The Future of Peripheral Nerve Stimulation

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Abstract
The field of peripheral nerve stimulation (PNS) is now experiencing a phase of rapid growth in number of patients, number of implanters, number of indications, and procedure types. This, however, appears to be only a beginning of major developments that could revolutionize the field of PNS. It is expected that the progress in PNS will continue simultaneously in several directions as new indications, new stimulation targets and new device designs evolve in the foreseeable future. Responding to a major need for safe and effective pain treatments and following a general trend toward less-invasive and nondestructive interventions, PNS has the potential of becoming a premier pain-relieving modality that will be used instead of or in combination with existing more established approaches such as spinal cord stimulation and pharmacological pain control. Recent technological advancements are cause for considerable optimism regarding the development of PNS and are likely to be a beginning of a major overhaul in our perception of PNS approaches. Expanding the number of applications will without question strengthen the field of PNS. The turning point, however, will not occur until sufficient scientific evidence is gathered to unequivocally prove its safety, clinical efficacy and cost-effectiveness, and when PNS applications become officially endorsed through regulatory approval of each indication. Such changes will allow implanters to use approved devices for approved indications – instead of the contemporary ‘off-label’ use – and at the same time give device manufacturers a chance to market these devices and support education on their appropriate use.

Peripheral nerve stimulation (PNS) is estimated by some to be the most rapidly growing field of neuromodulation. Despite its long history (first introduced in the early 1960s, even before the ‘gate control’ theory of pain was introduced), PNS has not become a mainstream pain-relieving modality, although many enthusiastic centers continued to use the technique on a regular basis. Currently, there is a significant increase in the number of patients treated with PNS and a corresponding surge in the number of publications dealing with this particular subject.
Current State of PNS: Key Issues

Accumulation of Objective Evidence
PNS, though a very promising methodology for alleviating medically refractory neuropathic pain conditions, is largely performed at present under research protocols or on an ‘off-label’ basis. In practice, evidence for its effectiveness based on randomized controlled trials (RCTs) is lacking. Mobbs et al. [1] have recognized the difficulty in pursuing such studies; they point out that a study that included randomizing patients to a ‘best medical therapy’ versus a peripheral nerve stimulator would be ideal, although not feasible as these patients are referred because they have failed the ‘best medical therapy’ option. In particular, two parameters necessary for conducting fully RCTs, i.e. blinding and sham control, are difficult to achieve in the PNS case. Patients implanted with a PNS system have been ‘taught’ to recognize associated paresthesias at the offending dermatome as an indicator of good system function; lack of such a sensation, therefore, precludes blinding of the procedure. Furthermore, the high cost of PNS technology renders it unethical and inexpedient to implant such expensive systems for satisfying only the ‘sham control’ component of a randomized control study without also offering patients the desired therapy. Nevertheless, it becomes obvious that to shape a brighter future for PNS, well-performed prospective RCTs of novel designs are needed to determine the true efficacy, best indications and most appropriate parameters of stimulation.

Understanding the Mechanism of Action
Experimental and basic research into the mechanism of action of PNS will help gain an understanding of its effects on pain and on improving organ function but, so far, such research is rather limited. Multicenter studies are under way to further define its mechanism and pathophysiology. For instance, it is noteworthy that syndromes in which the pain is mainly felt in a specified nerve distribution, e.g. the ophthalmic division of the trigeminal nerve, can be modified by stimulation in the corresponding dermatome. This significant observation implies that the key part of PNS may be closely related to brain function and, particularly, of brain plasticity. Apparently, when such observations are substantiated by research and clinical evidence, they are expected to refine the existing surgical indications of PNS, justify individual tailoring of appropriate treatment approaches, and contribute in optimizing implanted systems for each sufferer.

Cost-Benefit Analyses
In a modern era of medicine, cost containment has evolved as a major concern, the field of PNS being no exception. In this context, evidence-based medical practice increasingly becomes a fundamental issue for acceptance and financial support from third-party payers. Simpler and less-expensive devices will lead to further popularization and expansion of the technique. Moreover, if sufferers are trialed
objectively prior to implantations of the complete system, the cost of unnecessary system implantations will be lowered. In spite of the limitations inherent in conducting RCTs for the evaluation of implantable stimulators and long-term efficacy of PNS treatments, it is apparent that addressing the lack of level 1 and/or level 2 evidence for this neuromodulatory treatment should be a priority in the coming years. Medical industry and neuromodulation practitioners should continue to support relevant research by providing more advanced systems and conducting well-designed studies.

**Electrodes and Generators**

As mentioned earlier in this book, PNS procedures are currently performed with devices that are not specifically approved for this application. Most of the time, surgeons are using devices designed and approved for spinal cord stimulation (SCS). Those few electrodes such as OnPoint (Medtronic, Minneapolis, Minn., USA) and radiofrequency receivers Mattrix and X-Trel (Medtronic) and Renew (St. Jude Medical Neuromodulation, Plano, Tex., USA) that are approved for PNS are rarely used these days – mainly because of the patients’ and practitioners’ preference for implantable pulse generators and other electrode types [2]. Electrodes and generators that are dedicated for PNS applications are expected to facilitate surgical procedures, minimize hardware-related complications and maximize confidence of both practitioners and sufferers in using these promising treatment modalities.

**Future Prospects of PNS**

There is no doubt that PNS will continue to grow and while its future is bright, it is likely to develop in several directions. This account will attempt to review the potential for growth; while predicting the future is always difficult, and it is possible that some of these predictions may never materialize, others may become clinical reality even before this work is published.

**New Indications**

In the past, PNS has been used for a variety of focal neuropathic pain conditions [3]. The most common indications have been the pain from peripheral nerve injury, complex regional pain syndromes (CRPS) types I and II, postsurgical and post-traumatic neuropathies, pain from neuromas and amputation stumps. More recently, PNS has been successfully used for treatment of occipital neuralgia, trigeminal neuropathy, intercostal neuralgia, post-thoracotomy pain, inguinal and abdominal pain, postherpetic neuralgia in the face and body, cervicogenic headaches, migraines and cluster headaches. Chronic pain in the low back and in the neck, two very common clinical conditions, have also been successfully treated with PNS.
A new trend that may revolutionize the field is an attempt to treat not only focal neuropathic conditions, but also diffuse neuropathic pain. The best example of this is the use of PNS for treatment of pain in fibromyalgia [4, 5] – an idea that came about as a result of the rather serendipitous discovery of ‘whole-body’ pain relief from upper occipital PNS when it was used to control occipital pain associated with this disorder. The authors called this approach ‘C2 area neurostimulation’ as their electrodes were placed higher than the usual occipital PNS landmarks. Based on results of this uncontrolled series of patients, a larger randomized prospective study is currently in progress.

As a component of the surgical armamentarium in the field of pain management, PNS is likely to continue being considered for three distinct categories of conditions. The first of them includes focal neuropathies where it may seem intuitive to stimulate the involved nerve rather than attempt stimulation of the nerve roots or the spinal cord. Traumatic neuropathies, CRPS, as well as cases of postherpetic neuralgias and recurrent or persistent nerve entrapment symptoms that do not respond to focal decompressions also fit into this category.

Second would be those conditions in which the neuropathic pain cannot be attributed to a single nerve but which are also known to respond poorly to the ‘classical’ pain-relieving interventions such as SCS; this category includes low back pain, post-herniorrhaphy inguinal pain, post-thoracotomy pain, and other regional, rather than focal, pain syndromes.

The third group of indications includes those for which PNS may be the only neuromodulation option – such as patients with occipital neuralgia who may be considered for some destructive interventions (neurectomies, ganglionectomies) – or for those where surgery is generally not considered an option at all (migraines). Cluster headaches, which have traditionally been treated with medications, should also be included. PNS is essentially a less invasive alternative to recently introduced hypothalamic deep brain stimulation.

A major shift in thinking is the potentially useful PNS application in the treatment of not only chronic neuropathic pain but also nociceptive pain conditions. The recent introduction of PNS for pain of an osteoarthritic nature affecting the neck [6] and extremities [7, 8] may change the way we look at PNS in particular and neuromodulation in general.

The scope and volume of PNS are expected to increase dramatically. While most traditional and some newer applications of PNS are comparatively small in number (peripheral nerve injuries, CRPS, cluster headaches), quite a few of the newer and potential indications are extremely prevalent (migraines, post-herniorrhaphy pain, low back pain, etc.). Even if only a small percent of these patients might qualify for PNS use, the volume of PNS will expand dramatically. Before this can occur, two conditions must be met. One is that scientific data must conclusively demonstrate safety, efficacy and cost-effectiveness of PNS, and the other, related to the first one, is regulatory approval of PNS.
**New Targets**

In addition to new indications, development of new targets for PNS is expected to add momentum to growth in this field. Currently, PNS applications are focused on large (named) peripheral nerves – so-called ‘true PNS’ – and on unnamed nerve or nerve endings – so-called ‘subcutaneous PNS’ or ‘peripheral nerve field stimulation’.

Whenever one discusses PNS, the stimulation of peripheral and cranial sensory nerves comes to mind. In addition to this, there is some possibility of getting pain relief from stimulating nerves that are not involved with somatic sensory processing. An example of this may be stimulation of the vagus, and the initial experience with vagal nerve stimulation for treatment of migraines, cluster headaches and other daily headache conditions [9–11] is encouraging.

Since the peripheral nervous system consists of a number of components including large nerves, their divisions into smaller nerve branches, nerve roots and nerve plexuses, PNS targets are not limited to individual nerves. One of these targets has already been explored: implantation of a PNS device over the brachial plexus was recently described [12]. More PNS uses in the treatment of plexopathies (brachial, cervical, lumbosacral) are expected to occur in the future; selective stimulation of targeted parts of the plexus awaits innovated approaches and site- or target-specific technological developments.

Other potential PNS targets are nerve ganglia. It is appealing to consider neuro-modulation of sympathetic nerves and their ganglia. While stimulation of sympathetic ganglia or sympathetic chain may at first sight appear theoretical, stimulation of the sphenoplatine ganglion has already become a target and stimulation of sensory nerve ganglia is already a reality. The gasserian ganglion has been a stimulation target for the treatment of neuropathic pain in the trigeminal distribution for many years [13, 14]. A recent multicenter study of dorsal root ganglia (DRG) stimulation suggests that this modality may provide additional benefits in chronic pain treatment. This will most likely be a frequent target once appropriate devices become available.

The junction between central and peripheral nervous systems – the nerve root – has been subject to PNS. Stimulation of both spinal [15] and trigeminal [16] nerve roots has been undertaken. With development of new hardware and stimulation paradigms, nerve root stimulation may become one of the most promising PNS applications as an alternative to the use of SCS.

One issue that has been addressed in the past, but never resolved, is the use of PNS on mixed nerves. Having the capability of selective stimulation of sensory fascicles or even selective stimulation of certain fiber types, will allow the application to achieve maximal sensory stimulation without associated and unwanted motor stimulation.

**Combination of PNS with Other Neurostimulation Methods**

Finally, there is a possibility of combining PNS with existing pain-relieving approaches analogous to multimodal pain control. ‘Hybrid’ techniques that combine PNS and SCS [17–19], the combined use of stimulation of nerve and ganglion, or nerve and
nerve root, or the use of PNS in combination with focal or systemic pharmacological interventions is appealing. The latter approach may include both anesthetic drugs and newer agents that may sensitize nerves to the effect of neurostimulation.

**New Devices**
The most fascinating developments are now occurring in the field of medical technology as companies pursue PNS applications as their primary clinical objective. Not only are there new electrodes and generators, but new devices based on very different principles specifically conforming to the demands of PNS are being developed. Although the conceptual information presented here is derived from the authors’ understanding of the current state of affairs, the factual data are provided from publicly available sources in order to obviate any existing confidentiality agreements and intellectual property issues.

A single piece ultra-compact electrode/generator combination (BION®, Boston Scientific, Valencia, Calif., USA) has been used in many clinical studies [20, 21]. Initially developed for stimulation of peripheral nerves as a part of functional electrical stimulation approaches, BION was subsequently employed for chronic pain treatment. Most notably, it was used in the treatment of primary headaches [22] and hemicrania continua [23]. With its very small size and cylindrical shape, implantation is significantly simpler compared to the multicomponent systems, but its single contact setup and mobility within soft tissues have been problematic and prompted a series of technological advancements [24].

Importantly, having an integrated electrode and generator design allows one to eliminate a common problem encountered in PNS cases – the need for extension cables to cross mobile areas such as large joints in the extremities, neck or back. There are, however, other solutions for this issue. The StimRouter® device (Bioness, Valencia, Calif., USA), for example, is based on an integrated electrode and receiver that is powered transcutaneously by an external pulse generator. The electrode used in the published study [25] has an external component used for measurement of received electrical current, but the final version of the device is fully implantable such that three electrode contacts are positioned next to the target nerve while the opposite end of the lead is situated under the skin in order to receive electrical energy from the external pulse transmitter that is attached to the skin surface.

A somewhat similar approach is used by the SAINT® (Subcutaneous Array of Implantable Neural Transponders) system (Microtransponder, Dallas, Tex., USA) where the fully implanted electrode is powered by an external stimulator using an electromagnetic induction principle [26]. In this case, the implanted stimulator is 3.1 mm long, 1.5 mm wide and 0.3 mm thick. In addition to PNS application for treating chronic pain, this device is now being tested for stimulation of the vagal nerve in the treatment of tinnitus and neurological deficits after traumatic brain injury.

Miniaturization and simplification are not the only directions for technological advancement. The development of new stimulation parameters, waveforms...
and paradigms aimed at PNS applications will be supplemented by the creation of dedicated PNS systems. These, in turn, will have specially designed insertion and anchoring tools, all this will result in the further improvements of safety and efficacy of PNS.

Further, the standard practice of using biologically inert smooth metal surfaces for the current electrode contacts will undoubtedly change – the electrode contacts in the future may be of different texture to change the pattern of material interaction at the device/nerve interface. The contact may be concave instead of flat or convex and it may be supplemented by small ‘micro-teeth’ that both attach to and partially penetrate the epineurium in order to decrease the chance of migration or, more importantly, improve the device interface with the underlying fascicles. These future electrode contacts may have a special antibiotic coating to reduce the incidence of local infection or incorporate new materials at the terminal electrode contacts to facilitate electrical transmission to potentiate effects of the stimulation.

**Conclusion**

Given the current trend and increasing popularity of PNS as another means to manage chronic pain, one may expect to see growth in all aspects of this therapeutic modality. The development of new indications, new stimulation targets, and new equipment choices will strengthen PNS as a therapeutic field. The turning point will occur when sufficient scientific evidence is garnered to unequivocally prove safety, clinical efficacy and cost effectiveness of PNS and when PNS applications become officially endorsed through regulatory approval. These developments will allow implanters to use approved devices for approved indications – instead of their contemporary ‘off-label’ basis – which at the same time will signal to device manufacturers to both market these devices and support education for their rational use.

**References**


