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EXPERT OPINION

Consensus Guidelines for the Use of Peripheral Nerve Stimulation in the Treatment of Chronic Pain and Neurological Diseases: A Neuron Project from the American Society of Pain and Neuroscience

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Abstract: Peripheral nerve stimulation (PNS) has evolved substantially over recent decades in terms of hardware and evidence supporting efficacy. Treatment targets continue to expand and address both pain and functional applications. The American Society of Pain and Neuroscience (ASPN) seeks to substantially update and expand upon a review of the evidence supporting PNS as well as provide guidelines for clinical practice. A diverse multidisciplinary panel of experts was selected to provide opinions and guidance based on evidence-graded assessment and clinical knowledge. This document aims to serve as a resource for clinicians and payors in the interest of expanding awareness of the breadth of research in the field of PNS and expanding access to therapy.

Keywords: peripheral nerve stimulation, neuromodulation, pain, technique, evidence, nerve injury, review, guideline

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Introduction

Peripheral nerve stimulation (PNS) is an essential category of neuromodulation, allowing for a targeted approach to focal pain coverage via a peripheral axon. Early use of devices for this indication involved cuffed electrodes and paddle leads originally designed for spinal use. Significant technological advances have resulted in hardware customized for this application with implantable electrodes and decoupled internal pulse generators that operate in concert with external power sources. This is a shift from repurposing spinal cord stimulator (SCS) systems for this application.[1] Expanding payor coverage, growing research demonstrating efficacy, and proliferating descriptions of procedural techniques for burgeoning indications have increased the prevalence and accessibility of PNS for the benefit of patients.[2] The initial description of this therapy was by Sweet and Wall in 1967 via an open neurosurgical method. Weiner and Reed described a percutaneous lead placement technique that accelerated the procedure's adoption and ease.[3] Current work is focused on expanding indications, targets, and payor coverage while advancing the technology and design of leads and implantable and wearable hardware.

Methods

The American Society of Pain and Neuroscience (ASPN) is committed to increasing evidence-based access to treatment. In furtherance of that mission, ASPN created a multidisciplinary panel of authors consisting of anesthesiologists, pain medicine physicians, physical medicine and rehabilitation physicians, and neurosurgeons who are experts and leaders in PNS. This panel was supplemented with residents and fellow physicians demonstrating significant potential in the field. Critical focus areas were developed into an outline and refined by the lead author, senior authors, and a small group of section editors. The authors then worked in teams and undertook a search of global English-language literature from multiple databases, including Medline, EMBASE, and PubMed. Specific search terms, including MESH terms, were chosen to identify relevant peer-reviewed articles, such as meta-analyses, systematic reviews, and randomized controlled trials. The identified literature was then critically evaluated and graded using the United States Preventive Services Task Force (USPSTF) criteria for evidence level (Table 1) and degree of recommendation (Table 2). Following evidence-based analysis, each team formulated initial consensus points, which were then submitted to the entire author group for review. Through an iterative process of consolidation and refinement, the statements were developed until final consensus was achieved among all authors.

All authors disclosed financial conflicts of interest and were asked to recuse themselves on any issue with which they have a relationship and competing interests. In cases where conflicted authors were the authority in an area, a nonconflicted author served as the ultimate editor of any submitted material. The purpose and scope of this paper are to serve as a resource for clinicians and payors in the interest of expanding awareness of the breadth of research in the field of PNS and expanding access to therapy for patients suffering from chronic pain, post-operative pain, or functional issues. The goal is to provide comprehensive, evidence-based recommendations on the appropriateness, efficacy, and safety of the reviewed treatments to guide clinical practice as well as practical guidance on billing and payor coverage.

Table 1 Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force)

Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force)	
Evidence Level	**Study Type**
I	At least 1 controlled and randomized clinic trial, properly designed
II–I	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferable multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences
III	Clinical experience-based opinions, descriptive studies, clinical observations, or reports of expert committee

Notes: Adapted from *Am J Prev Med*, volume 20 (3 Suppl). Harris RP, Helfand M, Woolf SH, et al. Current Methods of the US Preventive Services Task Force: a Review of the Process. 21–35, copyright 2001, with permission from Elsevier.[4]

Table 2 Meaning of Recommendation Degrees (U.S. Preventive Services Task Force)

Meaning of Recommendation Degrees (U.S. Preventive Services Task Force)	
Degree of Recommendation	**Meaning**
A	Extremely recommendable (good evidence that the measure is effective and that benefits outweigh the harms)
B	Recommendable (at least moderate evidence that the measure is effective and that benefits exceed harms)
C	Neither recommendable nor inadvisable (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low-quality, or contradictory evidence; the balance between benefit and harms cannot be determined

Notes: Adapted from *Am J Prev Med*, volume 20 (3 Suppl). Harris RP, Helfand M, Woolf SH, et al. Current Methods of the US Preventive Services Task Force: a Review of the Process. 21–35, copyright 2001, with permission from Elsevier.[4]

Physiology

Neuromodulation systems, such as peripheral nerve stimulation (PNS), utilize electricity to modulate nerves, altering the transmission of pain signals to the brain. In the case of PNS, a peripheral nerve is targeted to alleviate peripheral neuropathic pain. Following injury, an inflammatory cascade activates pro-inflammatory cytokines and neuropeptides that heighten nociceptive afferents' excitability, sensitizing dorsal horn neurons and diminishing inhibitory transmission. This exacerbates pain transmission to the sensory cortex, altering pain representation and sensory processing.[5,6] Abnormal glial activation, ectopic firing, and interneuron excitation contribute to persistent neural hyper-excitability across peripheral, spinal, and cranial levels. Chemical and environmental shifts can induce prolonged nociception, triggering chemical and structural transformations at the spinal and supraspinal levels, culminating in a chronic neuropathic pain state.[7] Thus, peripheral and central sensitization are likely involved in the development of chronic neuropathic pain syndromes post-nerve dysfunction.[8]

The exact mechanism of action for PNS is uncertain. Several theories implicate central nervous system involvement, while others propose peripheral mechanisms, including stimulation conduction block in afferent fibers. Understanding neuropathic pathophysiologic mechanisms involving inflammatory cascades, changes in neural transmission, and cerebral vascular changes is crucial for effective pain management.[9] Ongoing research into peripheral nerve stimulation mechanisms holds promise to improve peripheral neuropathic pain relief and expand upon indications for use.

Mechanism of Action

Gate Control Theory

The process of electrical nerve modulation, rooted in the "gate control theory", remains incompletely understood.[10] Proposed by Melzack and Wall in 1965, this theory suggests that the analgesic effects of PNS may arise from both central and peripheral mechanisms.[10] Stimulating low-threshold, large-diameter A-beta fibers with non-painful stimuli activates inhibitory interneurons, suppressing conduction and discharge in nociceptive A-delta and C nerve fibers within the dorsal horn, impeding their transmission to the central cortex.[11] By stimulating A-beta fibers near C fibers, the "gate" in the dorsal horn of the spinal cord can be closed, halting the transmission of painful signals.[11] However, alternative theories propose various mechanisms for PNS-induced pain relief, including membrane depolarization blockade, reduced excitation of nociceptors, and suppression of dorsal horn activity.[12]

Local Chemical and Neurotransmitter Effects

Animal studies suggest the involvement of serotonergic, GABAergic, and glycinergic pathways in the analgesic effects of PNS.[13,14] PNS regulates the local neural environment by affecting endogenous opioid activity, glutamate, and aspartate signaling pathways, as well as decreasing neurotransmitters, endorphins, and inflammatory mediators, impacting their concentrations and efficacy.[15,16] It is important to note that these mechanisms depend on the type of nerve, type of stimulation, and type of condition being treated.[17]

Opioid responses via the enkephalin-delta opioid receptor pathway have been identified in transcutaneous electrical nerve stimulation (TENS) and may be implicated in PNS as well.[18,19] Anti-inflammatory effects of PNS have also been proposed.[20] In human studies, excitation failure of A and C fibers occurs through repeated electrical stimulation.[21]

Peripherally Induced Reconditioning of CNS

PNS may alleviate central sensitization and hyperalgesia by diminishing excessive peripheral nociceptive activity, inhibiting wide dynamic range neurons, and decreasing Aβ fiber-induced activity.[13] GABAergic and glycinergic activity augmentation, along with serotonin and dopamine metabolite alterations, may subsequently occur at the spinal level.[12,14] Substance P and CGRP level variations might alter central pain signaling.[22] Additionally, it has been proposed that peripheral reconditioning of the central nervous system can occur through prolonged alterations in central plasticity in neuropathic pain states.[22]

Consensus Guideline 1: The mechanism of action (MOA) of Peripheral Nerve Stimulation (PNS) is complex. It includes modulation of local transmission of pain signals, inhibition of local A and C fibers with repeated stimulation, impact on local inflammatory mediators, endogenous opioids and neurotransmitters, gate control theory, and peripherally induced reconditioning of the central nervous system. Future research will help further describe the MOA of PNS.

PNS Device

PNS is an established treatment approach that has been successfully used for the management of a wide variety of disease states, including motor dysfunction and chronic pain. Although the first series of patients with neuropathic pain treated with PNS was published by Wall and Sweet in early 1967,[23] the first documented use of this approach was even earlier, when C.H. Shelden used high-frequency PNS (14 kHz) for treatment of neuropathic facial pain in 1962[24] (Figure 1). Since that time, PNS has been utilized all over the world as a unique modality for the treatment of various neuropathic pain conditions, with complex regional pain syndromes (CRPS) initially being the most prevalent condition.[25] For the first three decades of PNS clinical use, the application of PNS electrodes required surgical exposure of the stimulated nerves, limiting access to this modality only to those who possessed significant surgical expertise.[26–28] The situation changed dramatically after the percutaneous PNS technique was introduced by Weiner and Reed in 1999,[29] making it available to pain specialists from non-surgical backgrounds and significantly increasing the utilization of this therapy.

The lack of percutaneous, FDA-approved PNS devices hampered the widespread acceptance of PNS as a pain-relieving treatment modality.[29] Over the last decade, a multitude of well-designed clinical studies with the use of novel dedicated devices[30–32] paved the way for multiple FDA approvals. The recent surge of technological advances and regulatory approvals marked a new era of PNS in the treatment of pain, where it quickly became a globally accepted part of the mainstream neuromodulation armamentarium.[32–34] PNS is a recognized component of the educational neuromodulation curriculum endorsed by professional pain societies.[35] In 2024, the American Medical Association (AMA) revised CPT codes to address industry confusion regarding the distinction between systems and physician work performed.

Mechanisms of Stimulation

Waveform Background

Stimulation waveforms are a pattern of delivery of electrical energy with the goal of excitation or inhibition of Aα/β afferent fibers to modulate pain. Nociceptive A and C fibers exhibit varying responses to electrical stimulation based on

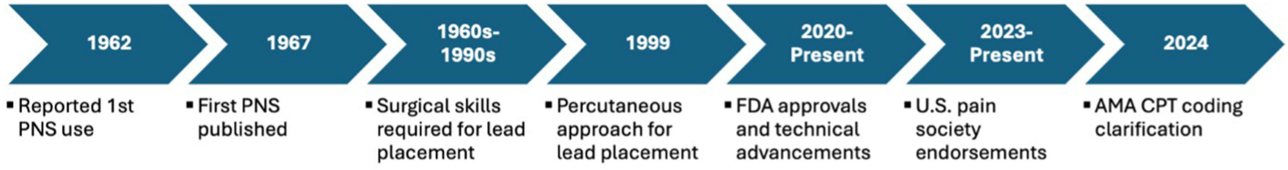

Figure 1 History of PNS The history of PNS from inception to advancements to coding.

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their diameters. Larger diameter fibers require lower intensity stimulation for activation than smaller diameter fibers. This phenomenon suggests using titrated stimulation intensities to primarily activate large diameter Aα/β fibers while avoiding the activation of small-diameter nociceptive fibers through a gating mechanism.[36,37] One of the challenges of PNS is that leads are often placed adjacent to mixed motor-sensory nerves, so fiber selectivity is paramount.

In many cases, sensory afferents are the primary targets for sensory stimulation. In certain instances, the emphasis is placed on targeting motor efferent nerves to elicit muscular contraction. The treatment strategy for core muscle atrophy, which centers on stimulating the multifidus muscle in the lumbar spine, has consistently reflected this approach.[38] Understanding the stimulation and waveform characteristics of each commercially available PNS device is vital due to their complex programming parameters and nuances.

Low-Frequency Stimulation

Low-frequency stimulation (20 Hz) has been employed in PNS for multiple conditions, including hemiplegic shoulder (HSP) and low back pain. When preferentially applied to mixed motor-sensory nerves, low-frequency stimulation stimulates motor efferent nerves, causing muscular contraction. When applied to the axillary nerve in the shoulder, resulting deltoid muscle contraction may help decrease pain in patients with HSP.[39] Although this form of stimulation has shown to have durable pain relief even with temporary therapy courses, subluxation of the glenohumeral joint is not reduced long-term.[40] Similarly, low-frequency stimulation of the medial branch nerves in the lumbar spine has decreased low back pain in patients who have failed conservative therapies.[41,42] Increasingly, there is an understanding that the multifidus muscle plays a vital role in lumbar stability, and restoring function and decreasing inhibition of this muscle in chronic pain states can be achieved with motor stimulation.[43] In a recent randomized, sham-controlled, double-blinded trial, patients in the treatment group received a stimulation frequency of 20 Hz, a pulse width of 214 µs, with participant-specific pulse amplitudes to elicit multifidus contractions for 10 seconds twice per minute during the stimulation session.

Mid-Range Stimulation

Mid-range stimulation (20–100 Hz) has traditionally been the therapy window for PNS devices, as this range preferentially targets afferent fibers, giving the patient a perception of paresthesia or vibration. This stimulation range primarily activates large diameter Aα/β fibers while avoiding activating small-diameter nociceptive fibers (C and Ad).[36] Recent studies on paresthesia-based, sensory peripheral stimulation have explored waveform parameters. In 2016, Deer et al conducted a prospective, multicenter, randomized, double-blinded, partial crossover study on a permanent PNS system. The typical settings used in this study included a pulse width of 200 µs, a pulse frequency of 100 Hz, and an amplitude set to induce paresthesia.[31] A prospective precursor study by Wilson et al involving eight patients examined PNS targeting the median nerve. The study used lower frequency settings, including amplitude (≤ 80 mA), pulse width (100 to 300 µs), and pulse frequency (20 to 45 Hz). Patients in this study reported experiencing paresthesia in the hand or distribution of the median nerve during the stimulation.[44]

High-Frequency and Ultra High-Frequency Stimulation

High-frequency (>1500 Hz) and ultra-high-frequency (>500,000 Hz) therapies are still under investigation. Because of their association with pain relief and the absence of paresthesia, it is of great interest to some investigators. Early data on high-frequency stimulation (5000–1000 Hz) in lower extremity amputees has been promising.[45,46] Additionally, a recent study by Abd-Elsayed and Moghim demonstrated the effectiveness of high-frequency peripheral nerve stimulation (PNS) in treating chronic pain.[34] The study involved 57 patients who received PNS treatment across various nerve targets. The results indicated successful pain management even 24 months post-procedure, in addition to a reduction in opioid medication. The treatment parameters included a pulse width of 32 us and a frequency of 1499 kHz, with varying amplitudes in on/off patterns. However, further research is needed to compare the benefits of these waveforms against other options.

Advanced Programming and Evolving Technologies

An analysis of nearly 84,000 PNS programs for over 5,300 patients from one device company indicates that lower frequencies (<100Hz) may not be typical for most patients using their device. Like SCS systems, complex programming was deemed correlated with long-term PNS success in this analysis, with parameters including pulse widths of ≥500 µs and frequencies ≥500 Hz. Over 96% of the analysis's commercial and ongoing RCT PNS programs utilized this approach. Notably, 58% utilized multi-area programming, and 39% employed frequencies ≥1,000 Hz. These findings highlight the need for PNS devices to offer diverse programming options to accommodate patient and nerve target variations. (Data Source: Nalu Medical). While this analysis was not designed to evaluate the efficacy of lower frequency parameters, it does indicate an ongoing reevaluation and evolution of advanced programming parameters and waveforms for PNS.

Consensus Guideline 2: Low and mid-range frequency settings can be utilized for motor, sensory, parasympathetic, and sympathetic stimulation, respectively, and are well-studied in the literature. High and ultra-high frequency and high pulse width stimulation have each been shown to be associated with promising outcomes and should be the focus of further research.

Definition: Peripheral Nerve Stimulation

It is crucial to differentiate direct Peripheral Nerve Stimulation (PNS), the focus of this paper, from the starkly different indirect Peripheral Nerve Field Stimulation (PNfS), indirect Percutaneous Electrical Nerve Stimulation (PENS), and Transcutaneous Electrical Nerve Stimulation (TENS) for clarity in clinical practice, alignment of understanding, and interpretation of evolving research.[33] PNS directly stimulates specific nerves and requires specialized knowledge of peripheral nervous system anatomy for successful lead placement using image guidance (fluoroscopy or ultrasound) and advanced procedural, often surgical, skills to avoid lead fracture and migration.

PNfS involves placing leads in subcutaneous tissues to diffuse stimulation across the painful loci, enhancing blood flow, blocking cell depolarization, and raising the nociceptive threshold.[47] PENS temporarily stimulates subcutaneous nerves. TENS relieves pain through skin electrodes without specific nerve stimulation.[48] Payors must differentiate PNS as a unique modality from these other nonspecific stimulation treatments, as this is delineated in the existing peer-reviewed evidence base.

Consensus Guideline 3: PNS should be clearly differentiated in payor policies from the divergent and unrelated therapies of peripheral nerve field stimulation (PNfS), indirect percutaneous electrical stimulation (PENS), and transcutaneous electrical nerve stimulation (TENS). Peer-reviewed literature has extensively differentiated PNS from these treatments.

Magnetic Nerve Stimulation

Magnetic fields (MFs) have been suggested as a potential treatment option for generalized myofascial pain syndromes and rheumatoid arthritis.[49] In their review, Fan et al examined 28 studies exploring the analgesic effects of static magnetic fields (SMFs) on humans and mice.[50] Findings indicate that 64% of human and all mice studies reported positive effects of SMFs on pain relief, with factors such as SMF intensity, treatment duration, and pain type influencing outcomes. SMFs are not considered a form of PNS.

Magnetic peripheral nerve stimulation (mPNS), on the other hand, is FDA-approved to treat chronic and intractable post-traumatic and post-surgical pain.[51] mPNS consists of applying biphasic, time-varying magnetic pulses at a frequency of 0.5 Hz to induce electrical fields in the nerve bundles in the center of the waveform. These pulses generate action potentials in the ascending and descending pathways of the peripheral and central nervous systems.[36] The recruitment ratio of A-beta (sensory) to A-delta (pain fibers) is 3:1 with traditional PNS, whereas it is 9:1 with mPNS.[51] Kapural et al randomized 65 subjects to mPNS vs conventional medical management (CMM) and observed that 71% of subjects had at least 50% pain relief in the mPNS as opposed to 13% in the CMM arm.

Strategies for Peripheral Nerve Stimulation

Nerve Blocks

A single shot low volume (3–5 mL) local anesthetic nerve block using 2% lidocaine or 0.5% bupivacaine before PNS may be used to isolate a neural target. It may also help to assess patient anatomy and identify the optimal stimulation target nerve if multiple nerves are innervating the dermatome. For example, the scrotum or testicular region is innervated by pudendal, ilioinguinal, genitofemoral, and posterior femoral cutaneous nerves. If a block is not performed, the dermatomal innervation is determined via clinical evaluation, specifically history and physical examination, when selecting a nerve target for PNS. A recent review evaluating diagnostic blocks and PNS outcomes at 3 and 6 months found no outcome difference when nerve blocks were performed before the PNS implant.[52] This may be due to the differences in mechanism of action as local anesthetic reversibly binds to Na+ channels while stimulation activates motor or sensory fibers.[53,54] However, no definitive mechanistic evidence exists to explain the lack of predictive value of nerve blocks for PNS.

Consensus Guideline 4: While nerve blocks may be utilized in the early diagnostic and therapeutic phases of patient care, the literature does not support their prognostic value in predicting response to a PNS trial.

Short Term PNS

In 2018, a single and dual lead peripheral nerve stimulation system was FDA-approved as indwelling therapy for up to 60 days for pain control. The system consists of a percutaneous electrode (micro lead- flexible, helically coiled) placed in proximity to the target peripheral nerve and connected to a wearable external pulse generator (www.accessdata.fda.gov/cdrh_docs/pdf18/K181422.pdf). This 60-day therapy is intended to supplant the "conventional trial followed by permanent implantation" approach. Many studies demonstrate continued pain reduction and clinical improvement beyond the 60 days of percutaneous stimulation treatment.[55,56]

Trial and Permanent Implantation of PNS

Permanent PNS systems are similar to SCS in that patients undergo a temporary trial, typically about one week, followed by a permanent implant if the trial is successful. Patients with chronic pain due to peripheral neuropathies often undergo targeted peripheral nerve blocks to help identify the stimulation target before a temporary PNS trial is performed, whereby a percutaneous lead is placed near the targeted nerve. A permanent system is implanted after a trial period of device utilization if the patient experiences satisfactory relief (>50% improvement in pain). Various nuances between device manufacturers dictate modifications to device placement for permanent implantation.

Technology and Device Design

Lead Design

The design of peripheral nerve stimulation (PNS) leads has evolved to optimize efficacy, durability, and patient comfort. Modern PNS leads encompass several key design elements to enhance performance and patient outcomes. A few crucial aspects are lead size, shape, and profile. Traditional designs often featured cylindrical leads with multiple contacts incorporated into the body of the lead. Still, newer iterations employ innovations such as open helical-coil designs with barbed singular contacts at the end of the lead. This has offered the advantage of lower infection rates (0.03 vs 0.83 per 1000 indwelling days for coiled vs non-coiled leads),[57] due to several factors including a small skin-to-lead interface (0.3mm diameter), the ability of the lead to expand and compress in response to movement of the body part in which it is implanted, and fibrotic ingrowth into the coil potentially creating a bacteriostatic seal albeit with the qualifier that these coiled leads are intended for 60-day placement, not permanent implantation.[58]

These monopolar leads differ significantly from traditional multiple-contact arrays. When combined with a relatively narrow pulse width, the former allows for remote placement of the stimulating contact away from the target nerve to better select for A-beta fiber activation.[59] The latter allows for more complex stimulation patterns using bipoles and guarded cathode configurations. This has implications for the placement of the lead relative to the target nerve, accommodating both perpendicular and parallel implant orientations.

Lead anchoring mechanisms are pivotal in maintaining lead stability and minimizing migration, one of the most common complications of early peripheral nerve stimulator implants. Recent innovations include anchoring sleeves or cuffs designed to secure the lead within surrounding tissues, reducing the likelihood of displacement.[60] Additionally, lead fixation techniques utilizing barbs or tines enhance anchoring for permanently implanted devices without compromising flexibility or patient comfort.[61] These features reduce or eliminate the need for separate anchors in many instances. However, granulation around the tines makes removal difficult in some cases and may lend toward lead fracture during explant. Non-tined leads are invariably used for peripheral nerve stimulation trials due to their ease of withdrawal. New technology allows for injectable electrodes composed of an in-body curing polymer/metal composite, though still in the early stages of human testing.[62] Newer revisions of the technology utilize a platinum-iridium microwire rather than a curing polymer to facilitate explantation.[63]

Integration of wireless communication capabilities represents a cutting-edge innovation in PNS lead design. By incorporating a receiver into the body of the stimulator array, wireless-enabled leads eliminate the need for percutaneous extensions and physically connected external pulse generators, offering flexibility and convenience for patients in respect to implant burden. Uncoupled external batteries with internally implanted generators are another strategy (See Figure 2).

Commercially available, permanent systems include Nalu Medical (Carlsbad, CA), StimRouter (Bioventus, Durham, NC), and Curonix (Pompano, FL). These systems have FDA approval for pain management in adults with severe, intractable chronic pain of peripheral nerve origin.[33] The StimRouter system has a receiver, electrodes, and anchoring mechanism (in the form of tines), which is implanted via a test probe using image guidance. The lead is 15 cm long, 1.2 mm in diameter, and has three stimulating electrodes. The lead is powered by an external pulse transmitter and controlled by a patient programmer (a handheld remote-control device).[31]

The Nalu system consists of a lead with electrodes (4 or 8 contacts, tined or untined) and a battery-free miniaturized implantable pulse generator (micro-IPG) that can accommodate one or two leads. It is powered wirelessly by an external therapy disc and controlled with a smartphone app (Nalu-Product-Catalog-MKT-400005-Rev-A.pdf). An advantage of the Nalu system is the implantation of a micro internal pulse generator and the ability to communicate bi-directionally with the internal device. The Curonix Freedom® Peripheral Nerve Stimulator (PNS) System (curonix.com) has an implanted electrode array (4 or 8 contacts), an implanted receiver, an external transmitter assembly, and a wearable accessory. The system is comprised of a two-component implant that the physician connects during the procedure. As with other implanted PNS, the physician must also create a pocket for the Curonix system. The Curonix implanted receiver is a coiled wire that is connected to the implanted lead. The system is fully programmable and powered by high-frequency electromagnetic coupling (HF-EMC). The HF-EMC technology delivers power and data at significant range and depth into the body. HF-EMC also accommodates individual patient wearable needs by maintaining power to the system through clothing without jeopardizing connectivity. StimRouter lacks a trial option among these systems, whereas Nalu Medical and Curonix offer trial capability. A trial can assist in appropriately selecting patients and introducing them to the therapy's process. A permanent implant can be considered if patients experience satisfactory pain relief during the trial period.[33] Additionally, many payors mandate a trial before permanent implantation.

Pulse Generation

Generator technology has evolved significantly in the past decade. Several generator options are now specific to PNS, including traditional implantable, external, and hybrid decoupled systems. Traditional implantable internal pulse generators (IPGs) rely on a hardwired connection between lead(s) and IPG through a ported interface and historically represent the majority of PNS use. Previously, spinal cord stimulator (SCS) IPGs were adapted for use with PNS; however, due to their large size, they were not ideally suited to the periphery. More recently, externally powered and

Figure 2 Commercially Available PNS Systems Examples of commercially available PNS leads and associated hardware.

hybrid decoupled systems were introduced, thus decreasing the size of surgical implants. There are three types of externally powered systems that are commercially available. One, the first described by Yu et al,[64] consists of partially implanted leads ported to an external generator.

In contrast, the second, as described by Abd-Elsayed and Moghim,[34] is composed of a fully implanted lead with a receiver wire that communicates with a rechargeable generator attached to a transmitting antenna via high-frequency electromagnetic coupling technology. The third of these systems features a fully implanted lead with an integrated receiver that communicates via elective field conduction with an external generator, as described by Deer and colleagues in 2010.[44] Finally, a hybrid system featuring fully implanted lead arrays directly ported to a micro-IPG decoupled from an external battery, as detailed by Kalia et al,[65] features near-field magnetic induction delivering power from the external battery to the IPG.

Consensus Guideline 5: Given the wide variability between implantable, external, and hybrid decoupled PNS systems, as well as the rapid pace of innovation in the field, payor policies should defer to shared medical decision making by the treating physician and patient to maximize patient satisfaction, safety and efficacy across diverse clinical scenarios when selecting a PNS platform.

MRI Conditionality

Patients with chronic pain may require advanced imaging for a multitude of reasons. Magnetic resonance imaging (MRI) is limited due to foreign ferromagnetic materials in the body of PNS components. The current PNS landscape is rich with various device options, each with its limitations regarding MRI. These limitations can be summarized here but may depend on specific details such as lead location, number of leads, and IPG type, given the extensive testing required to deem each configuration MRI conditional (Table 3). MRI conditionality of PNS components is rapidly evolving, and clinicians are encouraged to regularly review updates from device manufacturers to determine the exact compatibility of particular device components.

Table 3 MRI Conditionality

Type	Duration	MRI Conditionality	Pulse Generator	Battery
Curonix Freedom 4 PNS (1)	Permanent	MRI Conditional: Implanted Neurotransmitter 1.5T and 3T Whole body MR unsafe: External Transmitter	Internal	External
Curonix Freedom 8	Permanent	MRI Conditional: Implanted Neurotransmitter 1.5T Whole body MR unsafe: External Transmitter	Internal	External
Nalu (2)	Temporary 30d Permanent	MRI Conditional No external 1.5–3T Dependent on IPG, lead, and nerve target factors	Internal	External
Sprint (3) *	Temporary 60d	MR Unsafe MR Conditional: 1.5-3T with retained fragments[66]	External	External
StimRouter (4)	Permanent	MRI Conditional No external 1.5–3T Lead 50 cm from center of MR bore and outside coil	External	External

Notes: 1. Curonix webpage https://curonix.eu/about-us/mri-information, https://curonix.com/wp-content/uploads/2025/01/CX_Freedom-MRI-Guide_PROOF_11-1-1.pdf. 2. Nalu MRI Safety Information, MA-000105-Rev-A.pdf 3. Sprint; *Sprint lead fractures are MRI conditional 1.5T. https://www.sprtherapeutics.com/physicians/mri-safety-information/. 4. Stimrouter https://stimrouter.com/physicians/mri-safety-following-stimrouter-implant/.

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Consensus Guideline 6: MRI conditionality, and the variability and complexity of determining MRI implications in the setting of various devices, lead targets, orientation and patient factors, results in the requirement for physicians to consider MRI implications in partnership with the patient when selecting a PNS platform.

Technique Overview

Peripheral nerve stimulator (PNS) lead placement may be performed under ultrasound,[67–69] or fluoroscopic guidance.[70–73] Ultrasound offers the advantage of directly visualizing the neural target and surrounding vasculature using an in-plane needle technique. However, the operator must be proficient in the basic principles of ultrasound, including velocity of propagation, attenuation, frequency, acoustic shadowing, angle of incidence, and relevant anatomy.[74] A fluoroscopic-guided approach is reasonable when targeting nerves that reside in predictable, replicable locations along osseous targets. Imaging modalities may be combined for educational value, future reference for programming, to replicate lead placement for permanent implants, or as a guide for future revision procedures.

Ultrasound guidance is recommended whenever possible for brachial plexus (and its branches), axillary, suprascapular, median, ulnar, radial, intercostal, femoral, lateral femoral cutaneous, saphenous, sciatic, tibial, and common peroneal nerve lead placement.[75,76] Nerves that are commonly targeted using fluoroscopic guidance include medial branch nerves (cervical, thoracic, and lumbar), cluneal (superior and medial), genicular,[77] infrapatellar saphenous, and in some cases, suprascapular nerve. Multiple cadaveric studies have shown a predictable location for these nerves relative to bony landmarks with minimal risk for vascular trauma when utilizing fluoroscopic guidance.[78,79] Ultrasound has also been used effectively for these targets.[69,80]

When utilizing ultrasound, the skin entry should be at least 2 cm to 4 cm distal to the probe to ensure adequate lead length implanted to mitigate the risk of lead migration. The trajectory of the stimulating probe should violate as few muscles as possible to reach the nerve, and intraoperative sensory or motor testing should be performed before lead securement. Patients may describe sensory stimulation as pressure, tingling, tapping, or buzzing. Cases of uncomfortable or overly intense sensory stimulation that cannot be resolved with decreased amplitude may be solved by moving the lead contacts further away from the targeted nerve. If unintentional motor contraction is noted when approaching a sensory nerve, the stimulating probe is likely intramuscular and should be repositioned. When implanting at a motor target, contraction can be visualized on ultrasound, and needle movement due to contraction is noted.

Monopolar systems disburse energy in a field, allowing for placement to be parallel or perpendicular to the nerve, whereas bipolar systems are optimally placed parallel to the nerve. If a simple bi-pole program does not provide an adequate field of stimulation, a guarded cathode configuration may be programmed to capture a larger area. A low-frequency program (12–30 hertz) will provide motor activation, whereas a higher frequency (≥100 hertz) will provide sensory activation. The decision to place a single or dual lead is influenced by the site of service (hospital outpatient versus ambulatory surgery center), the number of dermatomes/nerves involved in pain transmission, and the size of the target nerve. When placing leads near large, mobile joints, care must be taken not to cross the joint line to mitigate the risk of lead fracture.

Consensus Guideline 7: Most PNS anatomic targets can be easily identified and accessed using ultrasound or fluoroscopic guidance while some targets may be preferentially identified using one modality or the other. Multiple factors including equipment availability and physician preference with imaging modalities may dictate an optimal approach for each case. Thus, payor policies should be inclusive of multiple approaches permitting physician selection of appropriate imaging guidance during PNS placement.

Anesthetic for Trial and Implant and Sensory Testing

The approach to PNS implants varies based on the targeted nerve, imaging modality, and preferred position (Table 4). Intraoperative testing is an essential tool in ensuring proximity to the target nerve. It is recommended to avoid injection of local anesthetic deep and proximal to the target nerve until sensory and/or motor testing is completed. Every manufacturer has a different testing paradigm, but the principle is the same: if neural activation is seen in a relatively low amplitude or predefined stimulation setting, the lead may be too close or intraneural and should be withdrawn. If the

Table 4 Recommended Approach by Nerve Target

Nerve	Imaging	Patient Position	Approach	Landmark
Suprascapular	US or Fluoroscopic	Sitting (± beach chair) or prone with pillows underneath the chest	Ultrasound-Transducer in a coronal oblique orientation over the posterior shoulder, parallel to the lateral third of the scapular spine. Tilt the probe to identify the floor of the supraspinous fossa deep to the trapezius and supraspinatus muscles. The suprascapular notch is anterior to the fossa where the nerve and artery traverse. Insert the needle in-plane and medial to lateral direction until tip contacts the bone.	Suprascapular notch
Axillary	US or Fluoroscopic	Sitting or prone	Ultrasound-transducer in a sagittal orientation over the posterior aspect of the upper arm midway between the acromion and the axillary fold. Slide proximal to distal until the neck of the humerus is visualized, adjust tilt until posterior circumflex humoral artery is visualized between teres minor, deltoid and triceps, superficial to the bone at the quadrangular space. Needle can be inserted in-plane or out of plane.	Humeral neck
Medial branches (C/T/L spine)	Fluoroscopic	Prone	For cervical placement identify the articular pillars and target lamina using A/P fluoroscopy. Start 2 to 4 levels below the target level to avoid the neck crease. Ideal entry at C7 or C6. Stay over bone until contact is made with the lamina. Thoracic/Lumbar- needle placement may be in trajectory view, cephalad to caudal or caudal to cephalad. Advance until contact is made with the lamina along the inferior medial aspect of the pedicle.	Lamina
Cluneal (superior, middle, lateral)	US or Fluoroscopic	Prone	Fluoroscopic- contralateral oblique roughly 20 degrees for trajectory view targeting the iliac crest for superior cluneal nerve, and the lateral margin of S1/S2 for middle cluneal nerve. Entry is based on patient ergonomics and preference for external power source. Avoiding implantation over future spinal intervention sites by staying lateral or below the beltline should be considered.	Posterior superior iliac spine and dorsal sacrum
Femoral	US	Supine, leg extended and slightly externally rotated	Transducer is placed in transverse orientation over the femoral crease until the femoral nerve, artery and vein are visualized. Insert the needle in-plane in a lateral to medial direction below the fascia iliaca, lateral to the femoral nerve	Fascia iliaca superiorly, sartorius muscle superolateral, iliacus inferior
Lateral femoral cutaneous	US	Supine, leg extended	Transducer is placed in a transverse orientation distal to the anterior superior iliac spine to identify the sartorius muscle. The nerve is a very small hypoechoic structure located between the sartorius and tensor fascia lata muscle and is superficial. In patients with low BMI, a parallel approach to the nerve may be necessary.	Sartorius muscle medially, tensor fascia latae laterally
Saphenous	US	Supine with leg extended and externally rotated	Transducer in transverse orientation in the middle third of the thigh. Scan proximally and distally to locate the medial border of the sartorius muscle where it meets the medial border of the adductor longest muscle. The femoral artery, vein and saphenous nerve are located below the sartorius muscle.	Sartorius muscle superior, vastus medialis laterally, and adductor longus medially
Genicular	US or Fluoroscopic	Supine with leg extended	Ultrasound-transducer positioned along the distal femur, the probe scanned medially to locate the superior medial genicular artery and nerve. The probe is then positioned along the lateral margin of the distal femur to locate the superior lateral genicular artery a nerve. Similarly the inferomedial genicular artery and nerve is located below the knee along the proximal tibia.	Distal metaphysis and epicondyle junction
Infrapatellar saphenous	Fluoroscopic	Supine with leg extended	Anterior posterior fluoroscopic guidance is used to locate the medial aspect proximal Tibia. The lead is advanced cephalad to caudad.	Medial condyle of tibia, medial shaft of tibia
Sciatic (tibial or common peroneal)	US	Supine with bump under foot, lateral or prone	Transducer placed in transverse orientation at the popliteal fossa crease. The probe tilted caudally to optimize the popliteal artery, vein, tibial nerve, common peroneal nerve. The probe is advanced cephalad 3 to 5 centimeters until the bifurcation of the sciatic nerve is visualized. An alternative approach (particularly in amputees) is the subgluteal approach as the nerve traverses beneath the biceps femoris muscle.	Biceps femoris laterally, semitendinosus medially

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energy required to activate the nerve is high, the electrode should be advanced closer to the nerve. SPR Therapeutics recommends lead placement approximately 1 cm distal to the target nerve for robust activation of A-beta fibers. SPR also defines their ideal stimulation window between an intensity of 20–70 on their programmer. Nalu, Bioventus, Curonix, and other manufacturers conduct testing in milliamps with an optimal stimulation window between 0.5–2.0 mA.

Most permanent PNS leads have tines to mitigate the risk of lead migration. It is essential to ensure satisfactory sensory and/or motor testing before deploying the tined portion of the lead. Due to this requirement, the PNS trial should be completed with local anesthetic and, at most, light sedation so that patients can provide feedback about stimulation efficacy. For implant, monitored anesthesia care can be considered with a period of light sedation for lead placement to confirm correct neural identification and appropriate target stimulation. Lower-concentration local anesthetic containing epinephrine can help avoid dense sensory block while providing hemostasis.

Nerve Regeneration and Low-Frequency Stimulation

Electrical stimulation (ES) of the peripheral nerves has been shown in animal models to improve axonal regeneration, myelination, and target reinnervation. The ES is conducted in a retrograde fashion to the soma of the neuron, which upregulates multiple genes associated with regeneration[81,82] (Figure 3). The pro-regenerative effect of ES has also been shown in 4 human randomized clinical trials, including severe carpal tunnel syndrome, repair of injured digital nerves, spinal accessory nerve traction injury, and severe cubital tunnel syndrome.[83–85] ES has also shown benefits in nerve transection and repair models, in isograft nerve repairs, traction injuries, and chronic compression injuries.[83,84,86–88] Initial animal studies found that brief electrical stimulation consisting of stimulation at 20 Hz for 1 hour was superior to higher frequency and/or longer duration in improving sensorimotor regeneration.[89–93] Recent clinical studies in humans suggest that 10 minutes of ES is as effective as 1 hour of stimulation for nerve regeneration.[81,86,88] Sequential ES may be superior to single-session ES for motor recovery, based on rat models.[94]

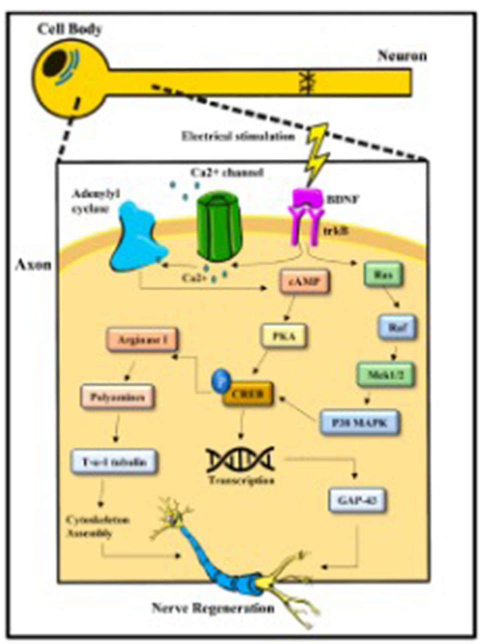

Figure 3 Nerve Regeneration Electrical stimulation proximal to the injury site stimulates the upregulation of RAG through a calcium-dependent mechanism. Increased expression of BDNF and trkB drives increased expression of cAMP which activates CREB to maximize the pro-regenerative axon phenotype, stimulating axonal sprouting and neuron survival.

Notes: Reprinted from Juckett L, Saffari TM, Ormseth B, Senger JL, Moore AM. The effect of electrical stimulation on nerve regeneration following peripheral nerve injury. *Biomolecules*. 2022;12(12). Creative Commons.[81]

Abbreviations: BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; trkB, tyrosine receptor kinase B; pKA, phosphokinase A; GAP-43, growth-associated protein; MAPK, mitogen-activated protein kinase.

Nerve Targets And Conditions

Efficacy of PNS

Multiple well-designed studies have explored the efficacy of PNS across a wide range of nerve targets and indications. The COMFORT randomized controlled trial consisted of two arms: patients in the active arm receiving PNS and conventional medical management (CMM) and patients in the control arm receiving CMM alone.[95] Pain target areas included the shoulder, low back, knee, and foot/ankle. At 12 months, 87% of patients in the active arm had at least 50% pain relief, with the average pain relief being 69%, compared to the control arm, which had a responder rate of 3%, with average pain relief being 6% (Level 1, Grade A).

The confirmatory randomized controlled COMFORT 2 Trial used an identical protocol to allow for pooling of data between the two studies.[96] Similar results were seen at 3 months in the COMFORT 2 subjects, with the active PNS group achieving an 80% responder rate (≥50% pain relief) and a 66% average pain reduction, compared to a 4% responder rate and 3% pain reduction in the control group receiving conventional medical management alone. These significant outcomes were sustained at 6 months, with the active arm maintaining a 79% responder rate and 64% pain relief (Level 1, Grade A).

Pooled data analysis of 250 subjects from the COMFORT and COMFORT 2 trials demonstrated a significant difference between the treatment groups at 3 months.[96] The active arm, receiving peripheral nerve stimulation, had an 81% responder rate with a 66% average pain reduction, compared to the control arm's 4% responder rate and 4% pain reduction ($p<0.001$). These benefits proved to be durable, as the active arm maintained an 82% responder rate and 66% pain relief at the 6-month follow-up with 33% having at least 80% pain relief. Responder rates and pain relief were robust at the 6-month follow-up across the four treatment areas, low back, knee, foot/ankle, and shoulder, all with a strong safety profile (Level 1, Grade A).

Huntoon et al published a retrospective review of 6,160 patients following 60-day PNS.[55] Seventy-one percent of patients (4,348/6,160) were responders with ≥ 50% pain relief and/or improvement in quality of life. Pain relief among responders averaged 63%. There were 38 different nerve targets within the population, and the responder rate and percent pain relief were relatively consistent across the multitude of pain indications and nerves (Level II-2, Grade A).

> Consensus Guideline 8: The evidence for PNS independent of nerve target or pain indication is strong. Due to the broad array of studies, including randomized controlled trials and large retrospective studies in addition to smaller, more focused studies, the overall evidence is Level 1, Grade A. It is important to note that responder rate and average pain relief are clinically significant and consistent across a variety of pain indications and nerve targets including within studies that examined multiple targets.

Upper Extremity

Shoulder pain is the third most common musculoskeletal complaint,[97] with a median prevalence of 16% globally.[98] Innervation of the shoulder is predominantly from the axillary and suprascapular nerves, with a small contribution from the lateral pectoral nerve.[99] Image guidance with either fluoroscopy or ultrasound can be used to target the suprascapular nerve deep to the transverse scapular ligament in the suprascapular notch or inferior to the spine of the scapula as it exits from the spinoglenoid notch. The axillary nerve can be targeted at the quadrangular space with ultrasound or via fluoroscopy at the posterior lateral aspect of the surgical neck of the humerus.[99] There have been two randomized control trials for PNS of the shoulder, and both used a temporary PNS system to treat the axillary nerve with low-frequency motor stimulation at 12Hz in patients with post-stroke shoulder pain. Compared to the control group, the PNS groups showed clinically significant sustained pain relief at 3–12 months. There is Level 1 Grade B evidence for PNS for treatment of post-stroke shoulder pain.[8,39,76,100,101]

There are various observational studies, case reports/series for PNS for other upper extremity pain syndromes such as mononeuropathy, brachial plexopathy, complex regional pain syndrome, acute post-operative pain, and other shoulder pathologies (impingement syndrome, adhesive capsulitis, primary osteoarthritis, post-operative shoulder pain) – demonstrating modest to moderate pain relief, Level II-2 Grade B evidence.[8,102–106] Ultrasound is conventionally used to place PNS at target nerves of the upper extremity to avoid neurovascular damage. The COMFORT and COMFORT 2 RCTs demonstrated efficacy and safety for shoulder pain with a pooled 6-month responder rate of 74% and pain relief of 62% ($p<0.001$).[95,96] (Level 1, Grade A)

Craniofacial Nerve Targets

The most common targets for craniofacial neuromodulation include the occipital nerve, supraorbital, and infraorbital branches of the trigeminal nerve, the supratrochlear nerve, the sphenopalatine ganglion (SPG), and the auriculotemporal nerve (Table 5). PNS may be utilized to manage chronic neuropathic facial pain and headache disorders. Given the limited tissue real estate and mobility of the craniofacial region, there may be an increased risk of skin erosion and increased lead migration or fracture, and an implanted pulse generator is often placed at the infraclavicular region.[107] Previous consensus recommendations support the consideration of neuromodulation for chronic craniofacial pain syndromes before long-term, long-acting opioid therapy[107,108](Table 6).

Occipital Nerves

Occipital PNS has been employed to treat primary headache disorders, such as occipital neuralgia, cluster, paroxysmal hemicrania, and migraines refractory to conventional medical management.[108] Traditionally, lead placement at the nuchal line using landmark or fluoroscopic techniques has been implemented to target the occipital nerve; however, advancements in high-resolution ultrasound have facilitated targeting the greater occipital nerve in the upper neck at C2.[109] The summarized results of several randomized clinical studies investigating the safety and efficacy of occipital nerve stimulation for chronic headache management indicate positive outcomes.[110–115] There is high-quality evidence for PNS of the occipital nerves for chronic migraines and low-quality evidence for occipital neuralgia, tension headaches, and cluster headaches.[116]

Trigeminal Nerve

PNS of the trigeminal nerve to treat craniofacial pain most commonly involves targeting terminal sensory branches such as the supraorbital, infraorbital, supratrochlear, and the auriculotemporal nerves.[107] There is low-quality evidence for

Table 5 Common Craniofacial PNS Targets and Indications

Target Nerve	Condition
Occipital	Migraine, Cluster Headache, Occipital Neuralgia, Paroxysmal Hemicrania
Supraorbital and infraorbital	Trigeminal Neuropathy
Auriculotemporal	Migraine, Trigeminal Neuropathy, Temporomandibular joint pain
Supratrochlear	Migraine, Cluster Headache
Sphenopalatine ganglion	Cluster Headache, Trigeminal Neuropathy, Paroxysmal Hemicrania

Notes: Data from Antony AB, Mazzola AJ, Dhaliwal GS, Hunter CW. Neurostimulation for the Treatment of Chronic Head and Facial Pain: A Literature Review. *Pain Physician*. 2019;22(5):447–477.[108]

Table 6 Quality of Evidence by Indication

Condition	Recommendation
Migraine	Level I, grade B, moderate quality evidence to recommend occipital nerve neurostimulation for migraine headache refractory to conservative management
Other craniofacial pain Trigeminal neuropathy	Level III, grade C, moderate evidence to recommend trigeminal nerve/branches (supraorbital, infraorbital, supratrochlear, auriculotemporal) neuromodulation for neuropathic craniofacial pain disorders
Cluster headache	Level I, grade C, moderate evidence to recommend sphenopalatine ganglion neurostimulation treatment for cluster headache when noninvasive measures have failed

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supraorbital and supratrochlear nerve stimulation for trigeminal neuropathic pain or other craniofacial pain syndromes, with a few clinical studies reporting limited benefit.[117–120] Low-quality evidence recommends infraorbital stimulation for trigeminal neuropathic pain and craniofacial pain, with three observational studies describing positive outcomes.[116] Limited evidence supports the use of auriculotemporal PNS for treating refractory head and jaw pain.[117,121–124]

Sphenopalatine Ganglion

The SPG is theorized to exert a pivotal role in the genesis of trigeminal autonomic cephalalgia, cluster headache, and paroxysmal hemicranias.[125,126] There is limited evidence to support the use of SPG neurostimulation in chronic craniofacial pain, with only one randomized controlled study and a few case series.[127–129] There is sparse literature to recommend SPG neuromodulation in idiopathic facial pain, trigeminal neuralgia, and paroxysmal hemicrania. Still, SPG neuromodulation combined with trigeminal PNS may play a role in treating cluster headaches in selected cases.[108,126,130] The evidence remains limited but promising for cluster headaches based on results from one high-quality study.[128,131]

Pudendal Nerve

The pudendal nerve originates from the second, third, and fourth sacral nerve roots and provides sensation to the anus, perineum, and genitals.[132,133] Urologists have utilized peripheral nerve stimulation (PNS) targeting the pudendal and sacral nerves for treatment of voiding dysfunction and interstitial cystitis associated chronic pelvic pain for over a decade - Level I evidence, Grade B recommendation.[134–137] These devices have been traditionally implanted through an ischial-rectal approach. Recently, pudendal nerve stimulation has been proposed as a means for the management of chronic pelvic pain in the field of pain medicine. Both ultrasound-guided and fluoroscopic-guided techniques have been proposed to minimize the risks of neurovascular injury, but large randomized control trials assessing efficacy and safety are lacking.[138,139] Pudendal nerve PNS for chronic pelvic pain is Level II-3 evidence, Grade C recommendation.

Transverse Abdominal Plane (TAP)

The transverse abdominal plane (TAP) is located between the transversus abdominis and internal oblique muscles,[140] and contains the thoracoabdominal nerves (arising from the seventh to eleventh intercostal, subcostal and first lumbar nerves)[141] and ilioinguinal and iliohypogastric nerves in the lower abdominal quadrants.[142] The thoracoabdominal nerves have been implicated as providing somatic sensation to the abdominal wall (between the T5-T12 dermatome).[143] As such, nerves within the TAP have been targeted by nerve blocks to treat chronic somatic and neuropathic abdominal pain.[144–147] Similarly, the ilioinguinal and iliohypogastric nerves have been targeted in the past for nerve blocks to treat somatic and neuropathic pain after inguinal herniorrhaphy.[142] Recently, utilization of a percutaneous, ultrasound-guided technique has been explored to place peripheral nerve stimulation leads in this region for the management of chronic abdominal pain. However, further investigation is needed to validate the safety and efficacy of this modality.[2] (Level II-3 evidence, Grade C)

Low Back Pain

When considering modern PNS devices, chronic low back pain is probably the most well-studied PNS indication in the literature. Permanent devices targeting the multifidus muscle directly at the lumbar spine provide functional improvement in disability and prolonged pain relief in 5-year, longitudinal randomized trial data, Level I-A, Grade A.[148] Furthermore, a direct target of the medial branch nerves innervating the multifidus muscle with temporary 60-day systems has shown efficacy beyond the treatment time. Prospective data supports that 60-day PNS treatment may lead to 12 months of 30–50% pain relief in patients with and without a previous thermal ablation.[149,150] Current literature suggests Level I-B, Grade B moderate evidence for PNS and low back pain syndromes, primarily related to heterogenicity of technique, device, and study population.[151] In a health economic study, PNS provides significant cost savings compared to conventional interventional therapies for chronic low back pain over a year of treatment.[152]

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Cluneal Nerves

Targeting the cluneal nerves for treating iliolumbar or chronic low back pain syndromes has been described in the literature. The superior and middle cluneal nerves are commonly implicated as pain generators in the lower back, buttock, and posterior thigh distribution and are composed of the cutaneous branches of the lateral dorsal rami branches from T11 to S4.[153] Evidence for this target consists of case reports and small series with promising results as well as two robust RCTs.[34,95,96,154–156] The cluneal nerve was one of the primary targets within the COMFORT and COMFORT 2 RCTs and demonstrated an 81% responder rate in the pooled cohort.[95,96] (Level 1, Grade A)

Intercostal Nerves

The intercostal nerve innervates the skin and muscle of the thorax and part of the abdominal wall.[69] These nerves can be targeted for treating rib pain, post-herpetic pain, and postsurgical pain. The neurovascular bundle runs inferior to the rib, deep to the intercostal muscle, and superficial to the pleura at each level. Case reports have shown the potential for this technique, especially for breast cancer treatment-related pain, post-herpetic neuralgia, and abdominal pain.[157–159] A case series for treatment of focal mononeuropathy pain with 39 patients revealed that 78% noted improvement in their pain, and patients with intercostal PNS had a 40% improvement in activity.[160] A retrospective review of 6,160 patients following 60-day PNS revealed consistent outcomes across a multitude of nerve targets, with a responder rate of 71% of patients having at least 50% pain relief or improvement in quality of life.[55] Sub-analysis of 103 patients with intercostal nerve PNS revealed equivalent outcomes. (Level II-3, Grade B)

Ilioinguinal/Iliohypogastric Nerves

Ilioinguinal and Iliohypogastric peripheral nerve stimulation (PNS) for groin pain has been achieved via surgical implantation, ultrasound-guided, and anatomic placement and has been published in multiple case presentations. One surgical implantation of the paddle (iliohypogastric) and percutaneous (ilioinguinal) leads yielded 0/10 pain 1-year post-implantation.[161] Another surgical implant (ilioinguinal) reported minimal pain at 3-months.[162] Four cases were described in a published series using ultrasound-guided placement (ilioinguinal), of which two were 7-day trials with >85% pain relief.[163] Other published cases yielded mixed results: one with >50% relief for 1 year and one without relief at 2 months post-implantation.[161,164] Eight cases of anatomic placement (ilioinguinal, iliohypogastric) reported pain reduction by >50%, ranging from 1 month to 2 years.[161,165–167] (Level II-3, Grade C)

Genitofemoral Nerve

Genitofemoral PNS for groin pain has also been described via anatomic, ultrasound-guided (USG), and surgical approaches. Three cases of anatomic placement with fluoroscopic confirmation reported 50–75% pain relief ranging from 1 to 5 months post-implantation.[166–168] Under USG, one case reported >90% pain relief at 5 months post-op and improved physical functioning on the 12-item Short Form Survey.[169] A retroperitoneal surgical approach, named the “sandwich technique”, reported >60% relief before losing efficacy from scar tissue formation and explant at 12 months.[161] Finally, one patient with genitofemoral PNS reported 50% relief at 1 year in a randomized control trial of 10 kHz PNS.[170] (Level II-3, Grade B)

Meralgia Paresthetica (Lateral Femoral Cutaneous Nerve)

Meralgia paresthetica is characterized by entrapment of the lateral femoral cutaneous nerve, originating from spinal levels L2-3 and often presenting with numbness, dysesthesia, and occasionally pain over the anterior thigh. Evidence is currently limited to case reports and one case series. One case report,[171] demonstrated 100% pain reduction using a 60-day temporary stimulator (SPRINT) sustained at 12 months with discontinuation of gabapentin. Another case report,[172] described 80% relief at 3 months with a temporary device (SPRINT). One final case series (n=3),[160] implanted a permanent peripheral nerve stimulator (Bioness Stimrouter) with an external generator and achieved 100% VAS improvement and 70% activity improvement. More extensive case series are necessary to assess long-term results for meralgia paresthetica PNS. (Level II-3, Grade B)

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Lower Extremity (Sciatic, Femoral, Saphenous Nerves)

Peripheral nerve stimulation has been applied to the femoral, sciatic, and saphenous nerves for managing nociceptive and neuropathic postoperative and chronic lower extremity pain. Femoral nerve PNS and sciatic nerve PNS are effective in a sham-controlled RCT managing immediate postoperative pain using temporary lead placement for 14 days and were effective in reducing opioid requirements and pain[173] (Level 1, Grade A evidence). Other studies have demonstrated the use of PNS in postoperative pain management, improving recovery times and reducing opioid requirements.[105] Femoral nerve PNS is a desirable target nerve for managing postoperative knee pain, particularly post ACL reconstruction.[174] Sciatic nerve stimulation has been used for postoperative pain after foot/ankle surgery. Unfortunately, knee and ankle pain can persist beyond the immediate postoperative period. Permanently implanted saphenous nerve stimulation has been used to treat persistent knee pain.[175,176] Future studies will help better understand candidates for therapy and long-term success rates. (Level II-3, Grade B evidence)

Knee Pain

Peripheral nerve stimulation for knee pain can include the femoral, saphenous, and genicular nerves. Genicular nerves have long been the target of radiofrequency ablation for knee pain. PNS of the genicular nerves has been used for persistent postoperative knee pain and osteoarthritis in the absence of surgical intervention. A case report,[177] of focal knee pain due to osteoarthritis showed successful treatment with temporary PNS of the superomedial genicular nerve and saphenous nerve, but the long-term benefit was not established. Several studies have applied genicular nerve PNS to patients with chronic pain after total knee arthroplasty or patients unable or unwilling to undergo knee replacement; PNS may be considered in temporary form for pain management. Small case series have shown limited success.[178] A systematic review,[179] identified 7 studies limited to case reports and series that showed improved pain and functionality; however, there was variability in technique workup and included both temporary and permanent devices. The COMFORT and COMFORT 2 RCTs demonstrated a pooled responder rate of 96% for subjects being treated for chronic knee pain.[95,96] By convention, lead placement for PNS should not span across a joint due to the risk of lead migration and lead fracture. Both fluoroscopic and ultrasound-based techniques have been used for genicular PNS, targeting the superior medial and superior lateral genicular nerves. Future studies are necessary to help characterize responders and best practice models. (Level I, Grade A evidence)

Ankle/Foot Pain

As with postoperative knee pain management, sciatic nerve PNS is effective in the immediate postoperative period in reducing opioid requirements and pain in a randomized, sham-controlled trial[173] (Level I, Grade A evidence). The ease and availability of ultrasound have allowed for better nerve visualization. Commonly targeted nerves for ankle pain include the sural, superficial peroneal, and posterior tibial nerves. Tarsal tunnel syndrome results in tendinous compression of the posterior tibial nerve posterior to the medial malleolus. The superficial peroneal and sural nerves can be injured in ankle fractures and operative intervention.[180] In a case series of permanent wireless PNS placement for peripheral neuralgias, one patient was treated successfully with PNS of the sural nerve.[167] Limited evidence exists for PNS of the nerves of the ankle. Some evidence suggests the utility of stimulating the sciatic nerve in postoperative pain management for ankle surgery.[173] The COMFORT and COMFORT 2 RCTs demonstrated durable benefit for ankle and foot pain with pooled data demonstrating a 75% responder rate and 65% pain relief at 6 months ($p<0.001$).[95,96] (Level 1, Grade A evidence)

Neuropathic Pain

Peripheral neuropathy may be present in up to 12% of the population and as high as 30% in older demographics.[181] A retrospective study of PNS for neuropathic pain in 63 patients found that NRS decreased from 7.24 at baseline to 3.43 at 2–3 week follow-up. Among the 24 patients who completed long-term follow-ups of 8 months or longer, 79% had pain relief of ≥50%. PNS for chemotherapy-induced peripheral neuropathy (CIPN) is an area of recent study, and a systematic review found that there is some evidence supporting PNS for CIPN based on a study with 50 subjects[182] (Level II-3, Grade B evidence).

Studies evaluating PNS for lower extremity neuropathic pain have focused primarily on mononeuropathies, which is appropriate given the focal nature of PNS treatment. One potential target application is peripheral small fiber neuropathy; however, no studies currently validate PNS for this indication. Spinal cord stimulation has seen wide implementation and innovation, such as variable waveforms and hardware optimization. PNS can experience similar growth as new indications are evaluated and specific nerve targets are explored.[183]

Complex Regional Pain Syndrome

The literature describing the use of PNS for CRPS encompasses the treatment of both upper and lower extremity CRPS with targets including the sciatic, common peroneal, tibial, femoral, lateral femoral cutaneous, saphenous, radial, median, and ulnar nerves.[184] In a case series of 3 patients with CRPS Type I affecting the foot, 60 days of percutaneous PNS therapy applied to the tibial and common peroneal nerves in the popliteal fossa resulted in the resolution of autonomic symptoms. Two of the three patients experienced pain relief for more than 8 months after discontinuing therapy.[185] Similarly, in a case series of 11 patients diagnosed with upper or lower extremity CRPS Type 2, all received an implantable PNS system after successfully responding to the trial phase. These patients experienced clinically significant pain reduction after a permanent PNS implant of about 5 points on the Numeric Rating Scale (NRS) of pain.[186] In a retrospective chart review of 165 patients receiving surgical PNS implantation for CRPS type 1 or 2 of the upper or lower extremities with paddle-type SCS electrodes to function as PNS, pain scores on the NRS were about 1.9 points lower after 12 months. Concurrently, the percentage of patients receiving opioid therapy decreased from 62% to 41% after 12 months. In addition, 51% of patients reported an improvement in functional status. As 34% of patients in this study required surgical revision, outcomes with modern, dedicated percutaneous PNS systems will likely improve with reduced complication rates.[187] In a case series of 14 patients with refractory upper extremity CRPS, 10 received permanent PNS implants at the brachial plexus after a successful trial. At 12-month follow-up, these patients reported a 57.4% improvement in VAS scores and a 60% improvement in neuropathic pain symptoms, similarly demonstrating sustained treatment response to PNS among patients with CRPS.[188] Goree et al reported on a randomized, sham-controlled trial of 60-day PNS for post-knee replacement CRPS Type 2.[189] Sixty percent of patients in the PNS group had at least 50% pain compared to a 24% response rate in the sham group. Additional randomized clinical trials will further establish the broad application of modern PNS systems in treating CRPS and determine patient and therapy-specific factors associated with positive treatment response. (Level I, Grade B)

Post-Amputation Pain

The ASPN Evidence-Based Clinical Guidelines for the Use of PNS in the Treatment of Chronic Pain recommend that

> PNS may be considered for lower-extremity post-amputation pain following the failure of conservative treatment options and is associated with modest to moderate pain relief.[8]

This recommendation stems in part from an RCT of 28 traumatic lower extremity amputees with post-amputation pain receiving either 8 weeks of percutaneous PNS targeting the femoral and sciatic nerves or 4 weeks of placebo followed by 4 weeks of PNS after crossover. At 12 months, 6 of 9 patients receiving 8 weeks of PNS reported ≥50% reductions in average weekly pain, while 0 of 14 patients in the control group reported a significant reduction in pain after the 4-week placebo period.[190] Given the 36% attrition rate from randomization to 12-month follow-up, additional research is needed to replicate these promising findings. In a pilot RCT of 16 veterans undergoing lower extremity amputation who had received femoral and sciatic peripheral nerve catheters, patients were eligible for enrollment if they reported pain scores ≥4 out of 10 in the 24 to 48 hours after catheter removal. Patients were randomized to 60 days of PNS targeting the femoral and sciatic nerves combined with standard medical therapy or standard medical therapy alone. Initial outcomes at 3 months demonstrate greater reductions in phantom limb pain, residual limb pain, and daily opioid consumption among those receiving PNS, signaling a role for PNS in the subacute phase after amputation.[191] PNS may serve as an important bridge therapy to prevent the development of persistent pain after amputation and phantom limb pain. (Level I, Grade A)

Consensus Guideline 9: In addition to strong evidence from RCTs and large retrospectives spanning a wide range of indications and nerve targets, focused studies support impactful treatment of a variety of anatomic targets, specific nerves, and specific painful conditions including shoulder (Level 1, Grade A), occipital nerve (Level 1, Grade B), sphenopalatine ganglion (Level 1, Grade C), pudendal nerve (Level 1, Grade B for voiding dysfunction and interstitial cystitis and Level II-3 Grade C for chronic pelvic pain), medial branch nerve (Level 1, Grade A), cluneal nerve (Level 1, Grade A), lower extremity (Level 1, Grade A), knee (Level 1, Grade A), ankle/foot pain (Level 1, Grade A), CRPS (Level 1, Grade B), lateral femoral cutaneous nerve (Level II-3 Grade B) and post-amputation pain (Level 1, Grade A). (See Table 7)

Postoperative Pain

While a few small (<20 subjects) randomized proof-of-concept studies have suggested reduced pain and opioid requirements with PNS following various surgical procedures,[174,191–193] only one trial prospectively powered to determine efficacy has been published involving postoperative pain.[173] Participants undergoing ambulatory surgery were randomized to receive either active stimulation (n=32) or a sham (n=34) for 2 weeks in a double-masked fashion. During the first 7 postoperative days, opioid consumption in participants given active stimulation was a median [IQR] of 5 mg [0, 30] versus 48 mg [25, 90] in patients given sham treatment (P<0.001). During this same period, the average pain intensity measured with a 0–10 numeric rating scale in patients given active stimulation was a mean ± SD of 1.1 ± 1.1 versus 3.1 ± 1.7 in those given sham (P<0.001). No intervention-related adverse events were identified. Perhaps most compelling, participants who received active treatment had far less physical and emotional interference due to pain throughout the day following lead removal as measured with the Brief Pain Inventory (Interference Scale).[194] While this

Table 7 Level of Evidence by Pain Indication

Target Area	Evidence Grade	Indication
Upper Extremity	Level I, Grade B	Post-stroke shoulder pain
	Level 1, Grade A	Post-surgical/post-traumatic shoulder pain, peripheral neuralgia including pain due to nerve injury, postsurgical scar formation, nerve entrapment, mononeuropathy and osteoarthritic pain
Craniofacial	Level I, Grade B	Occipital nerve PNS for refractory migraine
	Level III, Grade C	Trigeminal nerve/branches for neuropathic craniofacial pain
	Level I, Grade C	Sphenopalatine ganglion stimulation for cluster headaches
Abdominal/Pelvic	Level I, Grade B	Pudendal nerve for interstitial cystitis-associated chronic pelvic pain
	Level II-3, Grade C	Pudendal nerve for chronic pelvic pain
	Level II-3, Grade C	Thoracoabdominal nerves (TAP)
	Level II-3, Grade C	Ilioinguinal/Iliohypogastric nerves
	Level II-3, Grade B	Genitofemoral nerve
Low Back	Level I-A, Grade A	Multifidus stimulation
	Level I-B, Grade B	Median branch nerve
	Level I, Grade A	Cluneal nerve
Thoracic	Level II-3, Grade B	Intercostal nerve
Lower Extremity	Level II-3, Grade B	Lateral femoral cutaneous nerve for meralgia paresthetica
	Level II-3, Grade B	Sciatic, femoral, saphenous nerves for leg pain
	Level I, Grade A	Genicular nerves, femoral and saphenous for knee pain
	Level I, Grade A	Sciatic nerve for ankle/foot pain
	Level II-3, Grade B	Nerves of the ankle
	Level II-3, Grade B	Peripheral neuropathy
	Level I, Grade B	Complex Regional Pain Syndrome (CRPS)
	Level I, Grade A	Post-amputation pain
Postoperative Pain	Level I, Grade B	Upper extremity and lower extremity

technique's potential benefits include prolonged analgesia duration (up to 60 days currently) and lack of induced motor, sensory, and proprioception block, unit cost and time for lead insertion may be limiting factors.[195] (Level I, Grade B)

Consensus Guideline 10: PNS in the post-operative period has demonstrated reduced opioid consumption, pain scores, and physical/emotional interference scores with Level 1 data. PNS is a highly effective treatment in the postoperative period, but payor policies are a restricting factor.

Non-Pain Targets, Rehabilitation, and Motor Strengthening

Posterior Tibial Nerve

Tibial nerve stimulation (TNS) represents an important treatment modality for several urologic and gastrointestinal conditions via parasympathetic nervous system activation. Percutaneous TNS protocols for these indications often involve frequent visits for percutaneous needle placement to receive PNS. TNS applied via transcutaneous devices is an alternative approach. Percutaneous TNS represents a promising alternative to sacral nerve neuromodulation in treating fecal incontinence. In a meta-analysis of 4 RCTS spanning 439 adults with fecal incontinence, percutaneous TNS demonstrated superior efficacy compared to sham electrical stimulation in reducing weekly episodes of fecal incontinence, and a higher proportion of patients receiving percutaneous TNS reported a greater than 50% reduction in weekly fecal incontinence episodes.[196] Percutaneous TNS for the treatment of overactive bladder has demonstrated more efficacy in reducing urgency urinary incontinence compared to certain antimuscarinics and results in improved daytime micturition frequency and nocturia frequency comparable to other rehabilitation modalities.[197] Still, more research is needed to determine its role in managing overactive bladder compared to more first-line therapies.[198] When comparing neuromodulation modalities, including percutaneous/transcutaneous TNS, vaginal electrical stimulation, sacral neuromodulation, parasacral stimulation, pudendal neuromodulation, or placebo in a network meta-analysis of 21 RCTs spanning 1,433 participants with overactive bladder, both percutaneous and transcutaneous TNS were most efficacious for reducing urgency incontinence episodes.[199] Additional reported indications for percutaneous TNS include low anterior resection syndrome,[200] lower urinary tract symptoms (urgency, frequency, nocturia, urge urinary incontinence) among patients with multiple sclerosis,[201] and chronic prostatitis/chronic pelvic pain syndrome.[202] (Level I, Grade A evidence)

Vagus Nerve

The ability to modulate activity in the parasympathetic nervous system via the vagus nerve is central in disease management in a wide range of disorders. Through its afferent projections to the brainstem's nucleus tractus solitarius, which accounts for 80% of its fibers, the vagus nerve regulates brain physiology, chemistry, plasticity, and behavior.[203] Several methods of action have been identified with vagus nerve stimulation (VNS), including modulation of neurotransmitters such as glutamate, norepinephrine, and serotonin, modulation of cortical spreading depression and electrical excitability, modulation of the autonomic nervous system, and modulation of inflammatory cytokines.

VNS has been FDA-cleared in the United States for treating epilepsy, major depression, multiple primary headaches, abdominal pain in children, addiction, post-stroke rehabilitation, and painful diabetic neuropathy. A systematic review of transcutaneous VNS for treating epilepsy found that multiple studies showed improved quality of life and that two showed statistically significant reductions in seizure frequency.[204] The FDA also granted an EUA for known or suspected COVID-19 and a breakthrough designation for post-traumatic stress disorder. An RCT with 97 randomized COVID patients demonstrated reduced CRP levels in patients receiving non-invasive VNS[205] (Level I, Grade B evidence). VNS has also shown promise in inflammatory disorders such as Sjogren's disease, Rheumatoid Arthritis, and Crohn's Disease.[206] (Level II-3, Grade B evidence) Currently used implantable VNS devices include multiple systems by Livanova (formerly Cyberonics) (Houston, TX) that are used for the treatment of epilepsy[207] and depression[208] and by MicroTransponder (Austin, TX) that are used for post-stroke rehabilitation.[209]

Phrenic Nerve

Phrenic nerve stimulation was first introduced in the 1960s as respiratory support for high cervical spinal cord injury and central alveolar hypoventilation syndrome.[210] Following initial pilot studies of transvenous phrenic nerve stimulation (TPNS) in central sleep apnea (CSA) and co-morbid heart failure (HF), a large, randomized control trial evidenced long-term safety and efficacy in reducing CSA severity up to 4 years post-implant.[211–213] (Level I, Grade B evidence). Later studies demonstrated safety and efficacy in HF patients, including those with implantable electronic devices.[214,215] TPNS may be effective in weaning select ventilator-dependent patients; however, this was not substantiated in large, randomized control trials (RESCUE-2, RESCUE-3 NCT03783884).[216,217] Currently, the US FDA approves phrenic nerve stimulation using the Avery Mark IV Breathing Pacemaker (Avery Biomedical, Commack, NY) for various indications.[218]

Hypoglossal Nerve

Hypoglossal nerve stimulation (HNS) evolved after loss of genioglossus muscle tone at sleep onset was linked to pharyngeal obstruction and obstructive sleep apnea (OSA).[219,220] An initial 1997 study prompted further feasibility trials of fully implantable systems, confirming airflow dynamics and sleep apnea improvements.[221] Following a landmark trial (STAR), HNS obtained Food and Drug Administration (FDA) approval in 2014 as second-line treatment for moderate to severe OSA that is refractory to positive airway pressure (PAP).[222,223] Given proper patient selection, HNS has been extensively studied with evidenced effectiveness in reducing apnea-hypopnea index (AHI) up to nine years post-implantation.[221] (Level I, Grade A evidence)

Occipital Nerve

Luckey et al examined memory in 30 subjects in a double-blind, sham-controlled, randomized trial.[224] Half the participants received transcutaneous occipital nerve stimulation, whereas the other half received sham stimulation. Occipital nerve stimulation enhanced memory after just one session, with results lasting 28 days. The proposed mechanism is via the locus-coeruleus-noradrenaline pathway. This study observed changes in alpha-amylase, a noradrenaline biomarker, following occipital nerve stimulation. Additional studies have demonstrated that occipital nerve stimulation can boost the retention of memories when applied around the time of learning by enhancing memory consolidation via this pathway.[225,226] (Level I, Grade B evidence)

Trigeminal Nerve

Trigeminal nerve stimulation (TNS) has garnered interest in treating neurologic and psychiatric disorders.[227] Initially described in case studies, TNS for drug-resistant epilepsy has been proven safe and effective for up to 12 months.[228] Based on the trigeminal nerve projections to the ascending reticular activating system, spinal locus, and cortex, along with a case report of awakening from a coma, TNS has been studied in recovery from traumatic brain injury with modest yet promising results.[229] There is evidence to suggest that TNS may improve major depression, attention deficit hyperactivity disorder, and refractory schizophrenia.[230–233] One study showed improved olfaction with TNS.[234] (Level II-3, Grade B evidence) A recent prospective, double-blind, randomized controlled study evaluated the effect of trigeminal nerve stimulation on cerebral infarction occurrence in patients with aneurysmal subarachnoid hemorrhage. Still, no decrease in the stroke rate was observed secondary to vasospasm occurrence.[235]

Peroneal Nerve

Since the 1960s, common peroneal nerve stimulation (CPNS) has been investigated for improving post-stroke foot drop; the FDA has approved three distinct external devices.[236] Many studies indicate that external and implanted CPNS systems are non-inferior to ankle-foot orthoses (AFO) for foot drop in stroke and gait in multiple sclerosis.[237–239] Notably, combined sensory and functional CPNS variations in meta-analyses and a standalone study report contrasting outcomes[240–242] (Level I, Grade C evidence). CPNS has also been shown to be safe and effective in improving symptoms of medication-refractory restless leg syndrome (RLS) for up to 6 months, leading to its eventual FDA approval in 2023[243] (Level I, Grade A evidence).

Pudendal Nerve

Pudendal nerve stimulation has been described as a treatment for urinary retention.[244] Another study demonstrated that daily pudendal nerve stimulation accelerated recovery from stress urinary incontinence.[245] Feng et al conducted a parallel design randomized controlled trial with 96 subjects who had undergone radical prostatectomy, allocated as 64 patients in a group receiving pudendal nerve stimulation and 32 receiving pelvic floor muscle training and transanal electrical.[246]

Treatments were administered three times a week for eight weeks. The efficacy rate of 68.7% in the pudendal nerve stimulation group was nearly double the responder rate of 34.4% in the pelvic floor muscle training group. This indicates that pudendal PNS can almost double the likelihood of regaining urinary continence following radical prostatectomy. The mechanism of action is believed to be that pudendal nerve stimulation simulates pelvic floor muscle training. (Level I, Grade A evidence)

PNS for Sexual Dysfunction

Percutaneous tibial nerve stimulation (TNS) results in improvements related to both male and female sexual dysfunction in patients with overactive bladder, chronic pelvic pain, and nonobstructive retention. Patients report significant improvements in overall satisfaction, libido, and frequency of sexual activity in response to percutaneous TNS.[247] In a prospective observational study of 41 women receiving percutaneous TNS for OAB reporting sexual dysfunction, participants reported significant improvements in sexual function independent of urinary symptoms.[248] Among female patients with fecal incontinence who had failed to respond to biofeedback, percutaneous TNS resulted in significant improvements in bowel continence, bowel-related quality of life, and bowel-related sexual function, but not dyspareunia.[249] A systematic review of PNS across a variety of nerve targets for sexual dysfunction by Jin et al found that male patients experienced an improvement in erectile function, desire, and satisfaction, whereas desire, arousal, orgasm, lubrication, quality of "sex life", intercourse capability, and dyspareunia improved in female patients.[250] (Level II-3, Grade B evidence)

PNS for Tremors and Tics

Peripheral nerve stimulation has demonstrated benefits in treating tremors and tics. Small studies indicated that median and radial nerve stimulation reduced Parkinson's and essential tremors.[251,252] In 2021, the first FDA external stimulator device (Cala kIQ) obtained approval for Parkinson's disease (action hand tremors) and essential tremors. Though stimulation of the median and radial nerves is proven safe, larger studies report mixed results on efficacy[253,254] (Level II-3, Grade C evidence). Among tic spectrum disorders, case reports of Tourette's syndrome describe improved motor and phonic tics after a vagal nerve stimulator implant.[255,256] Two clinical trials of wearable median nerve stimulation (MNS) also evidenced efficacy in improving chronic tic disorder[257,258] (Level I, Grade B evidence).

> Consensus Guideline 11: A variety of nerve targets have demonstrated efficacy for non-pain applications, including posterior tibial nerve for urological issues (Level 1A), phrenic nerve for central sleep apnea (Level 1B), hypoglossal nerve for obstructive sleep apnea (Level 1A), occipital nerve for memory enhancement (Level 1B), common peroneal nerve for medication refractory restless leg syndrome (Level 1A), pudendal nerve to reduce urinary incontinence following radical prostatectomy (Level 1A), nerve stimulation for migraines, cluster headache, post traumatic stress syndrome, post stroke recovery (Level 1A) among numerous other inflammatory mediated disorders and median nerve for chronic tic disorder (Level 1B). (See Table 8)

Surgical Best Practices

Tined vs Non-Tined and Anchoring

When deciding between tined and non-tined electrodes for peripheral nerve stimulation (PNS), consider anatomical factors and the desired outcome. Tined electrodes are ideal for areas with frequent movement, requiring secure fixation to prevent migration. They are suitable for deep nerve targets or regions prone to lead displacement. Non-tined electrodes are simple to place, may be preferred for superficial nerves or sites with less expected movement, and can be anchored to fascia at the insertion site. Factors such as patient comfort, anticipated duration of therapy, and lead stability should also be considered. Ultimately, the choice between tined and non-tined electrodes should be based on individual patient needs and the specific requirements of the procedure.

Closure

Saline irrigation prior to closure may reduce microbial burden.[259] For optimal closure of a peripheral nerve stimulator (PNS) system, use absorbable sutures for deep tissue layers to minimize the risk of irritation and ensure stability. A cut-down should be deep enough to allow for a multi-layer closure to prevent future erosion of any implant material. For

Table 8 Level of Evidence by Functional Indication

Target	Evidence Grade	Indication
Posterior Tibial Nerve	Level I, Grade A	Fecal incontinence, overactive bladder
Vagus Nerve	Level I, Grade B	Epilepsy, Reduced CRP in COVID patients
Phrenic Nerve	Level I, Grade B	Central sleep apnea
Hypoglossal Nerve	Level I, Grade A	Obstructive sleep apnea
Occipital Nerve	Level I, Grade B	Enhances memory
Peroneal Nerve	Level I, Grade A Level I, Grade C	Restless leg syndrome Post-stroke foot drop
Pudendal Nerve	Level I, Grade A	Urinary incontinence following radical prostatectomy
Median Nerve	Level I, Grade B	Chronic tic disorder

superficial skin closure, options range from sub-cuticular absorbable sutures to non-absorbable sutures such as nylon or staples at the dermal-epidermal junction. Close the incision in at least 2–3 layers, ensuring that each layer is adequately approximated to promote proper healing.

> Consensus Guideline 12:Best surgical practice for permanent PNS includes strategies to promote optimal wound healing, infection prevention, and prevent lead migration. Effective strategies include saline irrigation prior to closure, a deep enough cut down to allow for multi-layer closure, and closing in at least 2-3 layers when appropriate based on the implanted hardware.

Post-Op Care

Advise patients to avoid bending, lifting, or twisting excessively for the first few weeks. Encourage gentle movement and walking to promote healing. Patients should keep the incision site clean and dry and follow the specific wound care instructions provided. They should immediately report any signs of infection, such as redness, swelling, or drainage. Emphasize the importance of attending the seven-to-ten-day follow-up appointment to monitor the system's function and make necessary adjustments. Providing clear and comprehensive postoperative care instructions can help ensure optimal outcomes for patients with PNS systems.

Troubleshooting and Complications

Due to the relative novelty of peripheral nerve stimulation, there have not been many publications on troubleshooting PNS systems. Most of the literature centers on sacral neuromodulation when used to treat urogynecological disorders. However, based on the properties of peripheral nerves, we can better understand best practices for troubleshooting PNS systems. One major issue with PNS is an inability to get stimulation to target. While pre-implant diagnostic nerve blocks do not necessarily predict the success of PNS,[52] some clinicians may use a peripheral nerve block to determine if the area supplied by the peripheral nerve gets appropriately anesthetized. Suppose the diagnostic block does not provide an appropriate response. This may predict an inability to get the PNS system to respond appropriately to electrical stimulation due to peripheral nerve damage.[52]

Undesirable motor and painful stimulation are also possible side effects of PNS. They are usually due to being too close to the nerve target, nonspecific stimulation, and/or using higher amplitudes than are required to achieve pain relief. New technologies that are not yet commercially available allow for selective stimulation of sensory and motor nerve fibers,[260] but current technology does not allow this yet. Lastly, loss of efficacy can be an issue with PNS, as it is with many technologies. Loss of effectiveness is most commonly due to lead migration,[261] with other possible etiologies, including lead fracture, habituation, and scar tissue around the lead contacts. Clinically, patients may also need a stimulation holiday when there is a perceived loss of efficacy, but more literature is required to support this theory.

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Complications with PNS are similar to those seen with Spinal Cord Stimulation (SCS). Complications can be divided into hardware-related and biological complications. Hardware complications include lead migration, which can be higher in PNS than in SCS systems.[261] Complications almost exclusively unique to PNS include lead erosion, which can be ~7% in PNS systems[261] and are less common in modern systems and when employing techniques with deeper implantation of lead anchoring devices. Finally, other serious complications for PNS systems include deep and superficial infection, pain over the implant site, and malfunction of the lead and/or implanted pulse generator.[261,262] Fortunately, serious complications are rare, and PNS allows avoidance of risks associated with SCS, such as serious spinal cord injury or inadvertent dural puncture.

Billing, Insurance Coverage, and Requirements

Billing

CPT Codes for Leads

Physicians utilize unique CPT codes for the different types of peripheral nerve electrodes on the market for peripheral nerve stimulation (Table 9). A peripheral neurostimulator system includes an implanted pulse generator or implanted receiver with an external transmitter, a collection of contacts, electrodes (electrode array), an extension (if applicable), an external controller, and an external charger (if applicable). The electrode array conducts the electrical stimulation. The pulse generator or receiver may be integrated with the electrode array (single-component implant) or have a detachable connection to the electrode array (two or more component implant).

Trial vs Implant

Trials are typically performed before implantation to assess the effectiveness of PNS in managing neuropathic pain. They are minimally invasive and reversible, offering a valuable opportunity to evaluate patient response and adjust stimulation

Table 9 wRVU Values for PNS CPT Codes (64555–64596) Compared to SCS CPT Codes (63650–63688)

CPT	Description	wRVU
64555	Percutaneous implantation of neurostimulator electrode	5.76
64575	Open Implantation of neurostimulator electrode array of peripheral nerve	4.42
64590	Insertion or Replacement of peripheral, sacral, or gastric neurostimulator pulse generator, requiring pocket creation and connection between electrode array and pulse generator or receiver	5.10
64596	Insertion or Replacement of percutaneous electrode array, peripheral nerve with integrated neurostimulator, including imaging guidance	0.00
64585	Revision or Removal of peripheral neurostimulator electrode	2.11
64595	Revision or Removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode	3.79
63650	Percutaneous implantation of neurostimulator electrode array, epidural	7.15
63685	Insertion or Replacement of spinal neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver	5.19
63661	Removal of spinal neurostimulator electrode percutaneous array(s) including fluoroscopy when performed	5.08
63663	Revision including replacement when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed	7.75
63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver, with detachable connection to electrode array	4.35

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parameters. However, trial success rates vary, and factors such as patient selection, trial duration, and trial lead location influence outcomes.

The decision to proceed with implantation after a successful trial is usually based on the degree of pain relief and improvement in function experienced by the patient. Although implantation is a more invasive procedure, it offers the potential for long-term pain relief in carefully selected patients.

Careful patient selection, proper trial design, and close collaboration between pain specialists and patients must be prioritized to optimize outcomes with PNS therapy.

Single vs Multiple Leads

The decision to use one or two leads for peripheral nerve stimulation depends on several medical factors already outlined. However, there are also factors related to payor coverage tied to Place of Service (POS). When POS is the Hospital Outpatient Department (HOPD), a flat charge is provided for lead placement and does not increase when two leads are placed. In the ASC setting, there is an additional payment for the second lead. Therefore, a local cost and payment analysis may need to be performed to determine the viability of two lead trials in a healthcare setting. POS is less important when considering permanent implantation as overall reimbursement rates generally support two lead placements in either setting (see Table 11).

Coding for IPG/Micro-IPG Placement

The updated CPT descriptions distinguish between integrated and non-integrated peripheral nerve stimulator (PNS) codes. For example, CPT code 64590 involves creating a pocket and connecting an electrode array to a pulse generator or receiver without specifying the size or type of the IPG. On the other hand, CPT code 64596 involves inserting an electrode array with an integrated neurostimulator, including imaging guidance, when performed. Incorrect labeling or coding can lead to non-reimbursement or the need for repayment after audit ("claw back"). An integrated neurostimulator contains the pulse generator or receiver and the electrode array as an all-in-one unit. A small incision is made, and the electrode array is tunneled percutaneously to the appropriate site. The same incision site is then used to create the pocket for the pulse generator or receiver. If more than one electrode array is used, add-on code 64597 may be reported for each additional electrode array. All of the aforementioned codes have a Global Period of 10 days.

> Consensus Guideline 13: Given the rapid advancement of PNS technologies and variability between platforms, physicians should be familiar with the details of the device they are utilizing and how it fits into the existing CPT code descriptions to ensure accurate coding.

Coding for Imaging Guidance

For peripheral nerve stimulator procedures, fluoroscopic needle guidance is included in CPT code 64555 for lead placement and should not be billed separately. However, ultrasound needle guidance can be billed separately, if performed, as CPT 76942, typically with the −26 modifier to indicate the professional component.

Insurance Coverage and Reimbursement

Medicare NCD (National Coverage Determination) and LCD (Local Coverage Determination) for PNS

CMS defines NCDs, and regional MACs define LCDs, which dictate the coverage and provision of care to patients (Figure 4). In simpler terms, NCDs can be viewed as the national standard and LCDs as regional guidelines that cannot override the national standard but can provide more specific criteria. There is currently an NCD - Electric Nerve Stimulators (160.7) from CMS and LCD - Peripheral Nerve Stimulation (L34328 and L37360) from the Medicare Contractor Noridian. This contractor covers the states of Washington, Alaska, American Samoa, Arizona, California, Guam, Hawaii, Idaho, Nevada, Northern Mariana Islands and Oregon.

The Medicare NCD describes electric nerve stimulators as prosthetic devices. It does not provide medical necessity requirements. The Medicare Local Coverage Determination (LCD) for Peripheral Nerve Stimulation (PNS) by Noridian

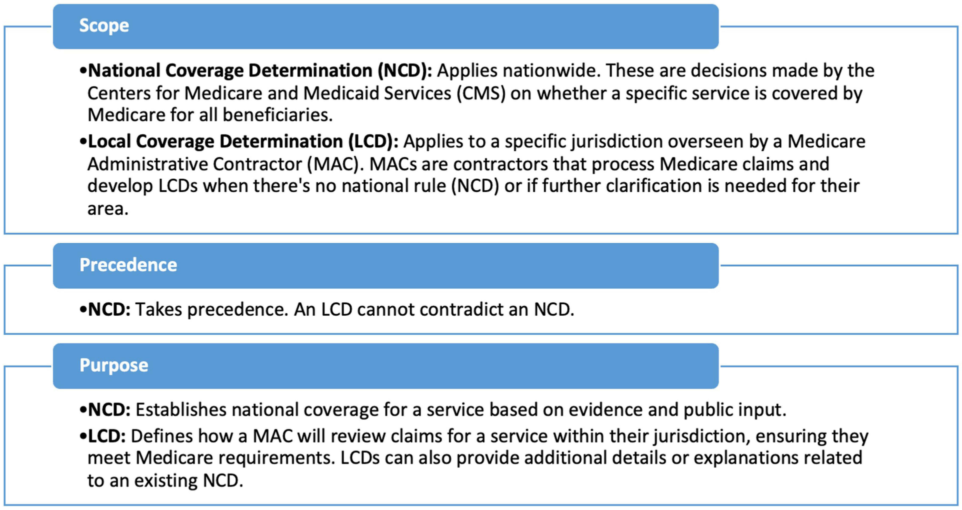

Figure 4 NCD and LCD Overview Overview of determinations for Medicare coverage.
Abbreviations: NCD, National Coverage Determination; LCD, Local Coverage Determination.

states that a peripheral nerve stimulation trial can be considered for the management of chronic pain if all the criteria are met (Table 10).

Peripheral nerve stimulation (PNS) may be covered for relief of chronic intractable pain for patients with conditions known to be responsive to this form of therapy after attempts to cure the underlying conditions, and appropriate attempts at medication management, physical therapy, psychological therapy, and other less invasive interventional treatments. An effective trial is a prerequisite for permanent implantation. The current LCD does not support the use of PNS for fibromyalgia, phantom limb pain, diffuse polyneuropathy, nociceptive pain in the trunk or lower back, or angina pectoris. Claims with these diagnoses will be denied as unreasonable and not medically necessary. The LCD provides a non-comprehensive list of indications with sufficient evidence of efficacy (Table 10).

There are significant access issues for PNS regarding coverage under Medicare Advantage plans, also known as Option C. Medicare Advantage plans are obligated to provide, at a minimum, coverage of all care that would apply under a Medicare plan. Specifically, Final Rule CMS-4201-F requires that Medicare Advantage plans must comply with established NCDs and LCDs (https://www.cms.gov/newsroom/fact-sheets/2024-medicare-advantage-and-part-d-final-rule-cms-4201-f). Unfortunately, many Advantage plans detail criteria that impede patients from accessing PNS coverage in violation of federal regulation. Some Option C carriers defer their policies to the Noridian LCD (L37360), while others do not provide such a path for patient selection and treatment. These authors have had nearly 100% success in taking denials to Administrative Law Judges (ALJ), where medical necessity is not a factor, but rather, cases are settled as a

Table 10 Noridian LCD Criteria

Noridian LCD Criteria
1. Documented chronic and severe pain for at least 3 months,
1. Documented failure of less invasive treatment modalities and medications,
1. Lack of surgical contraindications including infections and medical risks,
1. Appropriate proper patient education, discussion and disclosure of risks and benefits,
1. No active substance abuse issues,
1. Formal psychological screening by a mental health professional,
1. Successful stimulation trial with greater than or equal to 50% reduction in pain intensity before permanent implantation.

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matter of regulation on the basis that Medicare Advantage plans must comply with the traditional Medicare coverage determinants. Medicare Advantage plans rely on star ratings, which is a tool used by the Centers for Medicare & Medicaid Services (CMS) to measure and rate the performance of Medicare Advantage (Part C) and Medicare Prescription Drug (Part D) plans. These ratings help Medicare beneficiaries compare plans and make an informed decision about their healthcare coverage. These ratings are negatively impacted when they lose cases in front of ALJs, which indicates they impede patient access to care.

> Consensus Guideline 14: PNS is a covered therapy under traditional Medicare. Medicare Advantage (Part C) must comply with established NCDs and LCDs. NCD 160.7 grants coverage of PNS. Physicians should pursue appeal for Medicare Advantage denials as Administrative Law Judges (ALJ) primarily rectify denials to ensure coverage is aligned with CMS guidance.

Medicaid Coverage

Medicaid coverage of PNS is relatively poor. Most state Medicaid plans do not offer coverage of PNS and label it as experimental/investigational despite extensive studies, including RCTs, documenting the efficacy of PNS across a plethora of indications.[56,95,96,263] Where there are rare exceptions allowing coverage of PNS under Medicaid plans, the reimbursement is generally insufficient to make it a viable option (https://pcl.promedica.org/-/media/paramount/assets/documents/medicalpolicy/pg0406_implantable_peripheral_nerve_stimulation.pdf?rev=c1117433a00c409ead91da74695f745d). Due to significant advocacy efforts, Colorado, Kentucky, Michigan, and Tennessee have Medicaid reimbursement rates that closely mimic Medicare, providing patients access to 60-day PNS treatment. There is data to suggest that Oklahoma, Missouri, Idaho, New Mexico, and possibly Nevada and Florida have Medicaid reimbursement rates that support permanent PNS implantation.

Commercial Insurers

Most commercial insurance plans do not cover peripheral nerve stimulation despite the evidence mentioned throughout this publication. Insurers may respond to pretreatment queries for PNS coverage with a statement of “no preauthorization required.” This language is misleading, commonly misinterpreted as a treatment is covered, and may proceed without a preauthorization submission. This misinterpretation creates frequent conflict between care teams, their facilities, and patients as payment is denied post-treatment. The resultant 5-figure cost transfers to patients with chronic intractable pain, their care teams, and the healthcare system. In the opinion of these authors, the use of “preauthorization not required” or “no auth required” in response to a patient or clinical team query should not be permitted without a concurrent statement on whether the benefit is even theoretically covered versus noncovered in the plan itself. These authors have generally found that coverage among commercial payors is successful approximately 30% of the time, following prior authorization attempts, peer-to-peers, and appeals.

> Consensus Guideline 15: Given the large body of evidence supporting the efficacy of PNS across multiple indications and nerve targets as well as individual studies focused on specific indications, payors should cover PNS for chronic pain in patients who have failed to improve with conservative treatment.

Requirement of Nerve Blocks Before PNS Trial

Policies on the requirement for diagnostic nerve injections before the PNS trial vary by payors. Most policies do not have any clear guidance on nerve blocks before trial. CMS guidance states explicitly that the PNS trial is the ultimate determinant of the appropriateness of a patient for PNS implantation. While there may be a perception that nerve blocks help determine the pain generator, this has not been born out as a successful predictor of PNS success.[52] An analysis of 173 patients undergoing PNS by Hoffmann et al showed no difference in pain relief at 3- or 6-months post-implant between patients who had successful preimplant diagnostic nerve injections and those in the control group.

Reimbursement Variance by Location of Service

Place of service significantly impacts reimbursement for most medical procedures. Codes indicating the place of service include Office (code 11), ASC (code 24), and Hospital Outpatient Department (HOPD, code 22 or 19). While reimbursement and costs vary widely based on geographical location, supplier contracts, and payor policies, data on CMS reimbursement provides insight into the differential (Table 11).

Utility of Psychological Evaluation

Studies, reviews, and guidelines continue to recommend the exclusion of patients with "psychiatric disease" as resulting in a negative impact on patients' potential to respond favorably to PNS,[264,265] relying on "consensus", at best, rather than providing empirical evidence.[266] Even studies that have attempted to predict PNS outcomes have excluded patients based on psychological factors, irrespective of the lack of evidence for doing so.[267] Campbell et.al concluded that psychological evaluation is generally included pre-SCS", although no consensus to date has been reached regarding what specifically the assessment should include and what cut-off levels should be adopted for various questionnaire measures."[268] There has been no subsequent evidence basis for these assessments nor any consensus.

Although patients with pain are routinely denied PNS because of depression, the empirical literature strongly suggests that PNS is associated with decreases in depression scores in headache patients at 6 and 12 months following the initiation of treatment.[269] This finding is consistent with 3-month data in an earlier study of headache patients,[270] as well as data demonstrating post-PNS reductions in depression in post-amputation patients, those with chronic knee pain,[176] and likely other pain conditions. Accordingly, psychological evaluation requirements before PNS have the potential to exclude depressed patients when the empirical evidence points to this treatment's potential to reduce depression.

Even though strong, evidence-based guidelines[8] for PNS have recommended psychological evaluation before PNS, no empirical evidence supports such. Until data or even a strong consensus demonstrating a significant relationship between psychological factors and PNS outcomes is available, the insurance industry-mandated requirement for a psychological evaluation before PNS should be reconsidered.

Consensus Guideline 16: Given the lack of empirical evidence and a failure to establish a significant relationship between psychological factors and PNS outcomes, psychological evaluation before PNS should not be mandated by payors.

Health Economics

Increasing patient access to PNS will require improved payor coverage of the therapy. In addition to the growing body of evidence that strongly supports the efficacy of PNS and systematic reviews further reinforcing this, healthcare utilization and cost-effectiveness studies will help make the financial argument to payors. A cost-benefit analysis that looked

Table 11 Medicare National Average Reimbursement Differential Between ASC and HOPD

Procedure	ASC	HOPD
One lead trial	$5,620	$6,523
Two lead trial	$11,240	$6,523
One lead + IPG	$24,627	$29,617
Two leads + IPG	$30.247	$29,617
Revision/Removal one lead	$1,898	$3,245
Revision/Removal two leads	$2,847	$3,245
Revision/Removal IPG	$1,898	$3,245

Notes: Reference for table: CMS-1784-F. Medicare 2024 Physician Fee Schedule – January 2024 Addendum B updates. 2024 Conversion Factor $32.74. CMS-1786-FC Addendum B.-OPPS Payment by HCPCS Code for CY 2024 and Addendum AA – Final ASC Covered Surgical Procedures for CY 2024.

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collectively at PNS, as well as SCS, found that patients experience reductions in physician office visits, nerve blocks, radiologic imaging, emergency department visits, hospitalizations, and surgical procedures, totaling a net annual savings of approximately $30,221.[271] This resulted in an overall net per patient per year cost savings of roughly $17,903. Bulsei et al examined the financial impact of occipital nerve stimulation and found that while cost went up on a short time horizon, such as 3 months, it was lower by 1,344 Euros in one year.[272] Furthermore, when looking at indirect costs such as disability and sick leave, there was a reduction of 377 Euros for the occipital nerve stimulation group in the first 3 months.

Kalia et al evaluated the healthcare utilization and costs of 122 patients with chronic pain treated with PNS using a micro-implantable pulse generator.[273] The authors observed a postop vs preop reduction in outpatient visits (4.9 vs 5.7), a 50% reduction in mean total medical costs ($13,717 vs $27,493), and a 57% reduction in median total medical costs ($5,094 vs $11,809). Furthermore, the proportion of patients using opioids was 31.4% lower.

Consensus Guideline 17: Multiple healthcare economics analyses have concluded that utilization of PNS reduces healthcare visits and total medical costs. This evidence supports reductions in hospitalizations, other surgical procedures, and opioid use. Future prospective studies should incorporate these metrics as an additional outcome measure.

Moving PNS Forward

Future Areas of Research

The body of research in PNS has grown significantly over the last 40 years, with the most significant surge in the previous decade (Figure 5). To further establish PNS as a standard of treatment for common neuropathic pain conditions, additional high-level evidence will be beneficial. Prospective randomized studies do exist that add credibility to the grading and proof, as outlined in this paper. Further studies are required to better understand best practices for PNS. This would include more disease-specific studies that give insight into which disease states are most responsive and how to optimize patient selection. A prospective registry of future cases on PNS would provide insight into patient selection and target sites.

While RCTs are growing in prevalence and demonstrate the efficacy of PNS across many painful conditions, a continued focus on RCTs and, particularly, sham-controlled studies will help expand payor coverage of this beneficial therapy. Comparisons of lead designs, neural targets, and waveforms could be used in study design.[72,173,274,275] Additional research to further identify the potential role of age, gender, body mass index (BMI), tobacco and alcohol use, and other demographics may further clarify selection criteria, thereby further boosting PNS efficacy. Furthermore, with multiple available platforms for PNS, studies focused on the personalization and titration of stimulation to optimize responder rates will be useful for physician decision-making.

Expanding indications for PNS supported by safe and replicable procedural techniques for each novel target will help extend the reach of the therapy. Beyond pain indications, as discussed in this paper, there is great potential in applying PNS to non-pain indications. This promising research area may position interventional pain providers as best suited to

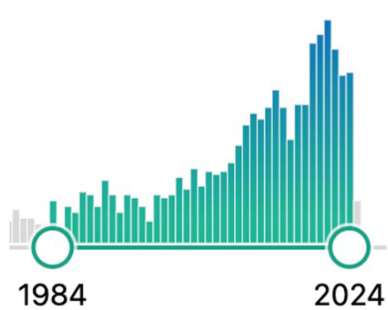

Figure 5 Clinical Trial and Retrospective Study Publications on PNS Annual PNS-related publications over a 40-year period. Source: PubMed Search, 02/10/2025.

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Table 12 PNS Innovations Discussed in the Literature

PNS Innovation	Description
Remote Electrical Neuromodulation (REN)	The device is placed remotely to target a more central focus, such as the upper arm stimulating peripheral nerves to reduce acute migraine
Brief Electrical Stimulation (BES)	Enhances neuronal regeneration after perioperative nerve injury by modulating the brain-derived neurotrophic growth factor (BDNF) pathways[84]
Neuroprosthetics	A mechanical device that can be controlled by or send sensory feedback to the patient's nervous system to generate PNS sensation mimicking their missing limbs.[277]
Percutaneous Stimulation	Treatment of the hypoglossal nerve and ansa cervicalis to treat obstructive sleep apnea.[278,279]

deliver innovative therapy across various atypical indications. The first step may be to collect a broader range of non-pain secondary outcome measures as part of future study design.

Future Product Development

Significant advances in the design of PNS-specific hardware have been made over the last decade, and current devices represent a substantial improvement over the initial implants that led to insurance coverage for this treatment.

There is still great potential to advance the physical and intangible technologies underpinning the therapy. New lead designs and miniaturization could expand the market for PNS by increasing physician confidence and comfort in placement across a variety of targets through collapsible lead tines for mobile areas such as joints and the axilla, smaller diameter lead designs for safety in facial, head, and neck applications, closed-loop PNS to improve consistency and reduce habituation and uncomfortable paresthesias, EMG feedback, resorbable leads for time-limited applications, and improved instrumentation to remove non-functioning implanted devices.[261,276] The future of pulse generators may lie in even smaller battery-inclusive, fully implantable devices or decoupled devices with external batteries with enhancements to minimize pairing issues with a greater tolerance for distance between the internal IPG/receiver and the external power source. Furthermore, smaller profiles and more form-fitting external devices will improve patient acceptance and compliance. Some innovations are already being reported in the literature in early form that may predict future products that could enter the market (Table 12).

Conclusion

Progress within peripheral nerve stimulation has brought us to a pivotal time in the field. Efficacy research, including RCTs yielding impactful data on outcomes, important work on healthcare utilization and economics is building the case for PNS among payors; data on secondary outcomes such as reduced opioid utilization, functional outcomes, and sleep as well as minimizing sick and disability leave all add to the value proposition of PNS for patients. The endless frontier of possibilities for nerve targets and indications and significant research and understanding in non-pain applications continue to expand. These consensus guidelines (See Table 13) provide an essential framework for skilled interventional pain practitioners, offering evidence-based recommendations intended to guide current clinical practice and support decision-making in this evolving field. These practitioners leading our field can help refine the education tracks of our training to optimize ultrasound skills, image-guided lead placement, and understanding of patient selection and nerve targeting. The future of PNS holds great promise powered by research, technological advancement, and the determination of practitioners who have seen transformative outcomes in their patients.

Consensus Guideline 18: High level evidence, including RCTs, on efficacy, healthcare utilization and economic data, as well as work focused on functional outcomes, opioid use, and indirect benefits all strongly support the use of PNS in patients with chronic pain. PNS is a well-established and evidence-based therapy for patients with chronic pain who have failed conservative treatment.

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Table 13 Summary of ASPN NEURON PNS Consensus Guidelines

Guideline Number	Topic	Statement
1	MOA	The mechanism of action (MOA) of Peripheral Nerve Stimulation (PNS) is complex. It includes modulation of local transmission of pain signals, inhibition of local A and C fibers with repeated stimulation, impact on local inflammatory mediators, endogenous opioids and neurotransmitters, gate control theory, and peripherally induced reconditioning of the central nervous system. Future research will help further describe the MOA of PNS.
2	Frequency	Low and mid-range frequency settings can be utilized for motor, sensory, parasympathetic, and sympathetic stimulation, respectively, and are well-studied in the literature. High and ultra-high frequency and high pulse width stimulation have each been shown to be associated with promising outcomes and should be the focus of further research.
3	Stimulation Types	PNS should be clearly differentiated in payor policies from the divergent and unrelated therapies of peripheral nerve field stimulation (PNfS), indirect percutaneous electrical stimulation (PENS), and transcutaneous electrical nerve stimulation (TENS). Peer-reviewed literature has extensively differentiated PNS from these treatments.
4	Nerve Blocks	While nerve blocks may be utilized in the early diagnostic and therapeutic phases of patient care, the literature does not support their prognostic value in predicting response to a PNS trial.
5	Device Choice	Given the wide variability between implantable, external, and hybrid decoupled PNS systems, as well as the rapid pace of innovation in the field, payor policies should defer to shared medical decision making by the treating physician and patient to maximize patient satisfaction, safety and efficacy across diverse clinical scenarios when selecting a PNS platform.
6	MRI Implications	MRI conditionality, and the variability and complexity of determining MRI implications in the setting of various devices, lead targets, orientation and patient factors, results in the requirement for physicians to consider MRI implications in partnership with the patient when selecting a PNS platform.
7	Imaging Guidance	Most PNS anatomic targets can be easily identified and accessed using ultrasound or fluoroscopic guidance while some targets may be preferentially identified using one modality or the other. Multiple factors including equipment availability and physician preference with imaging modalities may dictate an optimal approach for each case. Thus, payor policies should be inclusive of multiple approaches permitting physician selection of appropriate imaging guidance during PNS placement.
8	Strength of Evidence (Overall)	The evidence for PNS independent of nerve target or pain indication is strong. Due to the broad array of studies, including randomized controlled trials and large retrospective studies in addition to smaller, more focused studies, the overall evidence is Level 1, Grade A. It is important to note that responder rate and average pain relief are clinically significant and consistent across a variety of pain indications and nerve targets including within studies that examined multiple targets.
9	Strength of Evidence (Pain Indications)	In addition to strong evidence from RCTs and large retrospectives spanning a wide range of indications and nerve targets, focused studies support impactful treatment of a variety of anatomic targets, specific nerves, and specific painful conditions including shoulder (Level 1, Grade A), occipital nerve (Level 1, Grade B), sphenopalatine ganglion (Level 1, Grade C), pudendal nerve (Level 1, Grade B for voiding dysfunction and interstitial cystitis and Level II-3 Grade B for chronic pelvic pain), medial branch nerve (Level 1, Grade A), cluneal nerve (Level 1, Grade A), lower extremity (Level 1, Grade A), knee (Level 1, Grade A), ankle/foot pain (Level 1, Grade A), CRPS (Level 1, Grade B), lateral femoral cutaneous nerve (Level II-3 Grade B) and post-amputation pain (Level 1, Grade A).
10	Strength of Evidence (Post-Op Pain)	PNS in the post-operative period has demonstrated reduced opioid consumption, pain scores, and physical/emotional interference scores with Level 1 data. PNS is a highly effective treatment in the postoperative period, but payor policies are a restricting factor.
11	Strength of Evidence (Functional Indications)	A variety of nerve targets have demonstrated efficacy for non-pain applications, including posterior tibial nerve for urological issues (Level 1A), phrenic nerve for central sleep apnea (Level 1B), hypoglossal nerve for obstructive sleep apnea (Level 1A), occipital nerve for memory enhancement (Level 1B), common peroneal nerve for medication refractory restless leg syndrome (Level 1A), pudendal nerve to reduce urinary incontinence following radical prostatectomy (Level 1A), nerve stimulation for migraines, cluster headache, post traumatic stress syndrome, post stroke recovery (Level 1A) among numerous other inflammatory mediated disorders and median nerve for chronic tic disorder (Level 1B).
12	Surgical Practice	Best surgical practice for permanent PNS includes strategies to promote optimal wound healing, infection prevention, and prevent lead migration. Effective strategies include saline irrigation prior to closure, a deep enough cut down to allow for multi-layer closure, and closing in at least 2–3 layers when appropriate based on the implanted hardware.
13	Coding Compliance	Given the rapid advancement of PNS technologies and variability between platforms, physicians should be familiar with the details of the device they are utilizing and how it fits into the existing CPT code descriptions to ensure accurate coding.

(*Continued*)

Table 13 (Continued).

Guideline Number	Topic	Statement
14	Medicare and Medicare Advantage Coverage	PNS is a covered therapy under traditional Medicare. Medicare Advantage (Part C) must comply with established NCDs and LCDs. NCD 160.7 grants coverage of PNS. Physicians should pursue appeal for Medicare Advantage denials as Administrative Law Judges (ALJ) primarily rectify denials to ensure coverage is aligned with CMS guidance.
15	Commercial Insurance Coverage	Given the large body of evidence supporting the efficacy of PNS across multiple indications and nerve targets as well as individual studies focused on specific indications, payors should cover PNS for chronic pain in patients who have failed to improve with conservative treatment.
16	Psychological Evaluation	Given the lack of empirical evidence and a failure to establish a significant relationship between psychological factors and PNS outcomes, psychological evaluation before PNS should not be mandated by payors.
17	Healthcare Economics	Multiple healthcare economics analyses have concluded that utilization of PNS reduces healthcare visits and total medical costs. This evidence supports reductions in hospitalizations, other surgical procedures, and opioid use. Future prospective studies should incorporate these metrics as an additional outcome measure.
18	Strength of Evidence	High level evidence, including RCTs, on efficacy, healthcare utilization and economic data, as well as work focused on functional outcomes, opioid use, and indirect benefits all strongly support the use of PNS in patients with chronic pain. PNS is a well-established and evidence-based therapy for patients with chronic pain who have failed conservative treatment.

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