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Neurostimulation for Chronic Pain

A Rapidly Evolving Therapy

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Electrical stimulation has a long history of being used in medical practice; as early as 1500 BC, practitioners in ancient Greece and Rome used electric eels to treat pain. Scientific inquiry into mechanisms of pain led Melzack and Wall to introduce the gate control theory in 1966. This theory postulated a "gate" within the spinal cord dorsal horn which could be opened or closed to regulate pain transmission. Two years later, neurosurgeon Norman Shealy, MD, implanted the first neurostimulation system into the thoracic spine of a human and electrically stimulated the spinal cord to successfully relieve intractable cancer pain.

Since then, spinal neurostimulation has grown to be a worldwide, multibillion-dollar industry with multiple corporate vendors rapidly introducing new, minimally invasive technologies to block pain through electricity. This article hopes to cut through the hype of neurostimulation to explain the mechanisms of action, evidence-based benefits and downsides of this rapidly evolving therapy.

Neurostimulation is now used widely in the US and Europe by pain specialist physicians to treat a multitude of neuropathic chronic pain syndromes when more conservative therapies, including medication management, physical therapy, interventional pain procedures and surgeries have failed. Neurostimulation devices are sometimes described as cardiac pacemakers for the nervous system, since many vendors of cardiac rhythm technology, including Medtronic, Abbott and Boston Scientific also manufacture neurostimulation systems.

Common neurostimulation therapies

The most common neurostimulation therapy is spinal cord stimulation (SCS). It has been used to successfully treat regional pain in the upper, mid or lower body for the past three decades. Peripheral Nerve Stimulation (PNS) and more recently, Dorsal Root Ganglion (DRG) Stimulation are similar technologies increasingly used to treat more focal pain in specific body parts. The science and technology of neurostimulation has gradually evolved since its introduction in 1968 with especially rapid innovation occurring from 2015 to the present. Currently, there are several multibillion-dollar health care corporations including Medtronic, Abbott, Boston Scientific and Nevro, along with a multitude of smaller companies, all rapidly and aggressively researching, developing and bringing new and increasingly effective variations of neurostimulation to market. The global neurostimulation device market was valued at 4.4 billion dollars in 2018 and is expected to reach 11.3 billion dollars by 2026.

Neurostimulation has been shown to affect biochemical and molecular changes within pain processing systems in the spinal cord dorsal horn and may also have actions within other areas of the spinal cord, the peripheral nerves and the brain which contribute to pain relief. Basic science research has revealed the complex nature of neurostimulation, but we still do not have a complete understanding of the mechanism of action despite years of study.

Early stimulation systems that followed Dr. Shealy's initial implant targeted the spinal cord dorsal columns with a low frequency (60 Hz) electrical current that mimicked firing of the A-beta neural fibers involved in vibration sensation. When we touch our finger on a hot stove, we may shake the burned finger to feel better. It is thought that shaking generates vibratory impulses in the dorsal column A-beta fibers that modulate pain processing within the spinal cord dorsal horn. A-beta fiber transmission is thought to block pain by filling up the dorsal horn gate with vibratory input, effectively closing the gate to pain input. Electrical stimulation of dorsal columns mimics natural vibration and creates a pain-relieving buzzing, vibrating sensation called paresthesia in the affected body region. Paresthesia-based systems are effective at relieving neuropathic pain and dominated neurostimulation from its inception in 1968 through the mid-2010s. Unfortunately, paresthesia sometimes becomes uncomfortable and tiresome for patients over time, and in 2015, high-frequency stimulation at 10,000 Hz (HF-10) was shown to provide better pain relief without paresthesia. By 2016, HF-10 became a popular stimulation waveform and within two years replaced paresthesia stimulation as the dominant modality. However, high-frequency stimulation is power-intensive requiring daily recharging and is more sensitive to anatomic migration than other types of stimulation. In 2016, Abbott introduced a low-power alternative called burst stimulation which does not require recharging. Burst waveforms are intermittent and mimic natural nervous system impulses more closely than paresthesia stimulation and HF-10. In addition, the burst spinal cord stimulation waveform has been shown to reduce catastrophizing in chronic pain patients by stimulating the medial spinal pathways, which input into the emotional centers of the brain. Other technology vendors have recently iCompontroduced novel waveforms and programming algorithms, such as Medtronic's Differential Target Multiplexed Stimulation and Closed-Loop Stimulation, which ultimately may provide multiple effective stimulation options that can be targeted to specific patient needs.

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Composition of neurostimulation systems

Regardless of the waveform produced, neurostimulation systems are typically comprised of an electrode array designed to be implanted into the central or peripheral nervous system and connected to a power source with an integrated computer chip. These are called internal pulse generators (IPG), which are usually implanted under the skin but can be external to the body. Neurostimulation systems share many attributes with cardiac pacemakers and are produced by some of the same vendors–Medtronic, Abbott and Boston Scientific. Neurostimulators may be programmed to deliver a variety of electrical waveforms to a variety of neural targets and have the potential to relieve pain by stimulating the brain, spinal cord, dorsal root ganglion and/or peripheral nerves. Many systems are designed to allow software programming updates that can be transmitted wirelessly to the device as technology advances. IPG batteries are available in rechargeable and non-rechargeable forms, with battery life lasting from three to ten years depending on the power output required to control pain.

Chronic pain conditions

Neurostimulation has a strong evidence basis and has been scientifically proven to effectively treat challenging chronic pain conditions such as peripheral neuropathy, chronic radiculopathy and nerve pain after joint replacement and to improve blood flow and relieve pain in chronic limb ischemia. After rigorous evaluation of the existing evidence for efficacy and safety, SCS, PNS, and DRG stimulation has been approved in both the US and European Union to treat intractable neuropathic pain.

Neuropathic pain occurs when there is damage to the nervous system at the spinal cord or peripheral nerve level. Common neuropathic conditions include post-spinal surgery pain syndrome, which is the most common indication for neurostimulation, as well as peripheral neuropathy, complex regional pain syndrome and post-herpetic neuralgia. Neuropathic pain differs from nociceptive pain in that nociception involves pain impulses generated by

painful tissue pathology that course through a normal pain-sensing nervous system to be processed as pain sensation in the brain. Common nociceptive pain problems include rheumatoid arthritis, osteoarthritis, fractures, sprains and myofascial pain, none of which are typically responsive to neurostimulation. With respect to spinal pain syndromes, acute spinal radicular pain may be caused by an irritated and inflamed spinal nerve root and is nociceptive in nature, whereas chronic spinal radicular pain may persist beyond the resolution of inflammation and be neuropathic in nature, generated by an irreversibly damaged spinal nerve root. Neurostimulation has proven to be effective for neuropathic pain but there is minimal evidence that it is effective for nociceptive pain. When a patient with neuropathic pain is implanted with a neurostimulation device, the constant burning element of nerve pain is reduced, whereas pain from an acute fracture, sprain or strain of the affected body part would not feel different.

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Trial neurostimulation

One great advantage of neurostimulation compared to surgery and other invasive interventions is patients may trial stimulation therapy before deciding whether to undergo a permanent implant. In the United States, a successful trial of neurostimulation is required by healthcare payers in order to approve authorization for a permanent surgical implant of a device which can cost close to $25,000.

For a neurostimulation trial, a temporary system is placed non-surgically with electrodes advanced through needles under fluoroscopic guidance to the nervous system targets. The temporary neurostimulation wires are then connected to a power source outside the body to mimic the effects of a permanently implanted system. It is typically an outpatient procedure and may last up to one week. This neurostimulation trial demonstrates to the patient, the implanting physician and the health insurance payer what the system would be like if permanently implanted, thereby allowing for informed decision making. Currently, the outcome of a neurostimulation trial is judged by subjective feedback from the patient; the outcome must provide at least 50% pain relief and improvement in physical functioning to be considered successful. Soon, rapidly evolving technology in wearable devices should allow a more objective determination of trial success by tracking real-world physical data, including the amount of time upright, number of walking steps, heart rate variability, quality of sleep, opioid consumption and other measurable parameters correlating with pain relief and functional ability.

Importantly, a trial of neurostimulation is an image-guided needle procedure with no surgical incision and without any obligation to proceed to a surgical implant. The trial procedure itself typically takes under one hour in an outpatient facility and can be described like placing an epidural catheter to relieve labor or post-operative pain. The neural targets for spinal cord stimulation are the spinal cord dorsal columns, which transmit pain signals to the brain and are easily accessible from the epidural space in the cervical and thoracic regions of the spine. Stimulating dorsal column fibers can provide regional pain relief in the neck and arms, trunk and ribs or low back and legs. For DRG stimulation, the neural target is the dorsal root ganglion which contains the cell bodies of the pseudounipolar neurons responsible for dermatomal sensation. DRG stimulation is dermatome specific and can deliver electrical pulses to block pain in a specific body part such as the foot, knee, hip, groin or rib. DRG stimulation has proven quite useful in cases of localized neuropathic pain following joint replacement, hernia surgery and zoster infection (post-herpetic neuralgia) and is the treatment of choice for complex regional pain syndrome. Peripheral nerves can also be stimulated to provide focal pain relief along with the distribution of the nerve in cases of neuralgia, as first demonstrated by Wall and Sweet in 1967.

While neurostimulation offers non-destructive, reversible and medication-free pain relief for many patients, it is also relatively expensive, not always effective and may have technical failures. During trial stimulation, approximately 40-50% of patients fail to respond with adequate pain relief to justify permanent implant. Furthermore, once implanted, stimulation therapy can fail, and explant rates for ineffective stimulation are relatively high.

Case studies

Below are a few real-world examples of neurostimulation outcomes from my personal experience trialing, implanting and managing neurostimulation patients for the past 25 years:

Ms. A had severe bilateral foot and ankle pain from chemotherapy-induced peripheral neuropathy. Although her cancer had essentially been cured, she was taking high doses of oral opioids for her bilateral leg and foot pain, with poor pain control and unacceptable side effects of somnolence and constipation. We trialed a spinal cord stimulation system (with SCS good results) and then implanted a permanent SCS, which provided excellent pain relief and allowed her to taper and discontinue opioids. The system has now been in place for six years and continues to function well.

> Neuropathic pain is a very difficult problem with no easy solution.

Mr. B had successful left hernia repair with mesh in 2019 but developed chronic pain at his groin surgical site, which was severe and refractory to nerve blocks and medications. He was taking daily opioids with poor pain relief and side effects. We trialed and implanted a DRG system, which allowed us to specifically target the left L1 and L2 dermatomes by placing a tiny electrode onto the DRGs at left L1 and L2. Mr. B achieved good pain relief and is scheduled for IPG replacement for end of battery life seven years after implant.

Ms. C had severe low back and leg pain after multiple lumbar spine surgeries with instrumented multi-level fusion. Her pain was adequately controlled with oral opioids but her prescribing doctor would not continue opioids and tapered her off. We trialed her with an SCS system with excellent results. After permanent SCS implant, her pain was initially well controlled, but pain relief gradually faded over the next year despite multiple reprogramming efforts. She developed pain at the buttock IPG implant site and ultimately had the SCS system removed because of lack of efficacy after 18 months. There was no infection or malfunction of the system noted at explant.

Two successes and one failure. This seems to be the nature of neurostimulation–a wonderful, low-risk therapy that provides profound relief from neuropathic pain without medication for some patients, whereas for others, lead migration, lead fracture and/or fading efficacy over time results in therapy failure and high explant rates of SCS systems.

Outcomes

Recently published outcome studies indicated that approximately 20% of SCS systems are explanted prior to battery depletion and only 40% of SCS patients choose to have their systems re-implanted when the IPG battery expires after years of therapy. Contrast this with neuromodulation using a pain pump for targeted spinal drug delivery, where greater than 95% of pain pump patients choose to have their pump re-implanted when the battery reaches end of life.

Conclusion

Neuropathic pain is a very difficult problem with no easy solution. A damaged nervous system is often not fixable. Although surgeries may correct the structural problems causing nerve impingement and irritation, pain often persists because nerves have been irreversibly damaged by the underlying condition. Medications such as gabapentin and pregabalin may be effective for some patients but are often not adequate enough on their own to treat severe neuropathic pain. Neurostimulation offers an excellent alternative for patients and is rapidly evolving so that newer stimulation modalities may provide effective pain relief for more patients in the future.

David Schultz, MD, is the medical director and founder of Nura Pain Clinics. Dr. Schultz is a board-certified anesthesiologist with additional board certification in pain medicine from the American Board of Anesthesiology, the American Board of Interventional Pain Physicians, and the American Board of Pain Medicine. He has been a full-time interventional pain specialist since 1995.