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The Importance of Selection of Neuromodulation Therapy in Neurodegenerative Disorders

Abstract

Neuromodulation therapies generally deal with the provision of pain management, treatment of movement disorders, seizure control by the utilization of brain-controlled devices to individuals with compromised movement. Recent advancement in optogenetics has led to the development of techniques to explore the neural circuitry & biomarkers to track the progression of disease in neurodegenerative disorders. Further advancements contributing to neuromodulation therapies include engineering of nanotechnology, advances in genetics, exome sequencing and novel imaging techniques to detect connectivity deficits in motor and sensory networks that have been associated with neurological disorders. The following six neuromodulation therapies will be discussed in detail herein reference to neurologist awareness, candidate selection, and barriers to treatment. This article highlights the appropriate selection of neuromodulation therapy in the management of chronic pain and neurodegenerative orders that can lead to short-term and long-term clinical benefits.

Key Words: Neuromodulation therapies, Deep brain stimulation (DBS), Trigeminal Nerve Stimulation (TNS), Peripheral Nerve Stimulation (PNS), Spinal Cord Stimulation (SCS), Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS)

Introduction

Neuromodulation therapies involve the alteration of nerve activity with the help of external electrical stimulation to alleviate the causes of neurodegenerative diseases and manage acute and chronic pain. Neuroscience has partnered up with engineering to introduce such advance techniques that can control seizures and pain by using the right intensity of the stimulus. These therapies can also help out with disorders affecting mobility and movement.

Six such neuromodulation therapies have been discussed in detail in this article, with a focus on the indications for each therapy and its shortcomings and contraindications.

Deep Brain Stimulation (DBS)

DBS has been used since the 1980s for movement disorders. It is an invasive neurosurgical procedure costing more than 20k USD per patient, which utilizes stereotactic implantation of stimulating electrodes in the brain.

Following are the effective targets for placement of electrodes surgically in the brain:

1. Subgenual (subcallosal) cingulate cortex, Brodmann area 25 (SCG)
2. Ventral anterior internal capsule/ ventral striatum (VC/VS)
3. Nucleus accumbens (NAcc) and ventral striatum
4. Inferior thalamic peduncle (ITP)
5. Lateral habenula (LH)

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6. Internal globus pallidus (GP)
7. Median forebrain bundle (MFB)

- A multidisciplinary team will undertake the task to evaluate the patient for DBS (Drew et al., 2007) and further treatment; they may include:
- → Movement disorder neurologist
- → Functional neurosurgeon
- → Neuropsychologist
- The two electrodes are surgically placed into the targeted location that depends on the clinical outcome desired for the patient; they are connected to IPG; implantable pulse generator).
- A study reported that the clinical outcome achieved depends on the pulse width.
- The success of treatment depends on the proper selection of patient, experience and skill of the stereotactic neurosurgeon.
- Stimulation parameters should be adjusted to the needs of each individual patient to achieve the clinical outcome desired.
- A decade-year-old report indicates the increased incidence of suicide in patients who have undergone DBS. (Kennedy, Giacobbe & Rizvi, 2011).
- DBS should be avoided in patients with cognitive impairment.
- Concomitant DBS and dopaminergic substitution have proven to show hopeful results in movement disorders with an improved step length, improved walking speed, and less effect on axial locomotive components. (Chastan et al., 2019)
- DBS has been recognized as a favorable treatment in patients with PD with motor complications.

Indications

Candidates are selected based on the stereotactic neurosurgeon based on experience; a balance between clinical benefit and adverse effects should always be predicted before performing surgery. However, a review of clinical evidence suggests the success of DBS in the following diseases and the patients can be considered as candidates.

Parkinson Diseases (PD)

Recent clinical evidence suggests that DBS in PD can provide a 10-year survival rate of 51% and improved postural stability (Chastan et al., 2009).

But long-term results show that it does not stop the progression of PD, only provides symptomatic relief and maintains ADLs for patients with improved QOL and patient satisfaction (Hitti et al., 2019). DBS attained FDA approval for use in PD in 2002 (Cook, Espinoza, & Leuchter, 2014)

Parkinson Disease with Dementia and Dementia with Lewy Bodies

- The patient is evaluated by neuropsychology for DBS; implant electrode in the subthalamic nucleus.
- Contraindicated in PDD (Parkinson's disease with dementia) or DLB (Dementia with *Lewy* Bodies) patients who are cognitively impaired.
- Geriatric PD patients with MCI prior to DBS are at a greater risk for postoperative failure.

Post Stroke Pain Syndrome

Concomitant treatment of stereotactic radiosurgery of the pituitary and deep brain stimulation (DBS) are used with success.

Essential Tremor

FDA approval in 1997. Thalamic DBS is effective in contralateral tremor.

Obsessive-Compulsive Disorder (OCD)

FDA Approval in 2009, implant bilateral DBS electrodes in the anterior limb of the internal capsule (Dougherty, 2018).

Depression

Pain: DBS has been used for chronic pain for more than 25 years.

Epilepsy

Ah-DBS is shown to be clinically effective in epileptic patients with temporal lobe seizures.
Furthermore, the SANTE trial showed that DBS (implanting electrodes in ATN) shows long-term safety and efficacy in epileptic patients. (Salanova & Behavior, 2018)

Dystonia

GPi-DBS is considered as the treatment of choice in patients for disabling medically intractable generalized or segmental dystonia (Panov et al., 2013).

Phantom Limb Pain

Movement Disorders

Clinical evidence suggests that DBS provides sustained long-term benefits in movement disorders (Kern & Kumar, 2007).

Barriers to Providing DBS

- A multidisciplinary team is required to provide DBS.
- The management of PD patients with DBS requires joint care between the local hospital and the DBS center.
- The process is highly invasive and cost-ineffective.
- Following problems with DBS may be faced by patients:

1. Acute Surgical complications
2. Poor stimulation response
3. Side effects
4. Hardware Problems (depleted battery)

(Baig et al., 2019)

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation, or TMS, is a therapy that utilizes repeated magnetic pulses to safely and effectively regulate neural activity related to various mental health conditions. TMS is often referred to as repetitive TMS or rTMS due to the repetitive nature of the procedure. TMS has been used to investigate almost all areas of cognitive neuroscience. TMS is a rising and recently FDA-approved non-invasive treatment that utilizes a period differing attractive field to produce a current in brain tissue.

TMS is an emerging and recent therapy that uses a time-varying magnetic field to treat MDD in adults by inducing a current in brain tissue. It is being studied and researched for likely helpful applications in OCD, post-traumatic stress issues, and auditory disturbances in the case of schizophrenia. To achieve focal electrical stimulation on the cortical surface, the TMS technique uses a pulsed magnetic field introduced on the scalp surface. A magnetic field perpendicular to the coil plane is induced. It does not need anaesthesia, does not induce a seizure, and can be given in the office area. To induce excitatory or inhibitory effects on cortical neurons, the TMS field can be pulsed at varying frequencies. By preferentially activating GABA-ergic interneurons in the cortex, frequencies of less than or equal to 1 Hz are thought to have mainly inhibitory neuronal effects; this can result in trans-synaptic depression. It is assumed that the use of TMS frequencies greater than 1 Hz has mostly glutamatergic or excitatory neuronal effects.

Barriers to Providing TMS

The most prominent side effects are headaches and site application pain; the risk of epilepsy is estimated at less than 1 in 10,000 sessions of TMS. There are few side effects associated with monotherapy with TMS. Follow-up sessions can be prescribed every few weeks or months, based on the patient's outcome, to help sustain good outcomes.

Activation of a focal region of the motor cortex can also give rise to a transient depression of function. This depression would lead to a short lapse in muscle activation while a subject or patient were attempting to generate movement, which would be perceived as either asterixis or negative myoclonus.

Depression is common during pregnancy, and that pregnant women prefer non-medication depression is prominent during childbirth, and pregnant women want recovery methods that are not medicated. In order to know about the choice of medication, an acceptability survey was performed using an interactive video to improve participant awareness about TMS. As the most appropriate recovery choice, psychotherapy was identified. Before the educational clip, TMS was perceived as an inappropriate treatment choice for nearly all women. 15.7 percent found TMS an appropriate counseling choice after the clip. Therefore, the main hurdle is the acceptability of the procedure. (Kim et al., 2011)

Indications

The patient should speak to his or her psychiatrist, psychologist, or any source of mental health care before initiating any treatment for depression. Each patient is different, and for another, what works for one might not work. For patients who have a history of epilepsy, TMS treatment is not recommended. The treatment should not be performed for people who have a metal plate in their head or some other metal in and around their head.

TMS is used on people treated with depression who have not reacted to a medication. Promising outcomes from this procedure are recorded by many mental health providers. The technique, however, continues to undergo studies on its feasibility and long-term effects. (Khedr, Etraby, Hemeda, Nasef, & Razek, 2010

It has an important antidepressant impact on people with the unipolar disorder that may not respond to medication or cannot handle treatment.

Vagus Nerve Stimulation (VNS)

VNS is a neuromodulation therapy that targets the vagus nerve and alters nerve impulses to control the occurrence of seizures. It has a number of other indications, including TRD and TBI.

Components

- Implanted pulse generator implanted below the clavicle
- Lead that is wrapped around the left vagus nerve in the cartid sheath
- battery

Non-Invasive VNS

tVNS (transcutaneous vagus nerve stimulation) is a non-invasive therapy in which the auricular branch of the vagus nerve is suggested to be an alternative access path to the same neuronal network. Clinical evidence suggests its efficacy in drug-resistant epilepsy (Ellrich 2019).
Side effects:

- Hoarseness (most common)
- Sore throat
- Dyspnea
- Coughing

Indications

When selecting candidates for VNS therapy, the neurosurgeon must evaluate the present clinical evidence and certain parameters before deciding whether VNS is appropriate for the patient or not. This will lead to desired clinical implications in the short and long-term.
Following are the indications for VNS that are evaluated based on sufficient clinical evidence to support their VNS treatment and improve QOL.

Intractable Epilepsy

Clinical evidence shows about 50% of the decrease in seizure with the implantation of VNS (González, Yengo-Kahn, & Englot, 2019) with an overall protective effect on GABAergic neurons.

- Multifocal epilepsy drops attack (TSC)–related multifocal epilepsy, and respective unsuccessful surgery (Giordano, Zicca, Barba, Guerrini, & Genitori, 2017).
- Idiopathic and symptomatic generalized epilepsy.
- Lennox–Gastaut syndrome (Kostov, Kostov, Tauboll, & Behavior, 2009)

TRD Treatment-Resistant Depression

FDA approved the use of VNS in TRD for long-term adjunctive treatment in 2005.

- Candidates approved by FDA: age; 4yr or older, partial seizures, intractable epilepsy, TRD

Traumatic Brain Injury (TBI)

Preclinical studies were performed to evaluate the efficacy of VNS in TBI; outcomes suggest that VNS can improve motor and cognitive recovery and reduce secondary neuronal damage (Neren et al., 2015).

Limitations of VNS

1. Some health insurance carriers do not pay for this procedure.
2. VNS can only be provided in centers and hospitals where there is the provision of multidisciplinary teams involving psychiatrists and neurosurgeons.
3. If a patient develops one of the contraindications before or during the therapy period, then the neurosurgeon should evaluate whether to continue with therapy or not, considering the ratio of clinical benefit to adverse effects.

Contraindications: pregnancy, asthma, COPD, active peptic ulcer disease, IDDM, OSA (Obstructive sleep apnea)

Peripheral Nerve Stimulation (PNS)

PNS has been studied for about 50 years, and the neuromodulation experts have used the devices that were designed for SCS to stimulate the peripheral nerves with clinical success.

PNS is used to alleviate chronic neuropathic pain by targeting the nerves of the peripheral nervous system. Targets the nerve(s) that transmit pain signals to your brain. It is especially useful in patients contraindicated to SCS. Postoperative pain control is also controlled by the application of PNS (Trent & Jain, 2019). It involves the use of a tiny implant that delivers electrical impulses, similar to a pacemaker, to the nerve. These electrical pulses interrupt or change the pain signals sent from the nerve to the brain.

- A power source
- A thin wire connected to electrodes that deliver the pulses to the peripheral nerve
- A remote control-type device that allows the patient to adjust the pulse settings

Components of the Device

Sprint PNS

- A sixty-day implant (indicated by FDA for chronic as well as acute pain in back/extremities).
- Micro lead wire is inserted in the area of the target nerve
- Micro lead is linked to a pulse generator
- The patient controls the stimulation with remote control.

Indications

- Chronic pain: Narcotics, opioids and pain killers as such can be substituted with PNS for chronic pain relief.
- Further clinical evidence and research suggest the use of PNS in the following candidates with beneficial clinical outcomes.
- Sleep pattern improvements (Nava, Christo, Williams, & Reports, 2016)
- Peripheral vascular disease neuropathy
- Phantom limb pain
- Postherpetic neuralgia
- Post-thoracotomy syndrome
- Trigeminal neuralgia
- Diabetic peripheral neuropathy
- Migraine (Silberstein et al., 2012)

Limitations

Posttreatment Complications

- Lead migration (highest incidence)
- A study reports 8.6 % occurrence of adverse events in their clinical studies results in patients have to be hospitalized.
- Adverse events reported include migraine, pruritis, infection.
- 40.7% of patients are in need of further surgical intervention for management of posttreatment complication

Contraindication

- Bleeding disorders
- Active infection, bacteremia or direct involvement of the surgical region
- Major cognitive impairment
- Untreated depression
- Unsuccessful PNS trial
- Patients who require routine MRI follow up

Studies report clinical success in pain relief is less than 43%. (Slavin, 2008)

Spinal Cord Stimulation (SCS)

SCS is a neuromodulation therapy mainly used in the management of chronic pain; it is similar to PNS in which a spinal cord stimulator similar to a heart's pacemaker is used to transmit mild impulses to the spine targeted to the location of pain; this technique like the other 4 techniques discussed can only be performed by pain specialists and neurosurgeons. SCS can be considered as a safe technique as reported data suggest that life-threatening complications have a very low incidence in patients treated with SCS.

The patient undergoing SCS should have a trial if there is a need for permanent implantation of SCS. In this procedure, the percutaneous lead will be placed into the epidural space and connected to the pulse generator. Then the stimulator is turned on, and the patient will feel numbness and tingling. The stimulation covering the area of pain should decrease pain by 50%. If the patient under evaluation reports a pain reduction of 50% or more, only then permanent implantation should be done for this patient.

Indications

A psychological evaluation should be there evaluating the following criteria before selection of a candidate for provision of therapy:

- Clinical interview by the neurosurgeon
- Administration of a specifically structured inventory for pain
- Psychometric tests. (Beltrutti et al., 2004)

These parameters must be evaluated appropriately as the clinical outcomes on short-term and long-term depend solely on the correct selection of therapy for the patient. (Deer & Masone, 2008).

On the basis of clinical evidence reported, SCS has shown success in the following conditions; based on this evidence, patients in these conditions can be considered suitable candidates.

Chronic Pain

It is effectively being managed by SCS and epidural stimulation; furthermore, it is replacing the use of narcotics as pain killers and beneficial clinical implications.

- Complex Regional Pain Syndrome (CRPS)
- Failed Back Surgery Syndrome
- Isolated Nerve Injury Of Extremities
- Unremitting Pain Due To Peripheral Vascular Disease

Limitations of SCS

In clinical practice, the selection of candidates for SCS is made per the clinical criteria for SCS; still, a major portion of patients fail the therapy with no clinical benefit. (Bendersky & Yampolsky, 2013) This suggests that the clinical criteria for the selection of candidates need to be reviewed and adapted.

Furthermore, a few **complications** are associated with SCS:

1. 38% of hardware related
2. 22.6% lead migration (Main)
3. 9.5% lead connection failure
4. 6% lead breakage
5. 6.3% infection rate in patients with failed back surgery syndrome
6. 9% infection rate in patients with diabetics

To manage these infections, antibiotics are administered to the patients.

If a patient is contraindicated to SCS, then PNS should be provided.

Trigeminal Nerve Stimulation

Trigeminal nerve stimulation TNS is a novel non-invasive medical treatment in which electrical signals are applied to stimulate branches of the trigeminal nerve (largest cranial nerve) to modify the activity of aimed brain regions.

Indications

Traumatic Brain Injury

In traumatic Brain Injury (TBI), Ischemia and hypoxia worsen the brain damage, referred to as secondary damage. Modern TBI management involves the protection of neurons from secondary damage. Trigeminal nerve stimulation is capable of increasing cerebral perfusion by activating the rostral ventrolateral medulla and inducing pressor response. Therefore, TNS is a promising strategy for TBI management.

Major Depressive Disorder

Many patients with Major Depressive Disorder don't respond to initial pharmacotherapy and are given combination therapies. An experiment was conducted to evaluate the clinical efficacy of TNS in major depressive disorder. In that experiment, under double-blind conditions, when therapeutic TNS was applied to randomized subjects at 120 Hz or active sham with TNS stimulation at a very low frequency of 2 Hz, the treatment group showed more than twice improvement in the Beck Depression Inventory score of the sham control group.

Attention-Deficit/Hyperactivity Disorder (ADHD)

In addition, Trigeminal Nerve Stimulation TNS has shown potential benefits in attention-deficit/hyperactivity disorder (ADHD) in the unblinded open study with an expected treatment effect size similar to non-stimulants; it has the least side effects and is well tolerated.

Hemorrhagic Shock

TNS is also discovered as a new resuscitation tactic in an animal model of hemorrhagic shock.

- Craniofacial Pain
- Trigeminal deafferentation pain
- Supraorbital neuralgia
- Post-traumatic stress disorder

Advantages of TNS

Trigeminal nerve stimulation has an advantage over vagus nerve stimulation, both being cranial nerves that it has no autonomic outflow to cause cardiac risk; furthermore, large branches can be stimulated transcutaneously by external surface electrodes (e TNS); similarly, identical branches can be stimulated by subcutaneously implanted electrodes (sTNS).

Limitations of TNS

The studies conducted so far included smaller samples, so more studies involving larger samples are required to further confirm findings.

Conclusion

Neuromodulation therapies include both non-implantable as well as implantable techniques and are used for pain management, neuro-degenerative disorders, movement disorders and seizure control by manifesting brain-controlled devices. The article reviews six major types of neuromodulation therapies highlighting indications, leads and limitations of each therapy. The therapies mostly cover chronic disease which when treated with conventional pharmaceutical therapies present with large number of side effects and complications. This challenging gap can be conquered using neuro-modulation therapies. The review presents with the deep insight of technology generated by coupling of neurosciences with engineering to combat major challenges of medical care and selection of appropriate therapy.

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