecal incontinence, and sexual function. Afferent reflexes are sacral nerve activations that trigger reflex responses in the pelvic organs, resulting in better control and function of these systems[8,9].

The SCS is a commonly used neuromodulator worldwide to treat neuropathic pain in extremities. It has an estimated annual growth rate of 8.3%. However, its effectiveness in treating non-neuropathic or central pain is limited.

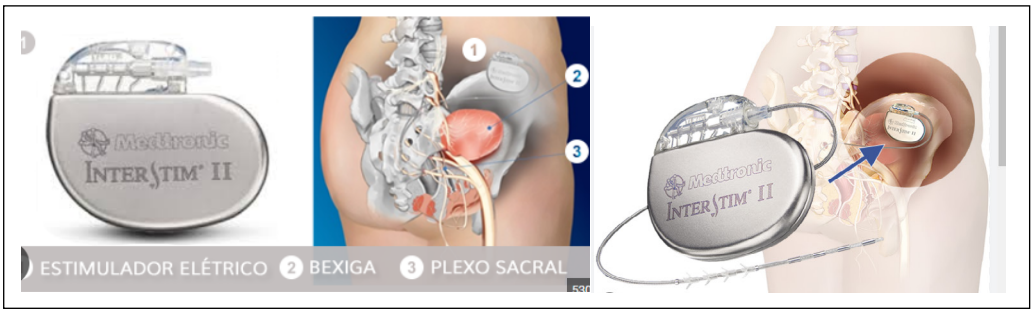
The benefits of SCS might decrease after 1 to 5 years. Before undergoing device implantation, patients are carefully evaluated to determine if they are suitable candidates for SCS. The success of the treatment may vary from person to person, but positive results may include a significant reduction in pain, improved physical function, and better quality of life[10].

The VANTA™ spinal cord stimulator from Medtronic is a pain relief treatment that utilizes advanced technology (Fig. 3). It provides personalized programming that modifies or blocks pain signals traveling to the brain, resulting in long-lasting pain relief. Patients who have used this device have reported an improvement in their quality of life and a reduction in the use of painkillers. In a 12-month follow-up period, 76% of patients reported using fewer painkillers. Additionally, the generator comes with an accelerometer that adjusts its settings based on the patient's movements and positions. The device is also compatible with magnetic resonance imaging[11].


Source: Medtronic

**Figure 3.** Device for sacral spin stimulation for the treatment of chronic pain, overactive bladder, urinary and fecal sphincter disorders.

Multicenter, randomized, placebo-controlled studies have demonstrated the efficacy of neuromodulation for the treatment of chronic pain in well-selected cases (e.g., neuropathic pain, especially in the extremities)[12]. For the treatment of urinary and fecal disorders there are some devices for this control (Fig. 4).



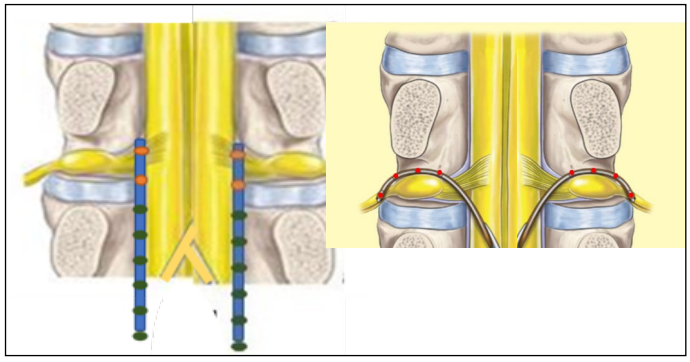

Source: Medtronic
**Figure 4.** InterStim II™ generator from Medtronic for the control of overactive bladder and urinary and fecal sphincter disorders.

## Dorsal root stimulation

Dorsal root ganglia are groups of cells located near the dorsal roots of spinal nerves in the vertebral column. They contain sensory neurons that transmit sensory information from the body to the central nervous system. This type of neuromodulation involves the use of small electrical impulses to affect the sensory neurons that transmit pain signals to the central nervous system. The pulse generator is placed below the ribs and provides significant pain relief for chronic pain. To reach the dorsal root ganglia related to the source of pain, electrodes can be placed directly on the dorsal root, using a lead placed parallel to the dorsal root or the dorsal root nerve endings. It can be stimulated using a lateral epidural stimulation lead. The advantage of lateral, epidural stimulation is that more Dorsal root stimulation (DRGs) can be targeted using one lead[13].

The Proclaim™ DRG Therapy involves the use of a dorsal root ganglion lead, which underwent testing in the ACCURATE study. The study found that after a 3-month follow-up, 81.2% of patients responded positively to DRGs, compared to only 55.7% for SCS. After a year, the study showed an average pain reduction of 81.4% and an improved quality of life for those with focal chronic pain.

The BOOST DRG study is a randomized, controlled trial that will compare the efficacy of SCS, DRGs, combination of SCS+DRGs (DUAL), tonic conventional stimulation, and burst in a crossover design for patients with chronic lower limb neuropathic pain and/or neuropathic back pain. The primary objective of this study is to compare the effectiveness of SCS vs. DRGs vs. DUAL on global pain relief for patients with chronic lower limb neuropathic pain and/or neuropathic back pain. The results will indicate comparative effectiveness on pain characteristics, quality of life, functional disability, psychological distress, and patient profile. The stimulation can be lateral epidural targeting the dorsal root nerve endings or on the right (Fig. 5).



Source: Medtronic and Dr. Lilian Kornett
**Figure 5.** On the left a schematic presentation of lateral epidural stimulation leads targeting the dorsal root nerve endings is shown and, on the right, the dorsal root ganglion is shown.

## Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique that applies electrical energy through the skin for the relief of neuropathic pain. The electrodes are placed on the skin's surface, near the site of pain, or along

relevant nerve pathways. The electrodes are connected to an external device (TENS) that generates low-intensity and controlled-frequency electrical pulses. The current is transmitted to the skin and penetrates the underlying tissues, reaching the sensory nerve fibers.

This electrical current can have different pulse patterns, durations, and intensities, depending on individual needs and TENS device settings. This type of stimulation can activate sensory nerve fibers to modulate pain processing, block the transmission of pain signals to the brain, and promote the release of endorphins, which are the body's natural substances with analgesic properties.

## Gastric electrical stimulation system (GES)

This is a peripheral implantable device that stimulates the gastric musculature (antral portion), regulating gastric motility and emptying. The neurostimulator (Enterra™ II gastric) is indicated for the treatment of chronic nausea and vomiting refractory to medication, secondary to gastroparesis (delayed gastric emptying), appetite disorders, and may help in controlling diabetes mellitus in patients aged 18 to 70 years.

The gastric neurostimulator consists of two main components: a pulse generator and one or more electrodes. The electrodes are placed strategically on or near the vagus nerve or other targeted nerve branches that innervate the stomach. It helps restore normal gastric motility and reduce symptoms.

Burlen et al. (2018) investigated the effectiveness of gastric electrical stimulation (GES) as a treatment for gastroparesis in patients from the United States and Europe. The study evaluated symptom relief, gastric emptying, and overall quality of life. Vomiting was decreased by 62% after GES implant in the European centers and by 45% in the US centers. Results showed that GES was effective in managing gastroparesis symptoms in both regions and provided insights into the consistent positive outcomes of GES in treating gastroparesis across different geographic regions[14].

## Vagus nerve stimulation

Vagus nerve stimulation (VNS) involves actions that regulate vital bodily functions such as heart rate, breathing, peristaltic movements, and reflexes like swallowing, coughing, and vomiting. Studies indicate that by stimutaling the left vagus nerve, which contains around 80% afferent fibers, various parts of the brain can be impacted and excitability can be enhanced. The VNS system delivers pulses to the brain in a "burst" pattern, which can alleviate abnormal electrical activity associated with seizure or be used as a treatment for after-effects of a stroke.

The VNS is FDA-approved for the treatment of epilepsy, particularly for individuals with partial-onset seizures that are resistant to other treatments. It's often considered as an adjunctive therapy, meaning it's used in addition to antiepileptic medications when those medications alone are not providing sufficient seizure control.

In 2019, González et al. conducted a study to determine the effectiveness of VNS therapy in managing epilepsy[15]. The study focused on numerical data and outcomes and found significant decreases in seizure frequency among participants. However, response rates varied among patients, some experienced dramatic reductions while others only achieved moderate improvements. Even though seizure freedom rates were low, patients who are not suitable for resective surgery should still be offered surgical treatment with neuromodulation techniques such as VNS therapy. With two to four years of VNS therapy, approximately 8% of patients will reach seizure freedom, and around 50-60% will have at least a 50% reduction in seizure frequency. Additionally, VNS has also received FDA approval for the treatment of treatment-resistant depression. This refers to cases of depression that have not responded adequately to multiple antidepressant medications, and VNS is usually considered when other treatments, such as medication and psychotherapy, have not been effective[16].

Cluster headaches are intense headaches that occur repeatedly over a period of time. Some research and clinical experience suggest that VNS can help reduce the frequency and severity of these headaches. However, its use for this purpose may vary and requires careful assessment[17].

The potential of VNS in treating chronic heart failure has been investigated. The concept behind this is that VNS could help regulate the autonomic nervous system to enhance heart function and alleviate symptoms in specific heart failure patients. Although research is ongoing, this particular indication is not as established as the others.

The ANTHEM-HF study involved 60 patients who had functional class II-III symptoms of New York Heart Association (NYHA). These patients had a left ventricular ejection fraction (LVEF) of equal to or less than 40%, and LV end-diastolic diameter (LVEDD) ranging from 50 mm to less than 80 mm. The study was conducted by Premchand et. al. in 2014, who randomly selected patients for implantation on either the left (n = 31) or right (n = 29) cervical vagus nerve. After a year of 10 Hz stimulation, there was significant improvement in LVEF, NYHA class, non-sustained VT, heart rate variability, and T-wave alternans. Although there was a slight inclination towards better outcomes with right-sided stimulation, the implant side did not appear to be a statistically significant factor[18].

The NECTAR-HF trial included 96 patients who had NYHA functional class II-III symptoms, LVEF of 35% or less, and LVEDD of 55 mm or more. These patients were randomly divided into two groups: VNS or control (the device was implanted, but VNS was switched off) in a 2:1 ratio for a period of six months. The stimulation intensity was adjusted as per patient tolerance, with a target of 20 Hz, a duty cycle of 16.7%, a pulse width of 300 ms, and a proposed maximal current intensity of 4 mA. Although VNS did not significantly affect cardiac remodeling and functional capacity in symptomatic heart failure patients, there was a significant improvement in quality-of-life measures[19].

The INOVATE-HF trial is a phase II study, conducted in multiple centers, that focuses on evaluating the safety and feasibility of the Biocontrol system (Cardiofit). The trial aims to assess the effectiveness of right VNS at a frequency of 1-2 Hz in treating patients with NYHA functional class III symptoms and LVEF ≤ 40%. A total of 707 patients were randomly assigned to either VNS or continued medical therapy in a 3:2 ratio and were followed up for 16 months. Patients in the VNS group underwent stimulation intensity adjustment four weeks after implantation, with a target of 3.5-5.5 mA. While the VNS group showed improvement in secondary endpoint outcomes such as NYHA functional class, QOL, and 6MWT, the primary efficacy endpoint was not met. The primary efficacy endpoint was a composite of death or HF hospitalization and/or IV diuretic use, and it occurred more frequently in the VNS group than in the control group[20].

There is limited research on the use of VNS for anxiety disorders such as generalized anxiety disorder and post-traumatic stress disorder (PTSD). While VNS can be beneficial, it carries certain risks like temporary or permanent vocal cord paralysis, difficulty in swallowing, infection, and pain at the surgical site. Therefore, it's critical to thoroughly evaluate the indications for this type of neurostimulator.

## Neuromodulation research

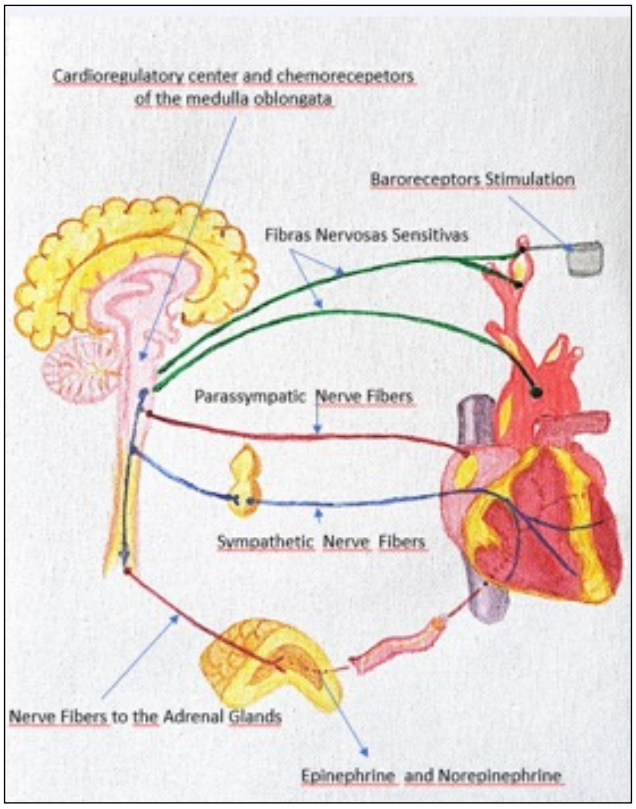
**"Baro-pacing" - Electrical stimulation of baroreceptors**

The control mechanisms of physiological blood pressure are intricate and rely on several bodily systems such as the endocrine, neural, renal, and cardiovascular systems. Resistant hypertension (RHTN) is defined as persistently high blood pressure levels (≥ 140/90 mmHg) even after taking at least three antihypertensive drugs, one of which should be a thiazide diuretic. Refractory hypertension (RH), on the other hand, is when blood pressure remains uncontrolled despite the use of five or more synergistic antihypertensive drugs[21].

The cardiovascular system's moment-to-moment variability is regulated by arterial baroreceptors, while medium-term variability is controlled by cardiovascular stretch receptors. Additionally, chemoreflexes originating from arterial receptors are activated by hypercapnia, acidosis, and hypoxemia. Stimulating carotid baroreceptors has been observed to lead to improved control of the sympathetic nervous system and fluid balance through the kidneys. This process is also associated with long-term blood pressure regulation[22].

Patients with hypertension often experience a decreased sensitivity in their pressor reflex. The baroreflex adapts by shifting the baseline blood pressure and causing bradycardia at higher levels. The autonomic nervous system uses a feedback system to maintain blood pressure within normal limits, obtaining a high-gain pressure reflex in seconds to minutes. The sensory endings of baroreceptor fibers can be found in the aortic arch, carotid sinus, and right subclavian artery.

Baroreceptors do not sense pressure directly, but rather respond to stretch changes caused by pressure alterations within the vessel. Cardiovascular baroreceptors also function as mechanoreceptors, participating in blood pressure control, and are more stimulated by increases in blood volume than changes in pressure. The nerve fibers from the aortic and carotid nerves converge through the glossopharyngeal and vagus nerves into the nucleus tractus solitarius (NTS) region, which is considered the first central region of sensory signals originating in the peripheral system. The baroreceptor reflex reduces sympathetic activity and increases parasympathetic (vagal) tone to the heart and blood vessels. Carotid baroreceptors detect intra-atrial pressure and regulate sympathetic tone, creating negative feedback. Elevated blood pressure stimulates carotid sinuses, sending a message to brainstem cells, which then send signals to reduce sympathetic tone, leading to a subsequent reduction in blood pressure (BP)[23,24]. This is the mechanism of action of this neuromodulation (Fig. 6).




Source: Elaborated by the author based on freely available images
**Figure 6.** Mechanism of action of baroreceptors stimulation.

The Rheos trial is a clinical study that utilizes the Rheos system prototype and second-generation Barostim neo to provide therapy for carotid baroreflex activation (CBAT). Those who participated in the trial and received CBAT experienced significant reductions in blood pressure compared to those who received the placebo[25].

In the Beat-HF study, 125 out of 408 patients were given the CVRx Barostim™ Neo system along with their medical therapy[26]. Patients who received the implant showed improvement in six-minute walking tests and quality of life measures, such as their ability to perform daily tasks. A subset of patients with less severe chronic heart failure also benefited from lower levels of a biomarker for the condition. The system involves the implantation of a pulse generator under the collarbone, which is then connected to a lead that attaches to the carotid artery in the neck. The generator delivers electrical impulses to baroreceptors, which sense the blood flow through the carotid arteries. Upon receiving the signals, the brain instructs the heart and blood vessels to inhibit the production of stress-related hormones, thereby reducing heart failure symptoms.

A BP evaluation system works alongside readings and a computer to analyze parameters to effectively lower blood pressure. The system determines the ideal heart rate and sends a command to the patient's pacemaker to execute the necessary physiological changes in resting and exertional heart rate. Patients can interact with the pacemaker to provide

feedback on their symptoms before the cycle is completed. This process is repeated twice a day to treat resistant hypertension (RHTN) and every 2 minutes using BP medication for patients with Congestive Heart Failure with Preserved Ejection Fraction (HFpEF).

The HOPE4HF trial is currently investigating the potential of baroreflex activation therapy (BAT) as a new therapy for (HFpEF). It is a prospective randomized trial with roughly 540 subjects across 70 sites in the US and 20 sites internationally. The study aims to evaluate the effects of baroreflex therapy on patients with heart failure. A total of 146 patients with heart failure with reduced ejection fraction (HFrEF) participated in the study, with 70 patients receiving control treatment and 76 receiving baroreflex activation therapy. The patients were monitored for six months, and the results showed that baroreflex activation therapy improved exercise capacity, quality of life, and NTproBNP levels in patients with both ischemic and non-ischemic cardiomyopathy. The study also showed a trend towards fewer hospitalizations for HF, although it is important to note that the lack of blinding in the study may have introduced a potential placebo effect[27].

Barostimulation therapy can offer benefits such as better blood pressure control, reduced risk of cardiovascular events, and improved quality of life. However, it also carries potential risks such as infection, device-related complications, and interactions with other treatments. More research and clinical trials are needed to ensure safety and effectiveness.

## Brain stimulations

**Non-invasive brain stimulation**

Non-invasive Brain Stimulation (NIBS) is a safe and temporary method of altering brain activity without requiring surgery or the insertion of devices into the brain. This technique is commonly used for research, treatment, and to gain a deeper understanding of brain functions. There are several NIBS techniques available, but the primary ones are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) as described above[28,29].

rTMS is a non-invasive technique that uses magnetic pulses to adjust neuronal activity in the brain. It can treat several neuropsychiatric conditions, and the primary objective is to balance neural activity and reduce symptoms. During the procedure, a magnetic coil device is placed on the patient's head, which emits magnetic pulses to specific regions of the brain. Side effects are mild and temporary[30].

There are two types of rTMS methods: 1) High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS-HF) and 2) Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS-LF). rTMS-HF involves applying high-frequency magnetic pulses to the targeted brain region for 5 to 20 minutes, while rTMS-LF involves applying repeated low-frequency pulses for a longer period of 30 minutes or more.

tDCS is a brain stimulation technique used to treat several medical conditions such as depression, chronic pain, and neuropsychiatric disorders. It involves using low-intensity electrical current to influence neuron activity by passing through the brain tissue from the positive anode electrode to the negative cathode electrode. The effects are temporary and can vary depending on the protocol. tDCS has been extensively researched in basic neuroscience to gain a better understanding of brain function. It has also been studied as a potential therapy for various neuropsychiatric conditions[31].

## Invasive brain stimulation

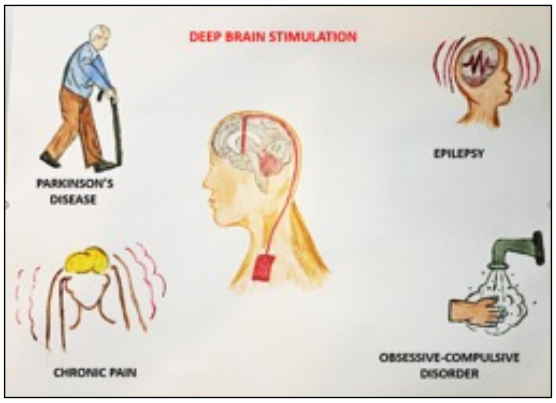
Invasive cerebral neuromodulation is a medical procedure that involves placing electrodes or other devices directly inside the brain to regulate neural activity. This technique is typically used when other treatments have not been effective or when the condition is severe and requires specific intervention.

Deep Brain Stimulation (DBS) consists of implanting electrodes in specific regions of the brain and a generator pulse in the chest or abdomen. By using low-intensity currents, brain activity can be modulated to achieve motor and behavioral control. Figure 7 illustrates the indications for DBS and the PRECEPT generator from MEDTRONIC, which is used in practice[32-35].

Mode of operation and main indications:

- Parkinson's disease (PD): Bilateral stimulation of the globus pallidus internus (GPI) or the subthalamic nucleus (STN). DBS is indicated as an adjunct therapy in patients who have been using levodopa for a few years and are no longer adequately responding to treatment, and whose tremor causes significant functional disability[33-35].
- Dystonia: Uni or bilateral stimulation of the GPI or STN for the management of chronic primary dystonia refractory to drug treatment, including segmental and/or generalized dystonia, hemi-dystonia, cervical dystonia (torticollis).
- Obsessive-compulsive disorder (OCD): Bilateral stimulation of the anterior limb of the internal capsule (ALIC) as adjunctive therapy for the treatment of severe, chronic OCD refractory to conventional treatment with failure of at least three serotonin reuptake inhibitor drugs (SSRIs). DBS is offered as an alternative to the old anterior capsulotomy treatment.

Stimulation testing (Fig. 7) for precise electrode location to be implanted is always performed for DBS, but it is less frequently done for motor cortical stimulation. Benefits are reduced after one year, in the case of pain treatment. The main complications are intracranial hemorrhage, electrode migration (less common than in other sites), infection, and hardware-related complications.




Source: Elaborated by the author based on freely available images
**Figure 7.** Indications of Deep Brain Stimulation (DBS).

Intracranial Electroencephalography (iEEG) involves placing electrodes directly on the brain's surface or within specific brain structures to record electrical activity. This method helps neurologists and neurosurgeons precisely localize the source of epileptic seizures or study brain activity in patients with severe epilepsy, guiding further treatment decisions.

Responsive Neurostimulation (RNS) is a specialized type of neurostimulation used for treating epilepsy. It involves the implantation of a neurostimulator in the brain, which detects abnormal electrical activity and delivers electrical impulses to stop or prevent seizures before they occur.

Invasive cortical stimulation involves the placement of electrodes directly on the brain's cortex to modulate neural activity in specific regions. It has been explored for various conditions, including pain management and certain neuropsychiatric disorders.

It's crucial to recognize that invasive cerebral neuromodulation techniques are not without risks. The procedures involve brain surgery, which carries inherent risks such as infection, bleeding, and potential neurological deficits. As with any medical treatment, the benefits, risks, and suitability for each patient are carefully evaluated by a team of specialists before proceeding.

## Emerging indications of neuromodulation

Obesity is a growing public health problem worldwide and is associated with a range of comorbidities such as cardiovascular diseases, type 2 diabetes mellitus, hypertension, stroke, neoplasms, sleep apnea, joint diseases, and hepatic

steatosis. Lifestyle changes, such as combating sedentary behavior, diet, and medication use, are not always effective in controlling obesity. Neuromodulation may become another therapeutic option for severe cases of obesity[36].

Preliminary studies suggest that DBS in the subthalamic nucleus and ventromedial hypothalamus nucleus may be associated with appetite and satiety control, making it a possibility to be explored in the treatment of obesity[25]. Research aims to modify neural circuits related to appetite, reducing the desire for excessive food intake. Other forms of neuromodulation are being studied for the same purpose, such as TMS, percutaneous neurostimulation, VNS, and gastric stimulation[37,38].

More clinical studies are needed to fully understand the efficacy, safety, and potential of these interventions in obesity. There are still challenges to overcome, such as optimizing stimulation settings and understanding the long-term effects of these stimulations on the brain.

As field of neuromodulation continues to evolve, it faces certain limitations that need to be addressed for further advancements and widespread adoption. Some of these limitations include:

- Lack of standardized protocols: Due to the relatively new and diverse nature of neuromodulation techniques, there is a lack of standardized protocols for patient selection, implantation procedures, and stimulation parameters. Standardizing protocols could improve the consistency of outcomes and facilitate comparison across studies.
- Need for more research: While there have been significant advancements in neuromodulation, more research is needed to fully understand the mechanisms of action, long-term efficacy, and safety profiles of these interventions. Large-scale, long-term clinical trials are essential to gather robust evidence.
- High costs: Neuromodulation procedures can be costly, making them inaccessible to some patients. Finding ways to reduce costs and improve cost-effectiveness will be crucial to making these therapies more widely available.
- Lack of testing in certain populations: Some neuromodulation techniques have not been extensively tested in specific populations, such as pregnant women and children. More research is needed to understand the safety and efficacy of these therapies in these groups.

Despite these limitations, neuromodulation holds great promise as a valuable therapeutic option for chronic pain and various other pathologies. Neurologists, with their clinical experience and advancements in brain mapping techniques, are better equipped to precisely target the neural networks involved in each disease. Non-invasive brain imaging techniques, such as functional MRI, and stereotactic electrode implantation have contributed to better localization and accuracy in neuromodulation procedures.

## CONCLUSION

Neuromodulation devices hold promise for treating diseases that do not respond to clinical treatments. Additional clinical trials and studies are required to fully understand their long-term efficacy, safety, and optimal use in different medical contexts.

## CONFLICT OF INTEREST

Nothing to declare.

## DATA AVAILABILITY STATEMENT

All datasets were generated or analyzed in the present study.

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