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EXPERT OPINION

Birds of a Feather Redux: Defining Ways to Stimulate the Peripheral Nervous System

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Abstract: Peripheral nerve stimulation (PNS) has become an essential component in the pain management plan for individuals suffering from peripheral nerve-mediated pain. The recent surge in interest in PNS can be attributed to the advancements in imaging techniques and the availability of minimally invasive stimulation systems along with a deeper grasp of PNS physiology. These advancements have made PNS more accessible to clinicians and patients alike. However, it is important to note that PNS requires a different set of technical requirements and skills compared to other pain management procedures. The work, knowledge, and surgical and interventional skillset required for PNS are in a class of their own. This article aims to educate and clarify the differences between procedures that may have similar names but are vastly different in terms of technology, expertise, and skill sets necessary for their safe implementation. Some of the procedures that this article will cover include indirect peripheral nerve field stimulation (PNfS), indirect percutaneous electrical nerve stimulation (PENS), PENS-Field Stimulation (PENFS), and transcutaneous electrical nerve stimulation (TENS). By understanding the differences between these procedures, patients and health-care providers can make informed decisions about the best approach for managing pain.

Keywords: peripheral nerve stimulation, neuromodulation, minimally invasive stimulation systems

Introduction

Neuromodulation is an evolving area of pain management that utilizes modern technology, including hardware platforms innovated by software that allows for the delivery of "electroceuticals" to the nervous system. It can be defined as the dosing of electrical current by implanted leads to treat pain as well as neurological dysfunction. Spinal cord stimulation (SCS) has been one of the foundations for the expansion of neuromodulation providing relief for chronic pain by modifying the neurotransmission of nerve signals at the level of the spinal cord, primarily at the dorsal columns.[1] In addition to the dorsal column target, dorsal root ganglion stimulation has been used to modify the peripheral nerve signal at the pseudo-unipolar nerve synapse in the epidural space.[2] In a more direct fashion, the peripheral nervous system can be impacted by stimulation of the fibers at the target nerve. In more recent years, the interest in impacting the C and A-delta fibers at the periphery has led to a growth in peripheral nerve stimulation (PNS) technologies. Several PNS systems have recently now also received Food and Drug Administration (FDA) approval for the treatment of chronic pain.[3] With the recent proliferation in peripheral nerve stimulation devices and methods, it is important that we define the various existing peripheral neuromodulation approaches. In this review, we hope to differentiate three distinct therapies including: Direct Peripheral Nerve Stimulation (PNS), Indirect Peripheral Nerve Field Stimulation (PNfS), and Indirect Percutaneous Electrical Nerve Stimulation (PENS). It is important that we differentiate these therapies, both functionally and procedurally, to better differentiate and describe these procedures and to clarify the various approaches as a reference for payers and providers alike. It is also important to align around these various taxonomies to assure understanding as we anticipate review of the data coming from the evolving data sets being created by research and registries in this arena.

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Peripheral Nerve Stimulation (PNS)

PNS is the application of electrical stimulation directly to a named nerve. Peripheral nerve stimulation actually preceded SCS, but widespread use was limited by lack of commercially available equipment and a poor understanding of indications and patient selection. The first report of electrical stimulation providing pain relief comes from Wall and Sweet in 1967.[4] In this study, eight patients with chronic neuropathic pain were given peripheral nerve stimulation. Parameters included 0.1ms pulses at a rate of 100 Hz for two minutes. Adjustments in stimulation were made until patients reported a tingling sensation in the affected area, resulting in greater than half an hour of pain relief in four of the eight patients. PNS had previously required extensive open dissection to locate the target nerve and then implant the neural electrodes. Such large and paddle-type neural electrode arrays required fascial grafts as insulation over the neural tissue to protect the nerve from both direct stimulation as well as neural impingement which was often intense and painful. These early PNS implants were sometimes helpful, but the invasive process of placement, complications and difficulty in using tools originally designed for spinal use made the method infrequent and was hampered by a lack of uniform recommendations for use.[3] In the past two decades, many specific leads were developed to target the peripheral nerve, and in a landmark IDE study, PNS was approved by the FDA for specific use. This prospective randomized study implanted 94 patients. Active stimulation patients had a greater response rate than the control group ($p = 0.0048$) in the primary effectiveness goal. The treatment group reduced pain by 27.2% from baseline to month three compared to 2.3% in the control group ($p < 0.0001$).[5] While this early work led to FDA approval, outcomes and utilization were hampered by lack of standardized approaches to the variety of nerves targeted, as well as the lack of consensus on techniques to keep the electrode in the desired position, to minimize surgical dissection and to avoid nerve damage from the electrode proximity.

Significant improvements in image-guidance, especially use of ultrasound, have enabled placement of percutaneous leads adjacent to, and in increasingly safe proximity to nerves allowing for procedural standardization and minimization of surgical trauma. In addition, lead modifications, such as tines to support lead stability and increased lead plasticity, have served to reduce migration and improved outcomes.

There have been several proposed mechanisms of action for PNS efficacy. Peripheral mechanisms consist of disruption of nociceptive afferent fibers, modification of the local microenvironment, and downregulation of inflammatory mediators.[6] Reversible conduction block has also been a proposed mechanism of action allowing for fast-acting and fast-reversing peripheral nerve block. This was primarily seen in animal models for the pudendal nerve with high-frequency alternating-current (HFAC) sinusoidal waveforms.[7] PNS also may modulate or recondition higher-level central nervous system (CNS) centers including the dorsal lateral prefrontal cortex, somatosensory cortex, anterior cingulate cortex, and parahippocampal areas. Modulatory effects of PNS systems on neural activity may also impact the spinal columns and lead to neuroplasticity through changes in endogenous neurotransmitters and NMDA pathways.[6,8]

Historically, percutaneous PNS devices were used for chronic neuropathic pain in patients that had either contraindication to SCS devices or were better suited to peripheral neuromodulation. Currently, the use and indications of peripheral nerve stimulators are expanding. Table 1 includes a list of indications for several commercially available PNS devices FDA-cleared or approved for the treatment of pain.

There have been several recent advantageous advances in PNS devices. The ability to place percutaneous leads under visual guidance from fluoroscopy or ultrasound allows for improved targeting of the specific peripheral nerve target, potentially improving safety, lead stability, and pain relief. There have also been advances in diminution of leads and generators, allowing for reduced invasiveness of lead and pulse generator implant procedures. Some of these devices include very small, implanted integrated systems of leads and receivers with external power sources. Additionally, other systems include ultra-minimally invasive percutaneous systems with the ability to provide direct nerve stimulation. This variety of options allow nuanced treatment for various painful conditions and co-morbidities.

It is important that we delineate the categories of use for direct PNS.

1. Trial or temporary use of direct PNS often can be used to help select proper patients and give an idea of response. In these settings, the device is removed after 3 to 14 days, and a permanent device is planned if the patient achieves acceptable relief, without deleterious effects.
2. Direct PNS treatments can be performed by a novel, coiled lead designed to reduce infection risk, allowing for long-term treatment up to 60 days. Not intended as a trial, this direct treatment doses the nerve for approximately

Table 1 FDA-Cleared or Approved PNS Devices for the Treatment of Pain

Company	Device	FDA Indication
Bioventus	StimRouter Neuromodulation System	• Pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (eg, medications).
Mainstay Medical	ReActiv8	• Indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3. • As an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction.
Nalu Medical	Nalu Neurostimulation System	• Indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach.
SPR Therapeutics	SPRINT PNS System	• Indicated for up to 60 days for symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain. • Symptomatic relief of post-traumatic pain. • Symptomatic relief of post-operative pain.
Stimwave	StimQ PNS System	• Indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach.

60 days, but may generate a much longer-term response that negates the need for permanent, indwelling direct PNS implant. This long-term response to a two-month dose delivery is thought to be related to protracted if not permanent changes in central neuroplasticity.[8]

3. A permanent implant may be placed in those who have experienced pain relief following placement of a temporarily implanted lead without sustained improvement. The FDA definition of an implant is as follows: "A device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants."[9] In the area of PNS, the receiver is often placed in the body with the programming being delivered via an external source via Bluetooth or external skin transmission. These "wearables" continue to evolve.
4. Direct PNS for pain relief as the result of motor recruitment involves the stimulation of a named nerve resulting in the activation of the nerve's subserved group of muscles. Proposed mechanisms for sustained pain relief may include changes in central plasticity following a 60-day treatment or stabilization of the anatomy subserved by that muscle group following permanent PNS system implantation.[10,11]

PNS Key Points

- Anatomical understanding of the peripheral nervous system and innervations of regions of the body is paramount to treatment success. Stimulation of a named nerve is required to achieve an acceptable outcome. If the painful condition does not exist within the watershed of a named nerve, then PNS should not be offered or performed.
- The ability to use fluoroscopy, ultrasound, or the surgical skill of open dissection and implantation is required for effective lead placement. Mapping by direct patient interaction during nerve stimulation may be used to ensure acceptable lead location.
- PNS devices require anchoring of leads to prevent lead migration. This anchoring by the physician either by lead tine, or by direct ligation of the lead to anatomy, or by both may require suture placement around a silastic anchor.

- A PNS lead can be implanted as a short-term trial or as a much longer-term treatment, and when warranted, the patient may be advanced to receive implantation of a permanent PNS system. Specific criteria should be followed to determine the need for placement of a permanent device.
- Placement of a permanently implanted PNS system to deliver medial branch nerve stimulation for the treatment of multifidus muscle dysfunction does not require a trial based on Level 1 data.[11] It is as yet unknown whether a PNS trial could improve the identification of responders and non-responders in this population.[12]

Peripheral Nerve Field Stimulation (PNfS)

PNfS has been proposed for the treatment of chronic cervical, thoracic and lumbar pain. In this procedure, leads are placed in the subcutaneous tissues within the region of pain to stimulate the cutaneous afferents rather than any named nerve associated with the patient's pain. This, in turn, creates a broad stimulation of the area or "field" of pain, which is neurally downstream from the primary anatomic source of pain. The mechanism of action is thought to be multifactorial, including increased local blood flow, blocking cell membrane depolarization, and increasing systemic endogenous endorphins, impacting the nociceptive threshold in the target zone.[3] An advantage of PNfS is the ability to be less specific in targeting a specific nerve due to the broad coverage created by the field generated. Overall PNfS may carry less risk of nerve-injury related complications when compared to other neuromodulatory procedures; however, lead migration, erosion, and infection with the device can occur.

The disadvantage of PNfS is the lack of a specific target that makes patient identification and selection much more difficult. The "field" is purely subjective with no specific physical findings, neurodiagnostic studies, or patient-specific characteristics. This could lead to poor selection and a higher failure rate, which could potentially lead to patient harm and poor health-care utilization. The other major disadvantage surrounds the lack of required technical training and skill, which could lead to over-utilization.

Key Differences Between PNfS and PNS

- PNS is well defined and has significant evidence-based support with high-level data supporting its use. PNfS does not have high-level support in the peer reviewed literature.
- In comparison to PNfS, PNS requires physician knowledge of peripheral neuroanatomy and surrounding vascular and osseous anatomy. PNfS conversely requires little anatomical knowledge and minimal interventional skills, thus the physician work required is much less.
- PNfS does not need specific placement, is less technically demanding, and less intellectually demanding since no knowledge of subcutaneous anatomy is required; however, for permanent implantation, surgical skill is required for lead ligature, tunneling and pulse generator implantation.
- PNS devices require knowledge and use of fluoroscopy, ultrasound and surgical skill for proper placement of leads.

Percutaneous Electrical Nerve Stimulation (PENS), PENS-Field Stimulation (PENFS), Transcutaneous Electrical Nerve Stimulation (TENS)

PENS involves the temporary, in-clinic stimulation of subcutaneous nerves in the painful region. PENS uses electrical stimulation to relieve pain by targeting specific peripheral nerves. The procedure involves inserting thin needles into the skin near the affected nerves and then passing an electrical current through the needles to stimulate the nerves. PENFS, is a variation of PENS and uses a low-frequency electrical current to stimulate the skin and underlying tissues in the area of pain rather than specific nerves. The goal of both is to relieve unremitting, chronic pain by placing needle-based electrodes through the high-resistance outer layers of skin to stimulate peripheral sensory nerves. PENS does not involve the implantation of leads but rather the insertion of needle-based electrodes generally placed during in-clinic treatment sessions administered multiple times a week, over several weeks.[13] The electrodes send out low voltage currents to the area of pain in an attempt to desensitize the nerve endings.

TENS is a device that uses electrical current to stimulate the nerves to relieve pain; the currents are delivered to the skin through electrodes that are placed on or near the area of pain. Neither PENS nor PENFS appear to offer any apparent benefits over TENS, however all do indeed confer benefits in pain relief.[14] Although PNS is considered relatively low risk, PENS, PENFS, and TENS are useful modalities, and may present even lower risk to the patient. A detailed understanding of pathology, anatomy, human disease, and surgical/interventional skill is requisite for PNS. PENS/PENFS can be administered by an assistant, is performed in the clinical setting and is materially different than PNS.

Key Differences Between TENS, PENS, PENFS and PNS

- In contrast to PNS, PENS and PENFS are more similar to TENS in that the cutaneous, terminal fibers of sensory nerves in the skin are the target.
- PENS and PENFS use micro needles to pass through the outer layers of the skin and thus reduce resistance to stimulation seen with TENS.
- PENS, while possibly efficacious, lacks the increasingly robust prospective body of data that supports the use and long-term effect of PNS. PENS does not meet the criteria to be considered an implant according to FDA criteria.
- TENS placement is not technical in nature, and PENS is much less complex than PNS, and thus does not require detailed anatomical knowledge.
- TENS and PENS both may offer pain relief to the patient, and may be considered in situations where surgery is contraindicated. Additionally, while PENS requires a clinic visit, TENS can safely be administered by the patient.

Conclusion

The use of PNS is an important part of the pain treatment algorithm for those with pain subserved by peripheral nerves. PNS is currently enjoying a renaissance of interest following clinician access to new imaging modalities, and the commercial availability of stimulation systems that significantly reduce the surgical trauma required to offer direct nerve stimulation. The work, knowledge, and surgical and interventional skillset requisite of PNS exists in a wholly different category than the other procedures discussed. This paper serves to educate regarding the differences between procedures with similar sounding names, yet set apart by a vast chasm of technology, skill and expertise when pursuing their safe utilization.

Disclosure

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