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Review Article

# Upper-Extremity Peripheral Nerve Stimulators

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## ARTICLE INFO

Chronic pain conditions are some of the most challenging problems upper-extremity surgeons face and often require a multimodal approach including neuromodulation. Peripheral nerve stimulation (PNS) is one of these modalities, delivering electrical stimulation to peripheral axons to modulate the spinal cord and block out nociceptive signals from the extremity. This blockade leads to long-lasting effects in both the peripheral and central nervous systems. Not only does PNS decrease peripheral pain signals but it also decreases the peripheral inflammatory response and assists with central nervous system plasticity for long-term pain control. Although PNS was initially developed in the 1960s, it has been underrepresented in the literature largely due to the advent of spinal cord stimulation and the lack of Food and Drug Administration—approved hardware for PNS. However, for upper-extremity pain, PNS provides notable benefits over spinal cord stimulation devices, as PNS allows for safer, more specific, and often more effective pain control. As clinicians attempt to limit narcotic use, therapies such as PNS have been revisited and are gaining popularity. We present a narrative review of PNS; discuss its mechanism of action, indications, and surgical technique; and provide a summary of the available literature for the upper-extremity surgeon. Peripheral nerve stimulation offers a solution for chronic, debilitating pain recalcitrant to other treatment modalities.

Pain has been a primal malady of the human condition and at the forefront of medical study for thousands of years. The first written descriptions of neuromodulation include acupuncture as described in the Chinese literature more than 2,000 years ago. Scribonius Largus, the Roman court physician of the first century, serendipitously noted that a patient had relief of gout-related pain when accidentally shocked by a torpedo fish. This led him to prescribe a foot bath of torpedo fish to patients with persistent gout pain. In the 1960s, Melzack and Wall[1] were able to expound upon electrical eels, describing a "gate control theory of pain" that fundamentally changed our understanding of pain (Fig. 1).[2] The gate control theory is based on the spinal cord processing acting as a neurologic gate, where networks of nociceptive signals are blocked by intense tactile stimulation from the same area as the pain signal. This is demonstrated when we reflexively rub our ipsilateral shin after stepping on a sharp object or grab our wrist after cutting a finger.

Shortly after the gate control theory was postulated and established in animal models, multiple techniques of neuromodulation were described. Methods of electroanalgesia soon included spinal cord stimulation (SCS), transcutaneous electrical nerve stimulation, deep brain stimulation, epidural motor cortex stimulation, and dorsal root ganglion stimulation. Wall and Sweet[3] published a landmark article in 1967 describing peripheral nerve stimulation (PNS), a safer and more precise tool than SCS.

The burden of peripheral nerve pathology can be particularly severe due to the intensity of pain and a dearth of curative treatment options. Innovation in the treatment of peripheral nerve pathology in the upper extremity due to neuroma, type I complex regional pain syndrome, phantom limb pain, and several other pathologies has been a particular focus over the last decade. Many surgical interventions have been described, including nerve grafting, nerve transfer, "nerve to nowhere," regenerative peripheral
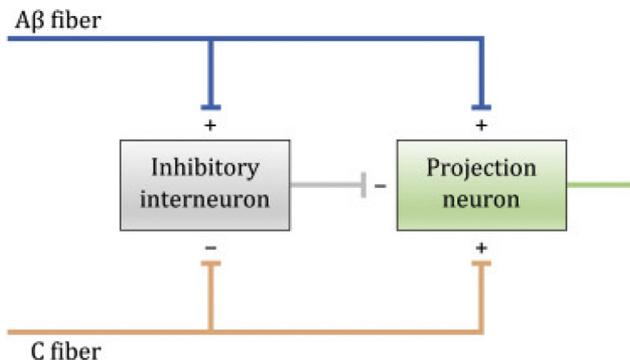
**Figure 1.** The gate theory of pain control, as originally proposed by Melzack and Wall.[1] Both somatosensory Aβ-fibers and nociceptive C-fibers synapse on to projection neurons, which send output to the brain. Projection neurons received inhibitory modulation by inhibitory interneurons, which are modulated by Aβ-fiber and C-fiber activity. The presence of somatosensory input excites the inhibitory interneuron that inhibits the projection neuron, "closing the gate" for nociceptive input. Nociceptive input at high enough intensities instead downregulates interneuron activity and thus keeps the gate "open" for signal transmission to the brain. Although the concept of gated nociceptive output is widely considered valid, the specifics of the circuit and molecular mechanisms remain controversial. Reprinted with permission (RightsLink License Number 5218290125994) from Kral et al.[2]

nerve interfaces, and various more classic neuroma management strategies; however, there is little evidence of superiority of one technique and less than perfect results from all.[4] Spinal cord stimulators have been successfully used for decades for nonsurgical management of chronic low back pain, whereas peripheral nerve stimulators for peripheral nerve pathology have been comparatively underused and underrepresented in the upper-extremity literature.[5]

## Mechanism of Action

Peripheral nerve stimulation is believed to block pain through a combination of central and peripheral mechanisms. Melzack and Wall[1] demonstrated that the stimulation of large, afferent axons (Aβ-fibers) that transmit signals of touch, vibration, and proprioception concurrently inhibit the nociceptive inputs of peripheral Aδ-fibers and C-fibers, which transmit pain signals. Inhibitory interneurons, located in the dorsal horn, will subsequently prevent the transmission of pain signals to higher central nervous system centers such as the somatosensory cortex. Additionally, repetitive stimulation of these peripheral nerves will lead to increased thresholds for Aδ-fibers and C-fibers and reduced excitation even after the inhibitory signal is stopped.[6] Peripheral nerve stimulation also alters the peripheral microenvironment, with alterations in blood flow and neurotransmitters and a reduction in the levels of inflammatory mediators (eg, interleukin 1, interleukin 6, tumor necrosis factor-α).[7]

Central mechanisms also play a role as PNS alters central γ-aminobutyric acid-ergic and glycine pathways.[8] Peripheral nerve stimulation leads to a central release of serotonin and dopamine, as measured by their metabolites in cerebrospinal fluid, that may directly decrease the perception of pain.[9] Peripheral nerve stimulation also alters N-methyl-D-aspartate—mediated plasticity that may have implications for centrally driven pain sensitization. Central and peripheral mechanisms play a role in PNS and may be independent of opioid pathways: PNS is similarly efficacious when also administered with naloxone.[10]

Waveforms of the electrical stimulus can be altered by adjusting the intensity, pulse width, and frequency. Classic settings of PNS involve a low frequency and tonic stimulation; however, this is a delicate balance. The wrong settings can undershoot the nerve threshold and will not lead to any pain relief, whereas a stimulus that is too strong can produce uncomfortable muscle contractions in mixed sensorimotor nerves. Therefore, a trial is often performed before an implant is placed. Furthermore, optimal waveforms are likely affected by the distance between the lead and target nerve, adjacent tissue resistance, and lead size and shape. Research into high-frequency stimulation has also shown promise, even more so in PNS than SCS. A related technique known as peripheral nerve field stimulation (PNFS) stimulates a field of nociceptive nerve fibers. Peripheral nerve field stimulation involves placing a subcutaneous electrode overlying the area of maximal pain and targets multiple peripheral nerves, whereas PNS targets a single nerve proximal to the area of pain.

## Indications and Surgical Patient Selection

Multiple pain conditions have been treated using PNS, including posttraumatic/postoperative neuropathic pain, postherpetic neuralgia, migraine, fibromyalgia, complex regional pain syndrome, and phantom limb pain. Patients with any of these pain conditions present to the upper-extremity surgery clinic, and it is thus imperative to understand alternative surgical therapies related to PNS.

Good patient selection is critical, with the patient being an active participant in their own care. Peripheral nerve pathology, particularly when unresponsive to other treatment options and when an organic cause is elusive, can present a particular challenge to the treating physician. It is for this reason that a clear diagnosis and management of comorbidities, including psychiatric comorbidities, is of utmost importance. The involvement of a pain psychologist is often a fundamental part of treating these patients as comorbid depression, catastrophization, or poor coping can lead to poor outcomes with neuromodulation. Furthermore, there must be a clear area of neuropathic pain or "causalgia" for a treatment to be routinely successful. This can be elucidated by a local anesthetic block or, ideally, a stimulator trial. Although PNS via an implanted stimulator has good outcomes, it certainly is not a cure for the underlying pathology; as a result, a workup to identify a treatable lesion should be fully undertaken and conservative treatments such as physical therapy, medications, and transcutaneous electrical nerve stimulation should be exhausted. If the workup identifies a lesion that may benefit from nerve decompression and/or neuroma excision, this should be attempted prior to embarking on nerve stimulation (barring complicating factors or patient preference).

After these criteria have been met, the patient can be considered for PNS surgery, provided they understand the following. First, although PNS may lead to a reduction in pain, it is unlikely to fully eliminate pain. Second, the patient will be responsible for the upkeep of the implantable device (charging, programming, understanding device compatibility with magnetic resonance imaging, etc). Lastly, the patient will need to undergo a successful trial stimulation prior to implantation of a permanent device. Most insurers require this to be done through the implantation of a temporary trial lead and external generator; however, there is at least one newer device that does not require a trial before a durable implant. A successful trial is generally defined as 50% or greater reduction in pain symptoms; however, patients are encouraged to also define measurable functional goals when possible.

## Surgical Technique

Sustained pain reduction via PNS requires placement of an electrode array near a nerve and connection of the array to a power

**Figure 2.** An image of a percutaneous PNS showcases the 3 components of the system: the external pulse transmitter (EPT) and electrode patch, the implanted lead, and the patient programmer. In the top portion of the image is the EPT on top of the electrode patch. Whenever the patient wishes to trigger stimulation for pain relief, they place the electrode patch on their forearm's skin, directly overlying the trajectory of the implanted lead. The EPT is subsequently attached to the electrode patch, delivering neuromuscular electrical field stimulation through the electrode patch to the implanted lead. In the middle portion of the image is one of the leads that were implanted parallel to the patient's left median nerve. In the bottom portion of the image is the patient programmer, which the patient and the medical staff use to adjust the stimulation parameters after implantation. Reprinted with permission (RightsLink License Number 5218290570729) from Ferreira-Dos-Santos et al.[11]



**Figure 3.** A PNS device placed over a volunteer's forearm skin shows the trajectory of the leads implanted in the patient. Reprinted with permission (RightsLink License Number 5218290570729) from Ferreira-Dos-Santos et al.[11]

source and pulse generator (Fig. 2).[11] Several stimulation devices are commercially available, including devices designed for SCS and those designed specifically for PNS. This results in a wide spectrum of implantation techniques that can be accomplished with 2 broad approaches, open or percutaneous, with variations such as PNFS, in which a percutaneous approach is used to place a subcutaneous electrode.

For a percutaneous approach, the nerve is targeted proximal to the site of injury and cylindrical leads are placed (Fig. 3).[11] Using ultrasound-based or landmark-based guidance, a trajectory to the nerve is defined that places the electrode array parallel to the route of the nerve, reducing the risk of lead migration and associated loss of effectiveness as a cylindrical lead in the periphery can retract or advance. With a patient who is awake, sensory paresthesia concordant to the pain region is verified with sensory stimulation parameters; however, in anesthetized patients and/or mixed sensorimotor nerves, motor stimulation parameters (frequency, 1–10 Hz; amplitude, 0.5–2 mA; pulse width, 100–200 μs) can be used to verify capture of the target. The patient can then undergo a quick, temporary trial with low settings (current, 0.3–0.6 mA; frequency, 2 Hz; pulse width, 0.1 ms) for half an hour or, for certain devices, the lead can be secured to the skin and a prolonged percutaneous trial of 3–10 days can be performed.[12] Trial success is measured by patient feedback, with the visual analog scale used to measure pain during the stimulation period, and settings are adjusted accordingly. A 50% reduction in pain symptoms is considered successful; however, often other functional measures, such as the ability to tolerate touch or perform maneuvers, are also evaluated.

For durable implantation of the percutaneous leads, an incision is made for lead anchoring or coiling, and a separate pocket is planned where an internal pulse generator (IPG) will be used. Leads are tunneled to the pocket. The pocket classically has been on the upper torso; however, with newer smaller IPGs, the internal battery can be on the upper arm to reduce traversing joint lines. Multiple peripheral nerve stimulator systems are also now available, including the ones that use an external pulse generator that transmits through the skin directly to the lead or inductively couples to it. These systems allow for fully percutaneous implantation with minimal stab incisions for small coils. Of note, the flexibility of the devices combined with placement permutations does require more attention to detail and planning compared with SCS systems.

For the open approach, the causative nerve proximal to the area of pain is exposed. Ideally, a percutaneous trial has been performed to verify that stimulation is helpful. The nerve is isolated in a longitudinal fashion, and paddle (Fig. 4) or cylindrical leads are placed around the nerve.[13] Leads that cross a joint should be placed with redundancy and strain relief loops to avoid lead breakage with movement and should be secured to surrounding muscle or fascia with permanent suture to prevent migration but, whenever possible, joint crossing should be minimized. The leads are tunneled subcutaneously to a distant area, such as a subcutaneous infraclavicular pocket, and connected to the IPG. Most models allow the IPG to be accessed transdermally (noninvasively) to alter device settings, and newer devices with external pulse generators would not even require much tunneling of leads. Postimplantation radiographs are obtained to determine baseline positioning such that
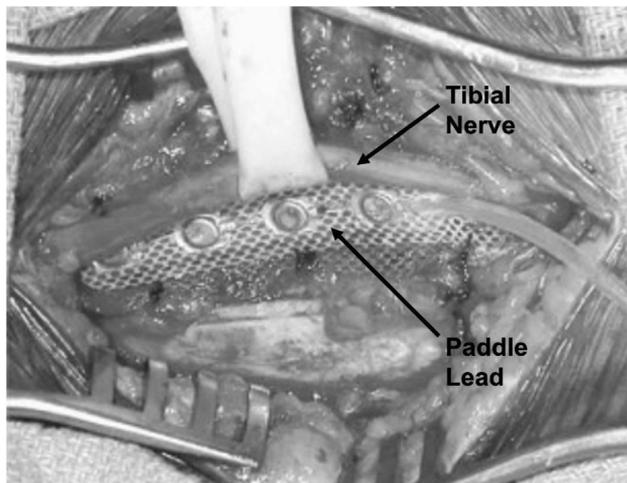
**Figure 4.** Open placement of a tibial nerve stimulator. Although this intraoperative photograph demonstrates a paddle lead, cylindrical electrodes may also be used. Reprinted with permission (RightsLink License Number 5218291114657) from Stuart and Winfree.[13]

migration can be evaluated if the effectiveness ever decreases. This procedure can be completed by trialing prior to final implantation, or the trial period can be omitted and the permanent implant can be placed during a single-stage procedure. Unfortunately, there is currently little evidence for or against a trial period prior to PNS, and even peripheral nerve blocks have shown little negative predictive value.

The PNFS approach differs from other PNS stimulators, whether open or percutaneously placed, because it is not placed proximal to the area of pain but instead sits superficially overlying the area of reported pain, bracketing it. A PNFS device generally uses cylindrical leads placed subcutaneously and stimulates the surrounding tissue locally. This technique targets multiple nerve fibers and their peripheral terminals, as opposed to a causative nerve's axon with PNS.

## Types of Devices

The first generation of PNS products was radiofrequency generator−coupled devices with split-ring electrodes, in which stimulation was provided by an external generator that was not waterproof. These devices are approved by the Food and Drug Administration (FDA) for nerve stimulation but were not commercially viable. Internal pulse generator−based devices were subsequently developed as an internalized alternative; however, these were not approved by the FDA for PNS and thus have primarily been used off label. A major disadvantage of these is that the battery requires exchange several years after placement and the battery needs a place with enough space to accommodate it, such as the torso, requiring tunneling of leads across highly mobile joints. Recently, multiple external generator systems have been introduced that are approved by the FDA for PNS, using either direct stimulation through the skin or transcutaneously or via radio-frequency coupling. There is also one FDA-approved PNS system, designed to be a temporary percutaneous 60-day therapy for acute or chronic pain, that directly attaches to a stimulating patch. The FDA-approved PNS leads are generally cylindrical leads with anchors incorporated into the lead design to reduce the need for open exposures. The newer FDA-approved PNS systems are also generally magnetic resonance imaging conditional when not being used in a percutaneous manner, although some still avoid magnetic resonance imaging directly over the electrode array.

## Complications

Complications with any implantable device include infection (4%) and skin erosion/breakdown (2%); due to the anatomic positioning required by PNS, device migration is always a concern (15%). Percutaneous approaches, often performed under ultrasound guidance, theoretically have more lead migration than open techniques because the device is not secured to the underlying muscle fascia and older leads did not have integrated anchoring technology. To date, no comparative studies have evaluated this; however, studies have shown improving outcomes with more experienced proceduralists. Older PNS devices used split-ring electrodes that wrapped circumferentially around the nerve, leading to increased rates of nerve strangulation and perineural fibrosis; the modern paddle-lead electrodes are designed to avoid this problem. Lastly, device failures, including faulty battery, short-circuiting, or wire fracture (11%), can occur. Data on the longevity of these implants are currently not available, although there is concern that migration may occur over time, limiting the efficacy of the device. Failure of adequate pain treatment is most commonly due to migration of the device. Ishizuka et al[14] retrospectively reviewed why patients required reoperation following initially successful PNS and found that 64% of the patients required one or more additional surgeries; migration of the electrode was the most common cause (33%) of device failure. Due to the high cost of IPGs, insurance companies often require a successful trial prior to implantation. Additionally, many insurance companies do not cover the cost of the PNS trial, and thus cheaper alternatives have been developed.[12]

## Narrative Review of Current Literature

Spinal cord stimulation has robust literature supporting its use. Peripheral nerve stimulation has increasingly been described in the literature, with promising results; however, data specific to the upper extremity are limited. There are a few randomized controlled trials (RCTs) with PNS. One RCT is an industry-sponsored study by Deer et al[15] that examined patients with chronic arm, leg, or trunk peripheral nerve pain. In this study, Deer et al[15] compared a treatment group with stimulation with a control group with an implanted device but stimulation turned off. At 3 months, 38% of the stimulation group had pain relief (defined as greater than 30% reduction) compared with 10% in the control group. Another RCT by Wilson et al[16] examined PNS versus usual care for hemiplegic shoulder pain following stroke. Patients started with an average pain score of 7.5, which dropped to 3.0 in the PNS group compared with only 6.1 in the control group.[16] Another RCT directly compared high-intensity SCS to PNS and reported that although both showed reduction in pain at 6 months, PNS had a greater pain reduction.[17]

Peripheral nerve stimulation has led to reductions in pain scores for a variety of peripheral neuropathies (occipital, ilioinguinal, lateral femoral cutaneous, tibial, axillary, median, ulnar, and radial nerves) and offers a more precise method of pain fiber isolation than SCS. With PNS, patients on average can expect a reduction in pain scores by 60% to 70%. An RCT by Gilmore et al[18] demonstrated that a 60-day treatment of PNS for patients with postamputation pain of their lower extremity led to persistent neuropathic and nonneuropathic pain relief, increased function, and decreased depression at 1 year. Quality of life is increased following initiation of PNS, in addition to the majority (63%) of patients being able to completely eliminate opioid use.[10] In addition to increased mood and functional scores, 40% to 50% of patients who were previously unable to work reported being able to return to employment.[19] Patient variables such as age and sex have not been shown to be predictive of the effectiveness of this treatment; however, traumatic pain tended to respond better than lower back pain or

metastasis-related pain.[20] Despite early literature showing improvement in some patients, neither complete relief nor guaranteed effectiveness is supported by the available data, and this should be discussed with patients when proposing these modalities as a treatment option. Furthermore, the optimization of waveforms, insertion techniques, and lead design will continue to benefit from further study.

In conclusion, pain syndromes can be frustrating challenges for patients and surgeons alike. The recalcitrant nature of these pathologies coupled with the importance of opioid avoidance has pushed surgeons to revisit the previously described but less frequently used pain treatment modalities. Unfortunately, despite many advances in pain management and peripheral nerve surgery, there continue to be patients who experience pain because of peripheral nerve pathology despite appropriate treatment.

Peripheral nerve stimulation is a longstanding but now again developing field that is currently underrepresented in the upper-extremity literature and clinical practice. In general, PNS appears to work similarly to SCS, taking advantage of the "gate theory" of pain, but allows for better capture of specific regions of pain. There are several commercial PNS products available, all differing in needs for exposed transcutaneous wires, battery changes, stimulation waveforms, and lead morphology. These implants can be placed via an open approach as well as percutaneously, each with their own risk/benefit profile. Peripheral nerve stimulation offers a unique alternative with comparable, if not superior, results over the previously established pain therapies such as SCS, making it a potentially helpful adjunct for the upper-extremity surgeon.

## Acknowledgments

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