



REVIEW

Peripheral Nerve Stimulation for Chronic Pain: A Systematic Review of Effectiveness and Safety

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ABSTRACT

Peripheral nerve stimulation (PNS) was the first application of neuromodulation. Widespread application of PNS was limited by technical concerns. Recent advances now allow the percutaneous placement of leads with ultrasound or fluoroscopic guidance, while the

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transcutaneous powering of these leads removes the need for leads to cross major joints. This systematic review was written to assess the current status of high-quality evidence supporting the use of PNS for pain conditions treated by interventional pain physicians. The available literature on PNS, limited to conditions treated by interventional pain physicians, was reviewed and the quality assessed. Literature from 1966 to June 2021 was reviewed. The outcome measures were pain relief and functional improvement. One hundred and two studies were identified. Five randomized controlled trials (RCT) and four observational studies, all case series, met the inclusion criteria. One RCT was of high quality and four were of moderate quality; all four case series were of moderate quality. Three of the RCTs and all four case series evaluated peripheral nerve neuropathic pain. Based upon these studies, there is level II evidence supporting the use of PNS to treat refractory peripheral nerve injury. One moderate-quality RCT evaluated tibial nerve stimulation for pelvic pain, providing level III evidence for this indication. One moderate-quality RCT evaluated surgically placed cylindrical leads for cluster headaches, providing level III evidence for this indication. The evidence suggests that approximately two-thirds of patients with peripheral neuropathic pain will have at least 50% sustained pain relief. Adverse events from PNS are generally minor. A major advantage of PNS over spinal cord stimulation is

the absence of any risk of central cord injury. The study was limited by the paucity of literature for some indications. No studies dealt with joint-related osteoarthritic pain.

Keywords: Peripheral nerve stimulation; Neuropathic pain; Neuropathy; Pelvic pain; Cluster headache

Key Summary Points

Chronic pain arising from peripheral nerve disorders is becoming more fully appreciated as a source of chronic pain.

Peripheral nerve stimulation has benefited from technological advances which allow its wider application.

There is a need for a systematic review, with inclusion of the underlying methodology supporting that review, of the high-quality literature supporting the use of peripheral nerve stimulation.

Five randomized controlled trials and four observational studies of high or moderate quality support the use of peripheral nerve stimulation.

The best evidence is for neuropathic pain.

INTRODUCTION

Popular conceptions of the cause of pain vary over time. In the early twentieth century, the sacroiliac joint was thought to be the primary source of low back pain [1]. With Mixter and Barr came the appreciation that the intravertebral disc was an important source of pain [2]. With Kuslich's intraoperative studies, the facet joint formed the third leg of this triad [3]. These studies focused primarily on the low back.

Only a small number of studies have focused on peripheral nerve disorders [4, 5]. Following the publication of a comprehensive text on

peripheral nerve entrapments [6], the role of peripheral nerves as a source of pain and as an avenue of treatment has become more widely recognized.

Neuromodulation of peripheral nerves to treat pain is an area of great intellectual activity. While spinal cord and deep brain stimulation have greater current public and clinical awareness than peripheral nerve stimulation (PNS), PNS antedates both. Melzack and Wall tested their gate theory of pain in 1965 by inserting electrodes into their own infraorbital foramina, generating paresthesia [7]. It is important to clarify that for the purposes of the Food and Drug Administration (FDA), PNS does not include stimulation of the dorsal root ganglion (DRG), although anatomically it is agreed that the DRG is located in the periphery. The proposed mechanism of action involves a gating mechanism whereby stimulation of large-diameter sensory neurons would “close the gate,” reducing transmission of painful stimuli from small nociceptive fibers to the brain [8]. Stimulation is delivered from a system which is designed to be placed adjacent yet still remote from the nerve to selectively activate $A\alpha/\beta$ fibers while avoiding $A\delta/C$ fiber activation—a process commonly known as remote selective targeting. Typically, stimulation of mixed nerves at 100 Hz can selectively activate the largest sensory afferents; however, stimulation of mixed nerves at a low frequency such as 12 Hz can equally stimulate muscle efferent fibers, leading to remote selective targeting. In contrast to conventional “intimate” electrode placement, it has been hypothesized that percutaneous PNS systems may activate a greater proportion of large-diameter fibers while avoiding the unwanted activation of nociceptive afferents [79]. Shealy first applied spinal cord stimulation about 18 months after Wall and Melzack's studies, in March 1967 [9]. The initial experimentation with PNS used both open and percutaneous placement of leads [10]. In the mid-1980s, surgically placed paddle leads were trialed. Around 1999, percutaneous leads began to be used for diagnoses such as occipital headaches [11].

PNS has now entered a fourth phase with the introduction of systems that provide power

percutaneously to the lead directly over the site of implant. This major advancement allows clinicians to avoid placing a lead (or extension) across a joint, lowering the risk of lead fatigue and migration [12, 13]. PNS has been applied for conditions including plexus injuries, mononeuropathies, post-amputation pain, back pain, sacroiliac joint pain, headache, facial pain, arm and limb pain, and joint pain [14]. It has also been used for postoperative pain, hyperactive bladder, and fecal incontinence.

The role of the current review is to assess the current status of the evidence supporting the use of neuromodulation of peripheral nerves to treat subacute or chronic pain, including treatment of cranial/facial pain, nerve entrapment/injury, joint degeneration, or axial or radicular pain. This systematic review will assess the literature on PNS for nerve entrapment, joint pain, or axial or radicular pain up until June 2021.

METHODS

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials and observational studies [15–30].

Criteria for Considering Studies for this Review

Indications which would not normally be treated by interventional pain management physicians, such as hyperactive bladder, acute pain, fecal incontinence, neurological disorders such as tremor, and psychological disorders are not covered by this review.

Only studies dealing with implanted devices were included. Only PNS, not peripheral nerve field stimulation, will be evaluated. PNS refers to the placement of a lead near a specific peripheral nerve. Peripheral nerve field stimulation (PNFS) refers to the placement of a lead subcutaneously in the general area of pain [31]. Percutaneous electrical nerve stimulation (PENS), in which multiple small acupuncture-like electrodes pierce the skin and provide

stimulation [32], is not reviewed. Medicare has used the term “percutaneous electrical nerve stimulation” to describe PNS, confusing the issue [33].

PNS was first used for the occipital nerve [11]. Occipital nerve stimulation has been the subject of many systematic reviews showing effectiveness [34–40], so it is not covered in this review. Stimulation of other nerves for headache will be reviewed.

PNS for pelvic pain has been the subject of systematic reviews in the gynecologic literature [41, 42] and is included here, as interventional pain physicians regularly treat pelvic pain. Shah et al. also described the numerous techniques of PNS for chronic pelvic pain, particularly pudendal neuralgia [43].

Deer et al. published a comprehensive systematic review of spine neurostimulation nerve stimulation [44]. This review differs in that it includes databases not previously utilized and non-randomized studies, and excludes both occipital and peripheral nerve field stimulation.

Deer et al. and Wu et al. each published a systematic review of PNS [45, 46]. The current review includes subsequent literature and provides a more detailed presentation of the underlying methodology.

Types of Studies

Randomized controlled trials (RCT).

Non-randomized observational studies, including cohort studies, case-control studies, cross-sectional studies, and case series.

Case reports and reviews were evaluated for adverse effects.

Types of Participants

Patients receiving peripheral nerve stimulators for the treatment of pain, excluding occipital nerve stimulation for headache.

Types of Interventions

Percutaneous PNS.

Types of Outcome Measures

The primary outcome measure was pain relief.

The secondary outcome measures were functional status improvement, change in

psychological status, or a reduction in either opioid use or reliance on health care interventions.

Literature Search

Searches were performed from the following sources, limited to articles published in English:

1. PubMed from 1966
<https://www.ncbi.nlm.nih.gov/pubmed>.
2. Cochrane Library
<https://www.cochranelibrary.com/>.
3. Google Scholar
<https://scholar.google.com/>.
4. Embase
<https://www.embase.com>.
5. Scopus
<https://www.scopus.com/>.
6. Previous systematic reviews
7. Clinical Trials
<https://clinicaltrials.gov/>.
8. Communication with investigators active in the field.
9. Bibliographies of reviewed papers were also examined.

The search period was from 1966 through June 2021.

Search Strategy

The following search terms were used with PubMed:

(((((peripheral nerve stimulation) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial” [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp]) NOT (animals [mh] NOT human [mh]))) NOT (bladder)) NOT (stroke)) NOT (vagus)) NOT (deep brain).

Data Collection and Analysis

Two review authors independently, in an unblinded standardized manner, developed search criteria, searched for relevant literature, and selected the manuscripts.

Selection of Studies

Two review authors screened the abstracts of all identified studies against the inclusion criteria. All articles with possible relevance were then retrieved in full text for comprehensive assessment of internal validity, quality, and adherence to inclusion criteria.

Inclusion and Exclusion Criteria

RCTs with statistical analysis and with at least 20 patients in the study were included. Observational studies, including case–control, cohort, cross-sectional, or case-series design, were included if they reported on at least 20 patients. Reports without appropriate diagnoses, non-systematic reviews, book chapters, letters to the editor, and case reports were excluded.

For any condition, if there were more than five randomized trials, non-randomized or observational studies were not utilized.

Methodological Quality or Validity Assessment

The quality of each individual article used in this analysis was assessed by:

1. Cochrane Review criteria [26] (Table 1),
2. American Society of Interventional Pain Physicians (ASIPP) Interventional Pain Management techniques–Quality Appraisal of Reliability and Risk of Bias Assessment (IPM–QRB) for randomized trials [47] (Table 2), and
3. ASIPP Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM–QRBNR) for non-randomized and observational Studies [48] (Table 3).

Tables 1, 2, and 3 are shown in Appendix I, Supplementary Material.

Utilizing Cochrane review criteria of risk of bias, studies meeting the inclusion criteria with

at least 8 of 12 criteria were considered high quality and 5–7 criteria were considered moderate quality. Those meeting fewer than five criteria were considered as low quality and were excluded.

Based on ASIPP criteria for randomized trials and non-randomized studies, the studies meeting the inclusion criteria scoring of 32–48 were considered high-quality trials, studies with scores between 21 and 31 were considered moderate quality, and studies scoring 20 or less were considered low quality and were excluded.

The Cochrane review criteria indicate that the primary analysis should only be on the results of RCTs and that if results from studies other than RCTs are included, the data from the observational studies should be analyzed separately and contrasted with the results of the RCT analysis [26]. More recently, the move has been to include all study types, including non-randomized studies, such as case series [49]. This review will both incorporate all available evidence and separate the discussion of the various study types.

Data Extraction and Management

Methodological quality assessment was performed by the authors, with groups of two authors reviewing multiple manuscripts. The assessment was carried out independently in an unblinded standardized manner to assess the methodological quality and internal validity of all the studies considered for inclusion. Any discrepancies in the methodological quality assessment were evaluated by a third reviewer and settled by consensus.

If there was conflict of interest with a reviewed manuscript, the involved author(s) did not review the manuscript for methodological quality assessment.

Meta-Analysis

If the literature search provided at least three randomized trials meeting the inclusion criteria and if they were clinically homogeneous for each modality and condition evaluated, a meta-analysis was performed.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Outcome Measurements

Previously, the consensus was that at least a two-point change on a pain scale of 0–10 was necessary to document a clinically meaningful change [50]. Because the body of evidence does not permit conclusions about the magnitude of change in either the numeric rating scale (NRS) or visual analog scale VAS that is clinically significant among chronic pain patients [18, 51], and given that 30–33% improvement has been recommended as a clinically relevant change [26, 52–54], this study will define clinically meaningful pain relief as a 30% reduction from baseline. Remission from chronic pain has recently been suggested to be defined as a pain score of ≤ 3.0 on an 11-point scale for at least 6 months [55]; because the reviewed studies have not generally adopted this definition, it will not be used as an outcome measurement.

Clinically meaningful functional status improvement is 40% or more.

Short-term efficacy is defined as less than 6 months; long-term efficacy is defined as 6 months or longer.

Grading of Evidence

The grading of the evidence was performed using ASIPP's modification of the United States Preventive Services Task Force (USPSTF) criteria and other criteria [56–62].

Table 4 shows ASIPP's method of rating evidence, ranging from level I, consensus, at the bottom to level V, multiple RCTs, as the strongest level of evidence. Table 4 is found in Appendix I, Methodological Quality Tables, Supplementary Material.

DATA ANALYSIS

Figure 1 shows a flow diagram of study selection as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [63].

There were 819 studies considered for inclusion [7, 13, 64–142]. Of these, 61 studies were excluded from further review.

Table 5, List of Excluded Randomized and Non-randomized Studies, shows the reasons for exclusion.

Table 6 illustrates the characteristics of the eight RCTs and 12 observational studies considered for inclusion.

Methodological Quality Assessment

Table 7, Cochrane Review Bias Analysis, shows the bias analysis of the eight RCTs considered for review.

Table 8, The ASIPP IPM–QRB Analysis, shows the ASIPP bias and quality analysis for the eight RCTs.

Table 9, The ASIPP IPM–QRB NR Analysis for non-randomized studies, shows ASIPP's bias and quality analysis for the 11 non-randomized studies.

Of the eight RCTs and 11 observational studies considered for inclusion, three RCTs [95, 134, 136] and eight observational studies [66, 98, 103, 104, 113, 116, 121, 142] were considered low quality on the appropriate ASIPP analysis and were excluded.

Of the five included RCTs, one [88] was of high quality and four [64, 131, 132, 135] were of moderate quality.

Of the four included observational studies, all of which were case series, all were of moderate quality [71, 74, 91, 99].

Tables 7, 8 and 9 are found in Appendix II, Data Results and Quality Assessment, Supplementary Material.

Meta-Analysis

There was insufficient homogeneity of the studies to permit a meta-analysis.

Study Characteristics

Table 10 shows the study characteristics of the five randomized trials and four case series evaluating PNS which were included for consideration.

Table 10 is found in Appendix III, Study Characteristics, Supplementary Material.

RESULTS

There are three RCTs and four case series evaluating the use of PNS to treat refractory peripheral nerve neuropathic pain, including complex regional pain syndrome (CRPS), nerve entrapment, and post-stroke pain. One RCT looked at cluster headache and one at pelvic pain.

Table 10, Summary of Study Results, provides an overview of these nine studies. Table 10 is shown in Appendix III, Study Characteristics, Supplementary Material.

Of the RCTs evaluating the treatment of peripheral nerve pain, Wilson et al. found 60% relief at 16 weeks [132]. Deer et al., using the Bioness StimRouter[®], found a mean pain reduction of almost 30% at 12 weeks, compared to a 2.3% reduction in the control group [64]. Gilmore, in the only high-quality RCT reviewed, found that 67% of the treated group had $\geq 50\%$ relief, compared to 0% of the sham group. Interestingly, when the sham group crossed over to active treatment, only 17% had relief; this finding may be related to the technique of lead placement in this group [88]. Of the case series, Hassenbuch et al.'s study [99] was of moderate quality despite being 25 years old, a finding attributable to Dr. Hassenbuch's skills as an investigator. The study looked at CRPS patients, with 63% achieving at least 50% relief over a mean follow-up of over 2 years. Eisenberg et al. [91], looking at peripheral nerve injury, also provided long-term follow-up, from 3 to 16 years, with 78% of patients having at least 50% relief. Bouch et al. [74], looking at neuropathic pain, also provided long-term follow-up, with a minimum of 1 year and over half of the subjects providing reporting for more than 2 years. Two-thirds of the study's patients

had at least 50% relief. Colini Baldeschi et al. [71] looked at a patient population of which over one-half had CRPS, with a 6-month follow-up. Their patients had 61% mean relief, with 69% having at least 50% relief at 6 months.

Of the three RCTs evaluating relief of peripheral nerve neuropathic pain at a minimum of 3 months, two showed greater than 50% relief at the end point. The third showed a mean reduction of 27% versus essentially no relief in the control group.

The four case series provide documentation of long-term relief, up to 16 years. The case series generally support the RCTs, with greater than 50% relief in roughly two-thirds of the patients. A recent review of surgically implanted leads placed on peripheral nerves for treatment of CRPS over a 30-year time frame, documenting the experience at the Cleveland Clinic from 1990 to 2017, showed a mean 25% relief at 12 months [138]. This lower level of relief may reflect both the problems faced by earlier CRPS studies with appropriate diagnosis of the syndrome [143] and the potential complications associated with surgically implanted leads and generators.

Of the two remaining RCTs, Schoenen et al. [131] showed that 67% of treated cluster headache attacks were controlled with surgically implanted cylindrical leads. Istek et al. [135] found that stimulating the tibial nerve for 30 min once a week for 12 weeks provided greater than 50% relief of pelvic pain.

Levels of Evidence Supporting the Use of Peripheral Nerve Stimulation

One high-quality RCT and two moderate-quality RCTs documented the efficacy of PNS in treating refractory peripheral nerve neuropathic pain. Therefore, there is level II evidence supporting PNS in the treatment of refractory peripheral nerve neuropathic pain. Four moderate-quality case series reports corroborate the findings of the RCTs and provide documentation of long-term, multiple-year relief.

As there is one moderate-quality RCT supporting the use of PNS for the treatment of cluster headaches, there is level III evidence for

the use of PNS to the sphenopalatine ganglion in the treatment of cluster headache.

As there is one moderate-quality RCT supporting the use of PNS to the tibial nerve for the treatment of pelvic pain, there is level III evidence for the use of PNS in the treatment of pelvic pain.

COMPLICATIONS

Generally, PNS is safe. The early cuff and paddle leads, which required open surgical dissection for proper placement, had a high incidence of scarring and concomitant nerve damage, limiting adoption of PNS [65]. The current circular percutaneous leads have eliminated that problem. Ishizuka et al. found that these earlier systems also had problems with migration, infection, and the need for revision [144]. McJunkin found that 15% of these early systems needed to be explanted [145].

Chmiela et al. reported the complications seen in their 27-year history of surgically placed PNS leads for CRPS [138]. This review, like much of the early CRPS literature, did not show efficacy of the procedure in part because of the difficulty in diagnosing CRPS. Their experience showed that explanation occurred in 32 of 165 patients. Lack of efficacy was the reason for explanation in 50% of cases, while infection was the cause in another 28%. The remaining 22% were divided between end of battery life, device discomfort, lead migration, and one case of motor loss.

Warner et al. described their 13-year history of PNS, reviewing 72 patients who underwent surgical implantation [142]. This study was felt to be of low quality in terms of documenting the efficacy of PNS, but the focus of the paper was on complications and indications rather than efficacy. Warner et al. found that 20 of 72 patients required explanation. Of these, five were explanted for infection, one for lead erosion, and four for resolution of pain. Seventeen patients required revision, nine for lead migration, five for device malfunction, five for lead or anchor erosion, and four for infection. Of note, all of Warner et al.'s procedures were done using devices designed for spinal cord stimulation,

with none using current technology designed for spinal cord stimulation.

Eldabe et al., in a review of complications of spinal cord and peripheral stimulation, found lead migration to be the primary concern [146].

Lead fracture is a rare occurrence. Wilson reported a retained lead fragment which had no clinical significance [132]. Choi et al. reported lead fracture from a lead crossing a large joint [147]. Current stimulator systems, in which leads do not cross joints, markedly reduce the risk of lead fracture.

Pain related to an internal pulse generator has been a major concern, with Eldabe documenting up to 25% of patients complaining of pain related to the generator implant site. Currently available PNS systems have external generators, eliminating this problem. Infection and erosion, which were already rare, have now become even rarer complications because of the smaller incisions and the percutaneous approaches utilized. Gilmore et al. found no serious adverse events in their study [145]. Of their 22 study-related events, 21 were skin irritation or redness from the bandage or pain due to implantation or stimulation. The one moderate event was pain from stimulation, which resolved by reprogramming. Five leads were suspected of being fractured during removal and were monitored, with no clinical sequelae. The infection rate in this cohort was documented as 0%. Deer et al. similarly reported no serious device-related adverse events [148]. Their adverse effects were rash, redness, and soreness related to the adhesive from the electrode patch. PNS systems target nerves outside the spinal canal, and therefore remove the risk of spinal cord damage associated with spinal cord stimulators.

DISCUSSION

PNS has been an area of interest since 1967, when Wall and Sweet, applying the gate theory of pain, first stimulated peripheral nerves [7]. Early adaptation of PNS was limited because of technical issues, including scarring, and because of the interest in spinal neuromodulation. Further, in the 1980s and 1990s, pain control using

fluoroscopically guided injection techniques was an area of great intellectual interest. Over the last five decades, we have experienced an explosion of studies evaluating the utility of PNS for a variety of “difficult-to-treat” pain indications, inclusive of cephalgias, CRPS, and post-amputation pain. It is important to review these studies for the reader to appreciate the efficacy and duration of relief. While conventionally implanted percutaneous leads have been the dominant mechanism of stimulation, certainly the newer, smaller short-term wearables demonstrate some promise. In these newer devices, sustained relief has been reported, although the exact mechanism still alludes us. We will review the published data of the more recent advancements in PNS over the past three decades.

In 1996, Hassenbusch et al. [95] published the first moderate-quality case series, evaluating surgically applied plate electrodes to major peripheral nerves for CRPS, with 63% experiencing good or fair relief over follow-up of up to 4 years. Twenty percent returned to some form of work. No further high- or moderate-quality studies were done evaluating PNS until 2004, when Eisenberg et al. [87] presented a case series looking at cuff and paddle leads placed over the involved nerves. With a follow-up of between 3 and 16 years, 78% of the peripheral nerve injury patients had greater than 50% relief and no need for analgesics.

In 2013, Schoenen et al. [127] published an RCT used minimally invasively implanted leads into the sphenopalatine fossa for cluster headache, with 68% of patients achieving $\geq 50\%$ reduction of either pain in treated attacks or the frequency of attacks over a 12-month period.

Istek et al. [131] published an RCT in 2014 evaluating tibial nerve stimulation for 30 min followed by removal, repeated weekly for 12 weeks, for pelvic pain. At 6-month follow-up, patients had a mean 55% reduction in pain.

Shoulder and upper extremity pain have also been successfully treated with PNS. Wilson et al. [128] published an RCT in 2014 evaluating the treatment of hemiplegic shoulder pain after stroke, stimulating the axillary nerve with 6 h of daily stimulation for 3 weeks. At 4 months, there was a 60% reduction in shoulder pain.

Deer et al. [60] in 2016 published an RCT evaluating percutaneously implanted stimulators for peripheral nerve pain, with a mean reduction of pain of 27% at 3 months.

In 2017, Bouche et al. [70] presented a case series of ultrasound-guided percutaneous stimulation of the upper extremity for neuropathic pain, with 65% of patients experiencing greater than 50% relief after at least 1 year. Both CRPS and peripheral nerve injury patients responded to treatment.

Perhaps the greatest strides with PNS have been made for CRPS patients. In 2017, Colini Baldeschi [67] published a case series of peripheral nerve injury, including CRPS, with an ultrasound-implanted lead. At 6 months, the mean pain relief was 61%, and 69% had at least 50% pain relief. Gilmore et al. [84], in the only high-quality study reviewed, published an RCT in 2020 looking at pain in amputees, providing ultrasound-guided placement of percutaneous leads with stimulation for 8 weeks, at which time the leads were removed. Of the treated group, 67% had $\geq 50\%$ relief at 12 months, versus 0% of the sham group.

These nine studies provide level II evidence for neuropathic pain, including CRPS, and level III evidence for tibial nerve stimulation for pelvic pain and sphenopalatine ganglion stimulation for cluster headaches. The level of evidence for neuropathic pain is supported by both RTCs and case series. RCTs provide high-quality evidence of efficacy, but by their nature are limited to relatively short-term results, up to 1 year. Case series, on the other hand, can provide evidence of efficacy extending out a decade or more. Combined, these two sources provide powerful evidence of the effectiveness of PNS.

Further studies are needed supporting the use of PNS for osteoarthritic or post-surgical joint or low back pain. Gilmore et al.'s preliminary study of stimulation of the medial branches of the dorsal rami of the nerve roots for low back pain was excluded from this review because the enrolled population was too small [97]. However, it is important to comment that long-term follow-up at 12 months demonstrated that 67% of enrolled subjects endorsed a 63% reduction in low back pain intensity after a 30-day trial of the externalized wearable

stimulator, irrespective of etiology of low back pain. Deer et al.'s subsequent study using the same methodology was also excluded because the enrolled population was too small and because of the extent of industry involvement [140]. However, these findings are supported by several other reports of stimulation of other nerves which are of interest even though they did not meet the inclusion criteria. Elahi and Reddy, along with Wilson et al., Kurt et al., Manzi et al. and Mansfield and Desai, found PNS to be effective in treating shoulder pain [68, 72, 76, 109, 110]. These multiple studies suggest that there is a neuropathic component to back or joint pain which is responsive to PNS. Their findings highlight the extent of the need for high-quality studies confirming the role of PNS in treating joint or back pain.

Two major systematic reviews authored by Xu et al. [44] and Deer et al. [45] agree on several key aspects of the level of evidence for PNS for the indication of cluster headache, shoulder pain, and mononeuropathies (level II evidence). These reviews diverge, however, on the level of evidence for migraine (level I by Xu vs. beneficial by Deer) and pelvic pain (level II by Xu and level III by Deer). These findings suggest that many more high-quality RCTs are needed to form more consensus recommendations for these indications.

The mechanism by which PNS works is unclear, but the prevailing mechanism is thought to follow Wall and Melzack's gating theory in which activation of the large-diameter sensory fibers inhibits transmission of small-diameter nociceptive afferents. Finch et al. [65] performed a high-quality double-blind analysis of the characteristics of PNS relief looking at the time necessary for PNS to provide relief (wash-in) and for pain to return after the stimulator was turned off (wash-out). The mean wash-in time was just under 3 h, with a range from the immediate onset of relief in 2 of 11 patients to 8 h. The mean time for pain to return after turning off the stimulator was about 5.5 h, with immediate return of pain in one patient and a range between 1 and 24 h in the remaining patients. Finch et al. also performed quantitative sensory testing (QST). Unlike changes in VAS with turning the device on or off, there was

no change in most QST parameters. This finding suggests that conduction blockade is not the primary mechanism by which PNS works, although, given that in a small minority of patients both pain relief and loss of pain relief can occur immediately, conduction blockade may be at work in this subset. Finch et al. hypothesize that the primary mode of action may be either modulation of input into the central nervous system or central sensitization.

Ristic and Ellrich found that PNS modulated the pain threshold [149]. Zhang showed that high-frequency stimulation over 6000 Hz can, in differing models, lead to either constant activation of potassium channels or the inactivation of sodium channels [150], supporting the conduction blockade. Yang et al. showed that PNS suppresses wind-up of wide-dynamic-range neurons and that PNS differs from spinal cord stimulation in that it does not induce a C-component response in the wide-dynamic-range neurons [151].

Currently, Wall and Melzack's gate theory of pain is considered the most likely explanation for the mode of action of PNS, with orthodromic stimulation of large fibers leading to inhibition of pain transmission through the dorsal horn [88, 152]. Further research is needed to confirm the mechanism of action of PNS. Recent industry-funded reviews have looked to both peripheral and central mechanisms and to the role of large-diameter afferent fibers [153, 154].

Despite all that we know about the mechanism of action, PNS technology is continually evolving from peripheral implantation to newer-design wireless miniature wearables. While it is imperative to identify patients who may benefit from PNS stimulation, we must also define what success with the technology looks like. We postulate that outcomes are not sufficient, and advocate rather for identifying which patients may benefit earlier in their treatment course and with which stimulation parameters and neural targets. As these technologies continue to become more and more minimally invasive wearables, pain physicians ought to consider these treatment options earlier in the pain continuum rather than an option of last resort. We anticipate that the use of PNS will

grow as more studies are completed and indications are expanded.

LIMITATIONS

Despite having been used for over 50 years, PNS has a paucity of high-quality literature supporting its use. Of the literature reviewed, only one study was of high quality. Some indications which are currently generating much clinical interest, such as the treatment of joint pain from osteoarthritis, have limited literature supporting their use. Since 2013, there has been increased interest in PNS. The modality requires further documentation of its effectiveness and expansion of its indications in order to become more widely accepted.

The studies reviewed also lack sufficient homogeneity to support a meta-analysis.

CONCLUSION

PNS was the first application of neuromodulation. Initially, cuff leads encircling the nerve were used, then paddle leads. Both approaches were limited by the need for surgical exposure of the nerve and attendant complications. With the development of cylindrical percutaneous leads that can be placed with either fluoroscopic or ultrasound guidance and powered without the need for a lead to cross a joint, PNS is undergoing a resurgence.

While the vast majority of the reviewed studies were of small samples, collectively they reveal significant improvement in pain utilizing PNS for treatment of neuropathic pain conditions. The best studied application is refractory neuropathic pain involving a peripheral nerve, an indication which has level II evidence.

Cluster headaches and pelvic pain treated with tibial nerve stimulation have level III evidence.

The mechanism of action of PNS is unclear but currently is felt to be related to large-fiber activation, as described by Wall and Melzack's gate control theory. There is also evidence conduction blockade may be involved.

Further research on the efficacy of therapy and on the mode of action will help expand the applications of PNS.

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has patents with Avanos and Soin Neuroscience. Shalini Shah, MD MBA, is a consultant for SPR Therapeutics, Allergan, Inc., and Masimo Corporation. Andrea Trescot, MD, is Medical Director for StimWave.

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