Guidelines

Comprehensive Evidence-Based Guidelines for Implantable Peripheral Nerve Stimulation (PNS) in the Management Of Chronic Pain: From the American Society Of Interventional Pain Physicians (ASIPP)

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Background: Peripheral nerve stimulation (PNS) has been used for over 50 years to treat chronic pain by delivering electrical pulses through small electrodes placed near targeted peripheral nerves those outside the brain and spinal cord. Early PNS systems often required invasive neurosurgical procedures. However, since 2015, the Food and Drug Administration (FDA) approved percutaneously implanted PNS leads and neurostimulators offering a much less invasive, non-opioid option for managing recalcitrant chronic pain.

The following FDA-cleared PNS systems are commercially available in the United States for the management of chronic, intractable pain:

- Freedom® Peripheral Nerve Stimulator (PNS) System (Curonix LLC, 2017)
- StimRouter® Neuromodulation System (Bioness, now Bioventus, 2015)
- SPRINT® PNS System (SPR® Therapeutics, Inc., 2016)
- Nalu™ Neurostimulation System (Nalu Medical Inc., 2019)
- ReActiv8® Implantable Neurostimulation System (Mainstay Medical Limited, 2020)

The American Society of Interventional Pain Physicians (ASIPP) has published evidence-based consensus guidelines for the application of PNS systems in managing chronic pain.

Objective: The guidelines aim to provide evidence-based recommendations for the utilization of peripheral nerve stimulation (PNS) in the management of moderate to severe chronic pain. These guidelines exclude field stimulation, or sacral nerve stimulation.

Methods: A multidisciplinary panel of experts in various medical and pharmaceutical fields, convened by ASIPP, reviewed the evidence, considered patient perspectives, and formulated recommendations for implantable peripheral nerve stimulation in chronic pain management.

The methodology included developing key questions with evidence-based statements and recommendations. The grading of evidence and recommendations followed a modified approach described by ASIPP, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, and the Agency for Healthcare Research and Quality (AHRQ) strength of recommendations methods. The evidence review includes existing guidelines, systematic reviews, comprehensive reviews, randomized controlled trials (RCTs), and observational studies on the effectiveness and safety of implantable peripheral nerve stimulation in managing chronic pain.

The quality of published studies was assessed using appropriate instruments for systematic reviews, RCTs, and observational studies.

In the development of consensus statements and guidelines, we used a modified Delphi technique, which has been described to minimize bias related to group interactions. Panelists without a primary conflict of interest voted to approve specific guideline statements. Each panelist could suggest edits to the guideline statement wording and could suggest additional qualifying remarks or comments as to the implementation of the guideline in clinical practice to achieve consensus and for inclusion in the final guidelines, each guideline statement required at least 80% agreement among eligible panel members without primary conflict of interest.

Results: A total of 31 authors participated in the development of these guidelines. Of these, 23 participated in the voting process. A total of 8 recommendations were developed. Overall, 100% acceptance was obtained for 8 of 8 items. Thus, with appropriate literature review, consensus-based statements were developed for implantable peripheral nerve stimulation in chronic pain management.

In preparation of these guidelines, evidence synthesis included 7 systematic reviews, 8 RCTs, and 9 observational studies covering all PNS treatments. The evidence was developed using GRADE criteria or certainty of evidence, and qualitative synthesis based on the best available evidence. The evidence level and recommendations are as follows:

- For implantable peripheral nerve stimulation systems following a trial or selective lumbar medial branch stimulation without a trial, the evidence is Level III or fair with moderate certainty.
  Evidence Level: Fair; Strength of Recommendation: Moderate
- For temporary peripheral nerve stimulation for 60 days, the evidence is Level III or fair, with moderate certainty.
  Evidence Level: Fair; Strength of Recommendation: Moderate

Based on the available evidence, it is our recommendation to expand the existing PNS related local coverage determination (LCD) to include craniofacial pain, phantom limb pain, and nociceptive pain in the lower back as present evidence shows Level III or fair with moderate certainty.

Limitations: The primary limitation of these guidelines is the paucity of the available literature.

Conclusion: These evidence-based guidelines support the use of implantable peripheral nerve stimulation leads and neurostimulators in patients with moderate to severe chronic pain refractory to two or more conservative treatments. These guidelines aim to optimize patient outcomes and promote health equity through the integration of PNS technology in clinical practice.

Key words: Chronic pain, interventional techniques, peripheral neuropathy, peripheral neuropathic pain, peripheral nerve stimulation, selective lumbar medial branch stimulation

Disclaimer: These guidelines do not constitute inflexible treatment recommendations. Clinicians are expected to establish a plan of care on a case-by-case basis, considering an individual patient's medical condition, personal needs, and preferences, and the physician's experience. Consequently, these guidelines do not represent a "standard of care."

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SUMMARY OF RECOMMENDATIONS:

1. There is evidence supporting the accuracy and value of diagnostic methods for diagnosing conditions amenable to peripheral nerve stimulation.

   Evidence Level: Low; Strength of Recommendation: Moderate

2. The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain, based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable peripheral nerve stimulation systems following a trial or selective lumbar medial branch stimulation without a trial, is Level III or fair with moderate certainty utilizing GRADE criteria.

   Evidence Level: Fair; Strength of Recommendation: Moderate

3. The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable stimulation systems following temporary peripheral nerve stimulation for 60 days is Level III or fair with moderate certainty utilizing GRADE criteria.

   Evidence Level: Fair; Strength of Recommendation: Moderate

4. Based on the evidence and the recommendations, indications may be expanded from present CMS guidance with addition of craniofacial pain, phantom limb pain, and low back pain, either nociceptive or neuropathic, with present evidence showing Level III or fair with moderate certainty utilizing GRADE criteria.

   Evidence Level: Fair; Strength of Recommendation: Moderate

5. It is important to understand each type of peripheral nerve stimulation implant with features of the equipment and technical requirements.

   Evidence Level: Moderate; Strength of Recommendation: Strong

6. Based on the available evidence and all the available guidance, patient education is a crucial aspect of success of peripheral nerve stimulation.

   Evidence Level: Moderate; Strength of Recommendation: Strong

7. Risk stratification of peripheral nerve stimulation, based on ASIPP guidelines: low risk for peripheral nerve stimulation trial and implantation of extremities and other superficial nerves, moderate risk for lumbar medial branches and high risk for thoracic and cervical medial branches, trigeminal and cranial nerve blocks and nerve stimulation.

   Evidence Level: Moderate; Strength of Recommendation: Moderate

8. Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized as per ASIPP guidelines for low- and high-risk procedures.

   Evidence Level: Moderate; Strength of Recommendation: Moderate

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1.0 Introduction

Chronic pain is a distinct and well recognized condition affecting over 20% of U.S. adults (1,2). According to a report from the Centers for Disease Control and Prevention (CDC) on chronic pain among adults in the United States from 2019 to 2021 (2), an estimated 20.9% of U.S. adults experienced chronic pain in 2021. Age-adjusted prevalence of high impact chronic pain was 6.4%, consistent with other studies (1-3). Chronic pain and high-impact chronic pain were more common among older adults, females, those unemployed but with prior work experience, veterans, adults living in poverty, residents in non-metropolitan areas, individuals with public health insurance, those with disabilities, people in poor health, individuals with a history of certain chronic medical conditions, those identifying as bisexual, divorced or separated individuals, and Alaska Native adults.

While low back and neck pain are leading causes of disability worldwide (1), neuropathic pain is a particularly severe form of chronic pain that arises due to lesions, or diseases affecting the somatosensory nervous system. Globally, neuropathic pain affects 7% to 10% of the general population, among whom 20% to 30% have chronicity (4,5).

In 2011, the International Association for the Study of Pain (IASP) redefined chronic neuropathic pain as: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system including peripheral fibers (A beta, A delta, and C fibers) and central neurons" (6-8). Neuropathic pain encompasses a broad range of clinical conditions and is categorized based on etiology (degenerative, traumatic, infectious, metabolic, and toxic) and site of neurological lesion (peripheral vs. central lesion) (7,8). Multiple neuropathies are seen in daily practices including complex regional pain syndrome (CRPS), phantom limb pain, traumatic nerve injuries, chemotherapy treatment for cancer, human immunodeficiency virus (HIV), diabetes, post herpetic neuralgia, and surgery. Multiple studies (9-11) have shown the significance of high prevalence of neuropathic pain in chronic pain with deleterious effects on quality of life, healthcare finances, and equity related issues.

Peripheral nerve stimulation (PNS) represents a unique approach in neuromodulation for pain as it focuses on the highly variable part of the pain-processing system, the peripheral nerves themselves. Since these nerves may be the actual source of pain (as in nerve injuries, neuropathies, and entrapments) as well as the conduits of information between the central nervous system (CNS) and the region of pain, the idea of using the peripheral nerve as a target for electrical stimulation, in fact preceded both spinal cord and brain stimulation approaches. However, much has changed since the time of the pioneering experiences of Wall and Sweet who used PNS to illustrate the nascent "gate-control" theory of pain in 1966 (12), and Shelden et al (13) who used high frequency PNS to address neuropathic facial pain in 1962. After several decades of gradual growth in interest to PNS with only few available and mostly "off-label" devices (14), the entire approach has experienced a major resurgence of interest over the last 10 years with a number of dedicated FDA cleared PNS systems available on the market (15-19).

Despite the growing interest, existing guidelines and reviews have not reached definitive conclusions due to the low quality and heterogeneity of available evidence (19-27).

The guidelines for implantable peripheral nerve stimulation in managing chronic pain have been based on U.S. Food and Drug Administration (FDA) clearance. Peripheral field stimulation, percutaneous electrical nerve stimulation, and sacral nerve stimulation were not included in the development of these guidelines.

Currently, peripheral nerve stimulation is cleared by the U.S. FDA for the treatment of acute or chronic pain located in the low back, upper or lower extremities, trunk, and craniofacial regions (17-27). Thus far, PNS has been used for a variety of conditions including mononeuropathies, neuropathic limb pain, post-stroke shoulder pain, headache, facial pain, plexus injuries, post amputation pain or phantom limb pain, CRPS, and chronic low back pain.

Therefore, recommendations are provided for proper guidance to incorporate PNS in the algorithms of neuromodulation and interventional management of chronic pain conditions. The guidelines for implantable peripheral nerve stimulation and selective lumbar medial branch stimulation for chronic pain are based on SAFE (Safety, Appropriateness, Fiscal Neutrality, and Effectiveness) principles of American Society of Interventional Pain Physicians (ASIPP). PNS guidelines are to evaluate the proper indications, patient selection criteria, device-related nuances, procedural risks and outcome expectations, and to assist the treating physicians, patients, referrers, and payers in understanding the value of PNS and its applications.

2.0 Methods

2.1 Rationale

Interventional pain management is defined as "the discipline of medicine devoted to the diagnosis and treatment of pain related disorders, principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment" (28). Interventional pain management techniques are defined as, "minimally invasive procedures including, percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic diskectomy, intrathecal infusion pumps and spinal cord stimulators (SCS), for the diagnosis and management of chronic, persistent or intractable pain" (29). Recent literature has shown increasing use of spinal cord stimulation with significant growth patterns compared to other interventional modalities (10,30-40). In addition, since 2013, peripheral nerve stimulation techniques have been more commonly utilized, leading to discussions on evidence, medical necessity, and indications (41-44).

Peripheral nerve stimulation (PNS) is a neuromodulation therapy that involves implanting an electrode near a peripheral nerve responsible for the pain. The electrode(s) deliver electrical impulses to the affected nerve, disrupting pain signal transmission and thereby reducing the sensation of pain. PNS has been applied in interventional pain management for chronic pain conditions of upper and lower extremities, entrapment syndromes, headache and facial pain, intercostal neuralgias, axial spinal pain, and other peripheral injuries and diseases (15-27,41-76).

In addition to percutaneous PNS for neuropathic pain, two minimally invasive approaches to stimulating the medial branches of the dorsal medial ramus (the peripheral motor nerves innervating the multifidus muscle of the lower back) have been advanced (48,61,67,73).

2.2 Objective

The objective of these guidelines is to provide a rational and systematic approach to the application of interventions in managing pain and lumbar muscle degeneration with a particular focus on PNS. These guidelines are based on the available evidence concerning the effectiveness and safety of PNS in the treatment of different types of pain including that which has been postulated to be induced by lumbar muscle degeneration. The literature emphasizes the importance of evidence-based guidelines and highlights the necessity for regularly updating these guidelines to stay aligned with current clinical practices. Specifically, peripheral nerve stimulation, as a targeted approach, involves the use of minimally invasive techniques to place leads near specific peripheral nerves affected by pain. This method is distinguished by its precision and direct modulation of pain signals at the nerve level, offering a vital tool in the spectrum of interventional pain management strategies.

2.3 Application

These guidelines are applicable across various specialties but are specifically intended for use by interventional pain physicians and surgical specialties employing neuromodulation techniques. The primary goal of these guidelines is to provide patients, practitioners, regulators, and payers with information that may be used to determine whether the available evidence supports the medical necessity for peripheral nerve stimulation techniques (43,44).

2.4 Peripheral Nerve Stimulation Systems

The following peripheral nerve stimulation systems are commercially available in the United States after having generally received broad FDA clearance for the management of chronic intractable pain.

- Freedom® Peripheral Nerve Stimulator (PNS) System (Curonix LLC, 2017)
- StimRouter® Neuromodulation System (Bioness, now Bioventus, 2015)
- SPRINT® PNS System (SPR® Therapeutics, Inc., 2016)
- Nalu™ Neurostimulation System (Nalu Medical, Inc., 2019)
- ReActiv8® Implantable Neurostimulation System (Mainstay Medical Limited, 2020)

These guidelines are developed only for peripheral nerve stimulation; these do not include field stimulation, or sacral nerve stimulation.

2.5 Achievement of Technology Evaluation Criteria as Established by the National Committee for Quality Assurance (NCQA)

The National Committee for Quality Assurance (NCQA) is a private, not-for-profit agency that maintains accreditation standards for health plans. They advanced five-point criteria as a consistent and appropriate approach to evaluating new technologies:

2.5.1 The PNS Technology Must Have Final Clearance or Approval from the Appropriate Governmental Regulatory Bodies

- Freedom Peripheral Nerve Stimulator (PNS) System (Curonix LLC, 2017)
  - FDA clearance to leave trial lead temporarily implanted for up to 30 days
  - The two-component neurostimulator, comprised of an electrode array and a separate receiver, are surgically connected and anchored within two separate incisions, including creation of a subcutaneous pocket
- StimRouter Neuromodulation System (Bioness, now Bioventus, 2015)
  - FDA clearance to permanently implant single component lead and receiver (no temporary stimulation component approvals)
- SPRINT PNS System (SPR Therapeutics, Inc., 2016)
  - FDA clearance to leave leads temporarily implanted for up to 60 days
- Nalu Neurostimulation System (Nalu Medical, Inc., 2019)
  - FDA clearance to leave leads temporarily implanted for up to 30 days
  - FDA clearance to permanently implant leads and separate mIPG receiver
- ReActiv8 Implantable Neurostimulation System (Mainstay Medical Limited, 2020)
  - FDA clearance to permanently implant lead and implanted pulse generator (IPG) (no temporary stimulation component approvals)

2.5.2 The Scientific Evidence Must Permit Conclusions Concerning the Effect of the Technology on Health Outcomes

- The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
  - PNS treatments have been studied in multiple RCTs (45-54).
- The evidence should demonstrate that technology can measure or alter the physiological changes related to a disease, injury, illness, or condition.
  - The theories of mechanisms of action date back to seminal work in the 1960's that identified mechanisms of pain control activated by electrical stimulation of sensory nerve fibers (12,13). Multiple clinical studies have demonstrated the ability of PNS to induce physiological changes associated with chronic pain states (55-59), producing clinically meaningful reductions in pain and related improvements in quality of life, function, sleep, and reductions in medication usage (19-27,45-54,60-76).
  - Two mechanisms of action of selective stimulation of lumbar medial branches have been advanced, however neither mechanism has demonstrated definitive evidence.
  - One mechanism proposes to override of the cycle of lumbar multifidus muscle degeneration in individuals with chronic mechanical low back pain. In this case, medial branch neurostimulation is thought to relieve intractable chronic low back pain by helping to retrain the low back muscles to strengthen again on their own (48).
  - The other mechanism purports that inducing cycling contraction of the multifidus over a 60-day period re-initiates afferent and proprioceptive messaging from the periphery to address the often overlooked aspect of central sensitization in low back pain rather than as an motor weakness, per se (56, 60).

2.5.3 Technology Must Improve the Net Health Outcome. The Technology's Beneficial Effects on Health Outcomes Should Outweigh Any Harmful Effects on Health Outcomes

- PNS has demonstrated clinically meaningful and sustained reductions in pain and related improvements in other domains of health (e.g., quality of life, function, disability, medication usage), and a safety profile (19-27,45-54,60-76).

2.5.4 Technology Should Improve the Net Health Outcome as Much As, Or More Than, Established Alternatives

- PNS treatment has been directly compared to and found to be superior to currently established alternatives in multiple studies (20-27).

2.5.5 The Improvement Must Be Attainable Outside the Investigational Settings

- PNS has been evaluated in real-world settings in multiple publications.
  - These studies have included outcomes from patients treated in routine clinical practice.

The rates of treatment response and sustained improvement have been corroborated in the findings of published clinical studies, demonstrating that improvements are attainable outside the investigational setting (20-27,60-76).

2.6 Adherence to Trustworthy Standards

In preparation of the guidelines for implantable PNS, the standards from the Institute of Medicine (IOM) and the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) were followed (1,39,40,77-80). The NEATS instrument, which was developed and tested as a tool to be used by the trained staff at the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (NGC), provides an assessment focused on adherence (80). This ensures that the guidelines for peripheral nerve stimulation adhere to the highest standards of reliability and evidence-based practice.

2.6.1 Disclosure of Guideline Funding Source

Comprehensive evidence-based guidelines for peripheral nerve stimulation in managing chronic pain were commissioned, prepared, edited, and endorsed by ASIPP without external funding.

2.6.2 Disclosure and Management of Financial Conflicts of Interest

Potential conflicts of interest for all panel members within the last 5 years were evaluated prior to the finalizing of these guidelines. Conflicts of interest extended beyond financial relationships, including personal experience, practice patterns, academic interests, and promotions. The panel members with potential conflicts were recused from discussion or preparation of the guidelines in which they had conflicts of interest, and these members agreed not to discuss any aspect of a given guideline with the related industry before data publication.

2.6.3 Composition of Guideline Development Group

A panel of experts in managing chronic pain and interventional techniques from various medical fields reviewed the evidence and formulated recommendations for peripheral nerve stimulation. Overall, the panel provided a broad representation of academic and non-academic clinical practitioners with interest and expertise in interventional techniques applicable to peripheral nerve stimulation.

The multidisciplinary panel composition included methodologists (e.g., epidemiologists, statisticians, ethicists, and health services researchers) with experience in research and conduct of systematic reviews.

Editorially, appropriate measures were taken to avoid any conflicting opinions from authors receiving funding from the industry. The panel was multidisciplinary with academicians and practitioners, and geographically diverse. Of the 30 members involved in preparing the guidelines, there were 20 anesthesiologists, 1 neurosurgeon, 6 physiatrists, 1 radiologist, 2 scientists/researchers, 1 pharmacist, and 2 statisticians, either in an academic setting or in private practice. All of them were involved in managing or researching chronic pain.

2.7 Evidence Review

The evidence-based guidelines for peripheral nerve stimulation were developed utilizing consensus among the panel members after they had reviewed all published literature concerning the use and safety of peripheral nerve stimulation procedures in patients with chronic pain. The recommendations have been developed using principles of best evidence synthesis developed by the Cochrane Review, incorporating multiple guidelines modified by ASIPP (81,82).

2.7.1 Grading of Evidence

The grading of evidence and recommendation were based on qualitative modified approach to grading of evidence described by ASIPP (81), the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (83-85), clinical relevance and pragmatism (86), and AHRQ strength of recommendations (79,80) methods. Table 1 provides a qualitative modified approach to grading of evidence described by ASIPP (81). Table 2 provides a guide for strength of recommendations as developed by NEATS instrument (80), as modified by the opioid guideline panel (1) and adapted by the present guideline panel.

The grading of evidence for peripheral nerve stimulation is based on RCTs, observational studies, and other clinical reports. In addition, systematic reviews and meta-analyses were utilized. This grading system specifies levels of scientific evidence and offers an approach to grading the quality of evidence and, secondarily, the strength of recommendations (80,83-85). Methods similar to AHRQ's approach to the strength of a recommendation were also recommended (77,78).

Table 1. *Qualitative modified approach to grading of evidence of therapeutic effectiveness studies.*

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate or low-quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant moderate or low-quality randomized trial or Evidence obtained from at least one relevant high-quality non-randomized trial or observational study with multiple moderate or low-quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low-quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists

Modified from: Manchikanti L, et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (81).

Table 2. *Guide for strength of recommendations as modified for ASIPP guidelines.*

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is substantial providing strong recommendation. Recommendation: Strong
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Recommendation: Moderate
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. ASIPP Adaptation: The consensus achieved that there is potential improvement in certain individuals or groups of patients based on individual professional judgement and shared decision making. Recommendation: Weak

Adapted and modified from: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (1,80).

2.7.2 Assessment Based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria

Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations (83-85). It is the most widely adapted tool for grading the quality of evidence and for making recommendations. GRADE has 4 levels of evidence - also known as certainty in evidence or quality of evidence: very low, low, moderate, and high, as shown in Table 3. Certainty of evidence is based on risk of bias or methodologic quality of the studies, imprecision, inconsistency, indirectness, and publication bias. Based on these factors, confidence in the evidence may be increased or decreased. Reasons rate certainty in evidence up or down are shown in Table 4.

2.7.3 Outcome Measures

An outcome is considered clinically significant if a reduction of 2 points on the Visual Analog Scale (VAS)

or Numeric Rating Scale (NRS), or at least 50% reduction in pain and improvement in the functional status occurs in 50% of the treatment group. A positive study is said to be clinically significant and effective, indicating that the primary outcome should be statistically significant at a *P*-value ≤ 0.05.

2.7.4 Analysis of Evidence

The evidence was analyzed utilizing qualitative and quantitative evidence synthesis. Quantitative evidence synthesis was performed utilizing conventional meta-analysis and a single-arm meta-analysis.

2.7.5 Qualitative Analysis

The qualitative analysis of the evidence was performed based on best-evidence synthesis, modified, and collated using multiple criteria, including the Cochrane Review criteria and United States Preventive Services Task Force (USPSTF) criteria as illustrated in Table 1 (81). The analysis was conducted using 5 levels of evidence, ranging from strong to opinion- or consensus-based.

2.7.6 Meta-Analysis

2.7.6.1 Dual-Arm Meta-Analysis

For dual-arm meta-analysis, software Review Manager [Computer program] version 5.4, The Cochrane Collaboration, 2020 was used. For pain and functionality improvement data, the studies were reported as the standardized mean differences (SMD) with 95% confidence interval (CI). Data were plotted using forest plots to evaluate treatment effects using random-effects models. Heterogeneity was interpreted through I2 statistics.

2.7.6.2 Single-Arm Meta-Analysis

For single-arm meta-analysis, software Comprehensive Meta-Analysis version 3.0 was used (Biostat Inc., Englewood, NJ). For pain and functionality improvement data, the studies were reported as the mean differences with 95% CI. Data were plotted using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I2 statistics.

2.7.7 Assessment and Recommendations of Benefits and Harms

These guidelines describe the potential benefits and harms of peripheral nerve stimulation interventions and explicitly link the information to specific recommendations.

Table 3. *GRADE certainty ratings.*

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Source: BMJ Best Practice. Evidence-based medicine (EBM) toolkit. Learn EBM. What is GRADE? Accessed 08/20/2024. https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/ (85)

Table 4. *Reasons rate certainty in evidence up or down.*

Certainty can be rated down for:	Certainty can be rated up for:
• Risk of bias • Imprecision • Inconsistency • Indirectness • Publication bias	• Large magnitude of effect • Dose-response gradient • All residual confounding would decrease magnitude of effect (in situations with an effect)

Source: BMJ Best Practice. Evidence-based medicine (EBM) toolkit. Learn EBM. What is GRADE? Accessed 08/20/2024. https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/ (85)

2.7.8 Evidence Summary of Recommendations

Guideline-supporting documents summarize the relevant supporting evidence for peripheral nerve stimulation and link this information to the recommendations.

2.7.9 Rating or Grading the Strength of Recommendations

For each recommendation related to peripheral nerve stimulation, a rating of the strength of the recommendation related to benefits and harms, available evidence, and the confidence in the underlying evidence is provided, utilizing rating schemes recommended by NEATS (1,80).

2.7.10 Specificity of Recommendations

The guideline recommendations are, to the largest extent possible, specific, and unambiguous, and are intended to provide guidance and what actions should or should not be taken in various clinical settings for PNS in diverse populations of patients.

2.8 Methodologic Quality and Risk of Bias Assessment

Key recommendations included transparency and reproducibility of judgments, separating risk of bias

from other constructs such as applicability and precision, and evaluation of the risk of bias per outcome.

2.8.1 Randomized Controlled Trials (RCTs)

2.8.1.1 Scoring Cochrane Review Criteria

Utilizing Cochrane Review criteria (87), as shown in Appendix Table 1, studies meeting the inclusion criteria with at least 9 of 13 criteria were considered high-quality; 5 to 8 were considered moderate quality. Those meeting criteria of less than 5 were considered as low-quality and were excluded.

2.8.1.2 Scoring IPM-QRB Criteria

Based on Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria for randomized trials (88), as shown in Appendix Table 2, the studies meeting the inclusion criteria but scoring less than 16 were considered as low-quality and were excluded; studies scoring from 16 to 31 were considered as moderate quality; and studies scoring from 32 to 48 were considered as high-quality.

2.8.2 Nonrandomized Studies

2.8.2.1 Scoring for Newcastle-Ottawa Quality Assessment Scale

Newcastle-Ottawa Quality Assessment Scale was used for case-controlled studies and cohort studies as shown in Appendix Tables 3 and 4 (89). Studies meeting the inclusion criteria but scoring less than 3 were considered low quality and were excluded; studies scoring from 3 to 5 were considered moderate quality; and studies scoring 6 or above were considered high quality and were included.

2.8.2.2 Scoring For IPM-QRBNR

Based on Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) criteria (90), as shown in Appendix Table 5, studies meeting the inclusion criteria but scoring less than 16 were considered low-quality and were excluded; studies scoring from 16 to 31 were considered moderate quality; and studies scoring from 32 to 48 were considered high quality and were included.

2.8.3 Quality Assessment of Systematic Reviews and Meta-Analysis

Quality assessment criteria tool to assess systematic reviews used in Cochrane reviews was incorporated into the present assessment (91-93).

As shown in Appendix Table 6, to be a systematic review, it must include multiple criteria.

The purpose of this rating tool (Appendix Table 6) is to evaluate the scientific quality of systematic reviews. It is not intended to measure the literary quality, importance, relevance, originality, or other attributes of systematic reviews.

The overall quality of the systematic review is rated as "Good," "Fair," or "Poor" using the guidance below (91-93) as follows.

Good = After considering items 1–12, item 12 is rated "Yes" with no important limitations. This means that few of the items 1–12 are rated "No," and none of the limitations are thought to decrease the validity of the conclusions. If items 3, 4, 7, or 8 are rated "No," then the review is likely to have major flaws

Fair = After considering items 1–12, item 12 is rated "Yes," but with at least some important limitations. This means that enough of the items 1–12 are rated "No" to introduce some uncertainty about the validity of the conclusions.

Poor = After considering items 1–12, item 12 is rated "No." This means that several of items 1–12 are rated "No," introducing serious uncertainty about the validity of the conclusions.

2.9 External Review

Guidelines have been subjected to external peer review as per the policies of the publishing journal, Pain Physician.

2.10 Updating Guidelines

The implantable peripheral nerve stimulation and selective lumbar medial branch stimulation for chronic pain guidelines will be updated within 5 years or less, based on significant changes in scientific evidence, public policy, or adverse events occurring before January 2029.

2.11 Consensus Development of Recommendations

We used a modified Delphi technique to achieve consensus on guideline statements (86). This method has been described to minimize bias related to group interactions and enable anonymity among panelists. Panelists without a primary conflict of interest voted on approving specific guideline statements using an online survey. Each panelist could also suggest edits to the guideline

statement wording and could suggest additional qualifying remarks or comments as to the implementation of the guideline in clinical practice. To achieve consensus and for inclusion in the final guidelines, each guideline statement required at least 80% agreement among eligible panel members without primary conflict of interest. If there were any disagreements, with guideline statements with some members disagreeing with either the strength or direction of the recommendation.

2.12 Key Questions

These guidelines focus on the following key questions:

1. What is the impact of chronic peripheral neuropathic pain or lumbar muscle degeneration on healthcare resource utilization?
2. What are the current trends and statistics regarding the use of healthcare modalities, particularly peripheral nerve stimulation (PNS)?
3. What are the structural and pathophysiological mechanisms behind peripheral neuropathic pain and chronic mechanical low back pain that could be treated with PNS?
4. What evidence supports the accuracy and value of diagnostic methods for conditions amenable to peripheral nerve stimulation?
5. How effective are peripheral nerve stimulation interventions in managing chronic pain, and what evidence supports their effectiveness?
6. What are the adverse consequences and harms, and related precautions in providing peripheral nerve stimulation interventions?
7. What are the various types of peripheral nerve systems available in the United States?
8. What are medical necessity criteria and indications for PNS?
9. What is the importance of patient education in peripheral nerve stimulation implants?
10. What are the precautions in patients on antiplatelet and anticoagulant therapy implanting PNS?

3.0 Impact of Chronic Peripheral Neuropathic Pain on Health care

Key Question 1. What is the impact of chronic peripheral neuropathic pain or lumbar muscle degeneration on healthcare resource utilization?

The IASP defined chronic pain as, "pain that extends beyond an expected timeframe of healing" (6,7). In 2011, the IASP redefined chronic neuropathic pain as, "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, including peripheral fibers and central neurons" (6,7). Multiple categories of neuropathic pain have been described based on the etiology and site of neurological lesion. Based on etiology, degenerative, traumatic, infectious, metabolic, and toxic, lesions and peripheral or central lesions can cause chronic neuropathic pain. Thus, examples of common causes of neuropathic pain include diabetes, HIV, and chemotherapy treatment for cancer, postherpetic neuralgia, multiple sclerosis, surgery, stroke, and spinal cord injury (3).

Recent analysis from the CDC reported an estimated 20.9% of U.S. adults experienced chronic pain with 6.9% suffering with high impact chronic pain in 2021 (2). Further, prevalence of chronic pain and high impact chronic pain was higher among certain categories including females, unemployed individuals, veterans living in poverty, adults in poor health, adults with certain history of chronic medical conditions, adults identifying as bisexuals, and adults who were divorced or separated. Even though low back pain and neck pain are considered as the leading causes of disability worldwide (1), neuropathic pain, particularly high impact or severe forms of chronic pain, have been described to be highly prevalent globally in 7% to 10% of the general population with 20% to 30% noting chronicity.

The annual U.S. expenditures related to pain, including direct medical costs and lost wages by some accounts, may be higher than those for cancer, heart disease, and diabetes combined. Even then, treatment covered by these expenditures doesn't fully alleviate pain in the United States or other countries. The IOM report of 2011, despite its inaccuracies, concludes that the epidemic of chronic pain demands a public health approach with public education to counter myths, stereotypes, and stigma that hinder better care (94). Further, a study of global burden of diseases and injuries of 2019 (95) showed continued increasing disability and significant overdose deaths in the United States, accounting for 50% of deaths across the world, due to assumed liberal prescribing of high dose opioids, inadequate provision of opioid substitution therapy, and the lacing of street drugs with highly potent opioids such as fentanyl. Healthcare spending effectiveness suggests that spending improved U.S. health from 1990 to 2016, yet low back and neck pain continue to be on a par with ischemic heart disease for negatively affecting disability adjusted life years (96). Dieleman et al (97,98) showed the economic impact on healthcare in the United States with an estimated spending of $134.5 billion in 2016, a 53.5% increase from 2013 when $87.6 billion was spent for managing spinal pain. The costs of other musculoskeletal disorders also increased 43.5%, from $183 billion in 2013 to $263 billion in 2016.

Baskozos et al (3), in an epidemiology study of neuropathic pain with analysis of prevalence and associated factors in the United Kingdom, showed that chronic pain was present in 51% of the participants with overall prevalence of neuropathic pain of 9.2%. They also showed that neuropathic pain was significantly associated with worse health-related quality of life, having a manual or personal service type occupation, and younger age compared to those with no chronic pain. Neuropathic pain was common with diabetes, but also was related to other conditions including pelvic pain, post-surgical pain, migraine, rheumatoid arthritis, osteoarthritis, and fibromyalgia. In a burden of illness study for neuropathic pain in Europe, Liedgens et al (9) showed that the highest prevalence was seen with diabetic peripheral neuropathy (20% to 25%), followed by spinal nerve pain or radiculopathy with prevalence of 17% to 22%. The total cost varied €10,000, with 60% to 70% being attributed to indirect costs. In the United States, the financial burden of neuropathic pain was estimated to be as high as U.S. $30,000 annually per patient in indirect costs (10,11).

The treatment of peripheral neuropathic pain poses significant challenges, in addition to its considerable economic burden. This condition is often resistant to standard pain medications, requiring specialized drugs like anticonvulsants and antidepressants, which can have significant side effects and require careful monitoring. This situation necessitates ongoing patient education and engagement, as effective management often involves lifestyle changes and adherence to complex medication regimens. The elusive nature of complete pain relief in many cases also demands constant adjustments in treatment strategies, making it a time-intensive endeavor for healthcare providers.

Furthermore, peripheral neuropathic pain has a

profound social and psychological impact on patients, which subsequently affects healthcare systems. Chronic pain can lead to social isolation, reduced mobility, and a decline in the quality of life, necessitating additional healthcare and social support services. The psychological toll of chronic pain, including increased rates of depression and anxiety, often requires psychological or psychiatric interventions. This broader impact highlights the need for healthcare systems to adopt a holistic approach to pain management, integrating medical, psychological, and social support services to effectively address the diverse needs of patients with peripheral neuropathic pain.

Chronic neuropathic pain is also a major contributor to the global burden of chronic pain and is associated with a substantial economic burden (99-105). It disproportionately affects women, older adults, and people with low education levels leading to increased labor absenteeism. Further, neuropathic pain is seen in patients with diabetes, obesity, HIV, and postherpetic neuralgia, all vulnerable populations. While the total cost of neuropathic pain has not been determined, neuropathic pain incurs substantial costs to society such as direct medical costs, reduced ability to work, reduced ability of caregivers to work, and greater need for institutionalization (101). In the United States, access to healthcare and health equity are additional issues. It has also been claimed that neuropathic pain is underdiagnosed and undertreated despite guidelines such as the National Institute for Health and Care Excellence (NICE) and the Neuropathic Pain SIG (NeuPSIG) recommendations. Inadequate response to such treatment is still a significant unmet need in neuropathic pain patients (100). In general, U.S. healthcare costs have been increasing substantially. The latest data available for 2022 shows healthcare expenditures in the United States reached $4.5 trillion with the growth of 4.1% from 2021 (106).

Overall, the global burden of polyneuropathy is largely unknown, with most studies conducted on diabetic peripheral neuropathy (107,108). The economic impact of diabetic peripheral neuropathy on the healthcare system in the United States is significant. In 1997, the total direct medical and treatment cost of diabetes, which includes the management of diabetic peripheral neuropathy and its complications, was estimated to be $44 billion, representing a significant portion of the total personal health care expenditure in the U.S. This cost is attributed to the long-term and resource-intensive treatment required for diabetic peripheral neuropathy and its complications, such as foot ulcers and lower-limb amputations (109).

A U.S. survey by Gore et al (110) in patients with painful diabetic peripheral neuropathy found that among the approximately 30% of respondents who were employed, nearly 65% reported missing work and/or decreased productivity at work due to their neuropathic pain. Those with severe pain had the highest total annual indirect costs, approximating U.S. $3,927 (111).

4.0 The Trends in Utilization of Healthcare Modalities in Managing Peripheral Neuropathic Pain

Key Question 2. What are the current trends and statistics regarding the use of healthcare modalities, particularly peripheral nerve stimulation (PNS)?

Overwhelming health care costs constitute a major burden on the United States' overall economy, and this has led to the implementation of various health care reform measures and regulations (1,39,40,112). However, some guidelines have been based on public policy priorities to reduce health care costs and have not necessarily been based on best evidence available to date. On the other hand, some guidelines have been based on individual priorities, ultimately increasing utilization patterns not based on the best available evidence. There has been an escalating growth of various modalities for the treatment of chronic pain including drug therapy, physical therapy, and other non-invasive modalities, interventional techniques, and surgical interventions (1,8,30-40,112-119).

4.1 Non-Opioid Pharmacologic Therapy

Pharmacologic treatments have been beneficial in many neuropathic pain states. First-line drugs include gabapentinoid agents and serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine, second-line drugs such as capsaicin and lidocaine patches and creams, and third-line drugs including opioids.

Gabapentinoids, including commonly utilized medications such as gabapentin and pregabalin, are commonly prescribed pharmacological treatments for neuropathic pain states. These medications function through binding to voltage-gated calcium channels (VGCCs) found on the presynaptic membrane. By doing so, these medications diminish the number of calcium channels localized along neuronal plasma membranes, reducing calcium influx at presynaptic terminals. This mechanism effectively modulates aberrant signaling pathways associated with neuropathic pain conditions. Gabapentinoids represent primary therapeutic classes of medicine that exhibit efficacy in neuropathic pain states. However, while gabapentinoids can be efficacious in certain patients, they also induce adverse effects, resulting in patients discontinuing treatment related to insufficient efficacy or intolerable side effects (113).

Serotonin-norepinephrine reuptake inhibitors, including venlafaxine and duloxetine, have emerged as key pharmacological treatments in neuropathic pain management. These medications impede reuptake of serotonin and norepinephrine, resulting in increased levels of these neurotransmitters within the synaptic cleft. Furthermore, this class of medicine amplifies select descending pathways originating from the brainstem, serving to deter the transmission of pain signals to the brain. Venlafaxine and duloxetine are both highly therapeutic options in neuropathic pain states, attenuating pain signaling in patients with neuropathic pain syndromes (114). However, they also may have significant side effects, leading to discontinuation.

Lidocaine transdermal patches and capsaicin cream act as viable second-line pharmacologic interventions for alleviating the pain associated with neuropathic pain (115,116). These topical remedies operate through distinct mechanisms to mitigate neuropathic discomfort. Lidocaine works through impeding firing of peripheral nerves through the inhibition of Voltage-Gated Sodium Channels (VGSCs), whereas capsaicin cream interacts with Transient Receptor Potential Vanilloid 1 (TRPV1) receptors on nociceptive fibers, resulting in desensitization of nociceptive neurons. These topical treatments present an alternative avenue for management in patients with neuropathic pain states.

Current research shows potential roles for other novel treatments of neuropathic pain states, including small molecule inhibitors, voltage-gated ion channel inhibitors, stem cell therapy, anti-tumor necrosis factor agents, and gene therapy. In this regard, there is evolving research focused on LX9211, Voxotrigine, Mirogabalin, Adalimumab and infliximab, and Engensis (117-119).

4.2 Opioids

The literature shows that neuropathic pain is generally poorly responsive to analgesics such as opioids or nonsteroidal anti-inflammatory drugs (NSAIDs). Instead, nonopioid therapy with gabapentinoids, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors, as discussed above, are recommended as first and second line treatments. Even so, opioids are widely used in clinical practice to manage neuropathic pain. As described in ASIPP's opioid guidelines (1), over the years, multiple reviews have been performed in reference to opioid use overuse, abuse, and a multitude of adverse consequences including opioid-related deaths. Manchikanti et al (1,120) described an evolution of a fourth wave of opioid-related deaths, a modification of the 3 distinct waves described by the CDC, beginning

in 2016, and which has been steadily expanding due to multiple factors, including misapplication of 2016 CDC guidelines, an increased availability of illicit drugs, spillover effects of COVID-19 pandemic, and policies that have served to reduce access to interventional procedures for treatment of chronic pain (Fig. 1) (1,120).

There has been substantial debate regarding the relationship between opioid overdoses and prescription opioid pain relievers, including the associated terminology (1,120,121). The evaluation of the relationship between opioid overdoses, opioid treatment admissions, and prescription opioid pain relievers in the United States has been described for the period from 2010 to 2019 (121). As shown in Figs. 2 and 3, the relationships between total opioid doses, accidental opioid deaths, prescription opioid deaths, opioid treatment admissions, and annual prescription sales (measured in morphine milligram equivalents, or MME, per capita) are either nonexistent or significantly negative/inverse (122).

According to preliminary data published by the CDC, almost 110,000 drug overdose deaths were recorded in the United States in 2022, with synthetic opioids involved in 75,000 (70% of those deaths) (123). To put this in perspective, the United States lost 58,220 people in the Vietnam war, meaning that fentanyl and similar drugs are now taking more American lives each year than that war did in more than a decade (Fig. 4). As shown in Fig. 5, opioids appear to be more likely to kill than car crashes or suicide, based on the U.S. data in 2022, with opioid overdoses contributing 1 in 55, suicide 1 in 87, motor vehicle crashes 1 in 93, and gun assault 1 in 219.

4.3 Interventional Techniques

Multiple interventional techniques are utilized in managing chronic pain; however, the majority of these, including epidural injections, percutaneous adhesiolysis, facet joint interventions, sacroiliac joint interventions, and spinal cord stimulation are employed to manage spinal and non-spinal chronic pain. Literature is scant in reference to utilization of peripheral nerve injections for the management of chronic pain, though there are multiple publications describing the usage of peripheral nerve injections intraoperatively and postoperatively (124-128).

Barad et al (19), to evaluate of percutaneous interventional strategies for migraine prevention, performed a systematic review and developed guidelines. In this evaluation, they included various types of procedures, including occipital nerve injections, supraorbital nerve injections, sphenopalatine ganglion injections, cervical spine percutaneous interventions, and implantable stimulation, all receiving weak recommendation for their use for chronic migraine prevention. Further, the committee found insufficient evidence to assess trigger point injections in migraine prevention, and highly discouraged the use of intrathecal medication. Cervical facet joint nerve

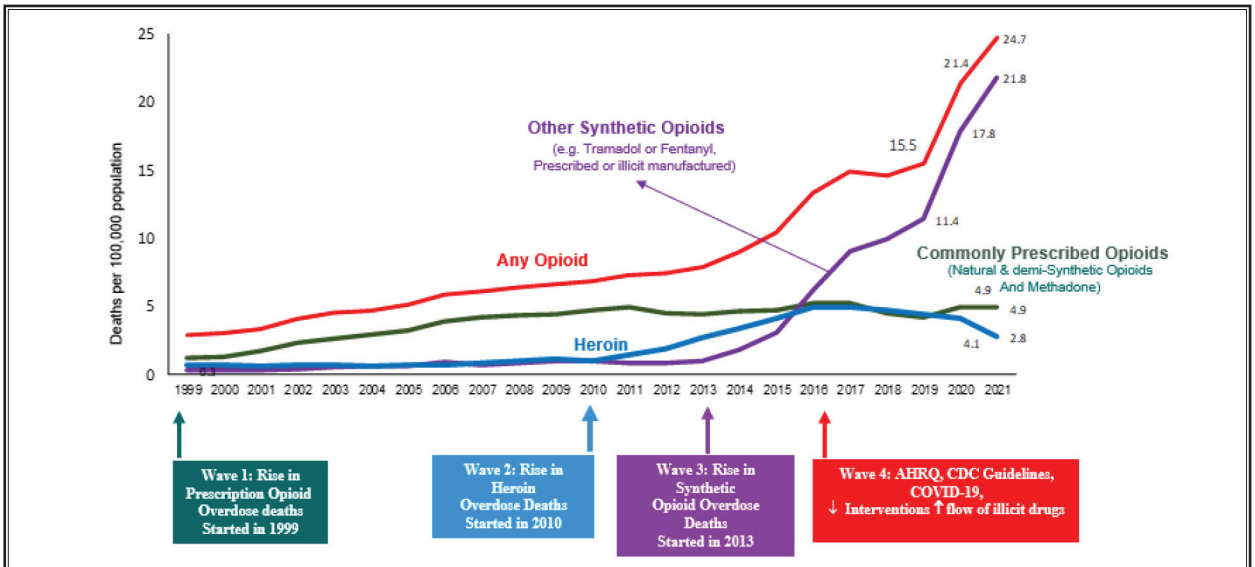


Fig. 1. *Four waves of rise in opioid overdose deaths. Redrawn and modified from CDC figure.*

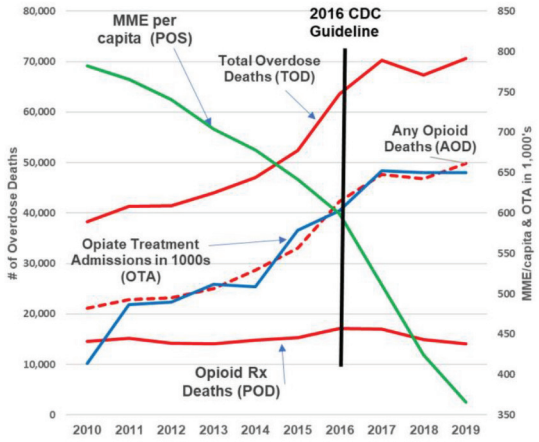


Fig. 2. *2010–2019 update.*
AOD = any opioid overdose death; POD = prescription opioid deaths; POS = prescription opioid sales; OTA = opioid treatment admissions; TOD= total overdose deaths; MME= morphine milligram equivalents
The green line represents opioid prescribing (POS, MME/capita); the red lines are opioid deaths (POD, AOD, and TOD); the blue line represents opioid addiction (OTA). Over the past decade, as the green line (prescription opioids) declined by +50%, prescription opioid deaths remained flat while opioid addiction, any opioid and total overdose deaths continued increasing "exponentially (122)".

Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (121).

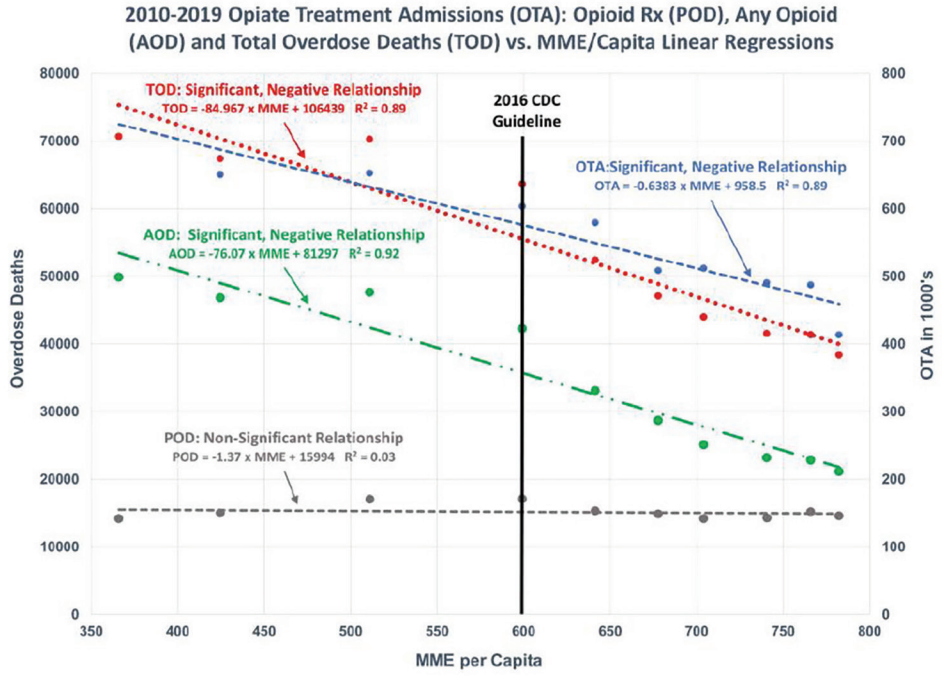


Fig. 3. *2010–2019 regression models: Illustrates the regression of opioid treatment admissions.*
OTA = opioid treatment admissions; POD = prescription opioid deaths; AOD= any opioid overdose death; TOD = total overdose deaths; POS = prescription opioid sales
Significant, negative relationships were found for OTA, AOD, and TOD. No significant relationship exists between POD and POS.

Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. Front Pain Res (Lausanne) 2022; 3:884674 (121).

injection and radiofrequency neurotomy also have been evaluated for the treatment of headache, along with C2 ganglion blocks, greater and less occipital nerve injections, and C2-C3 dorsal ramus injections (40,129-136).

4.4 Nonpharmacologic and Noninterventional Techniques in Managing Chronic Pain

There are multiple noninvasive or noninterventional techniques for managing chronic pain, including neuropathic pain. These techniques include exercise programs, physical therapy, acupuncture, massage, transcutaneous electrical nerve stimulation (TENS), biofeedback therapy, and chiropractic treatments.

The role of various programs has been described in opioid guidelines (1). It is also essential to perform medication therapy as well as noninterventional techniques including exercise programs, physical therapy, or chiropractic treatments prior to embarking on peripheral nerve injections or peripheral nerve stimulation. All these techniques have shown moderate

evidence in improving the functional status in conjunction with other modalities; however, only on a short-term basis and as an adjuvant treatment, and there are no studies that we were able to identify applying these interventions specifically in neuropathic pain.

In treating lumbar multifidus dysfunction, core stabilization exercises have traditionally been recommended for managing generalized low back pain symptoms, regardless of the underlying cause. From a physiological perspective, core stabilization exercises are suitable for patients experiencing spinal instability due to muscle weakness or imbalance.

Several published studies have examined the effectiveness of therapeutic exercises specifically targeting the multifidus muscles, with those focused on the multifidus showing positive outcomes (137). However, in practice, many patients find it challenging to perform targeted multifidus exercises due to pain. Additionally, arthrogenic muscle inhibition, especially in advanced stages of chronic low back pain, can further impede muscle contractions (138). Researchers have explored the use of transcutaneous stimulation of the lumbar paraspinal muscles, which has been reported to be reasonably well-tolerated by older adults with chronic low back pain (139). However, selective transcutaneous stimulation of the multifidus muscle is not possible. Directly stimulating muscle mass requires significantly more energy than stimulating the motor nerve that innervates the muscle. Many participants find the energy required to transcutaneously activate the deeper multifidus fascicles to be painful (140).

4.5 Surgery

Surgery is one of the most common interventions performed in managing chronic pain, specifically spinal pain; however, the role of surgery is limited in managing peripheral neuropathic pain. Decompressive surgery can be considered appropriate in cases of compression neuropathy. Peripheral nerve injections and peripheral nerve stimulation can be performed to manage neuropathic pain or pain developing after various types of surgical interventions.

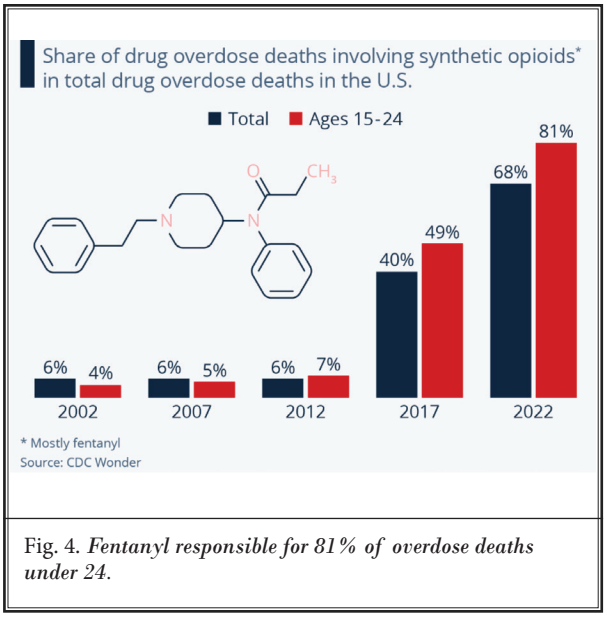


Fig. 4. *Fentanyl responsible for 81% of overdose deaths under 24.*

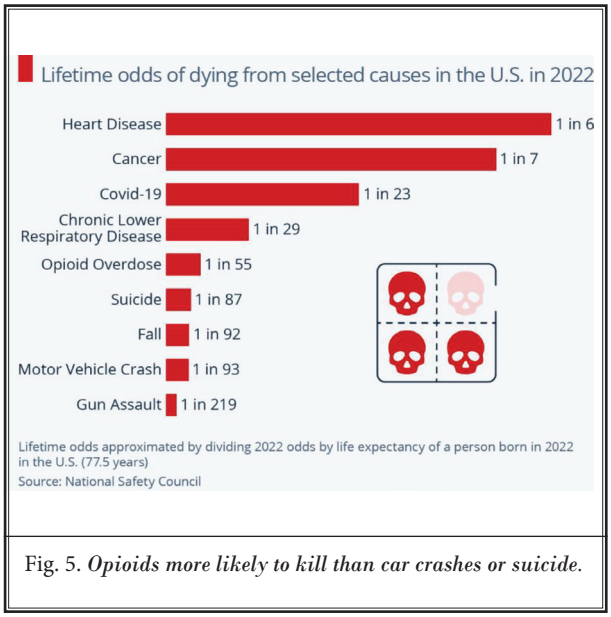


Fig. 5. *Opioids more likely to kill than car crashes or suicide.*

5.0 Structural and Pathophysiologic Basis of Peripheral Nerve Stimulation

Key Question 3. What are the structural and pathophysiological mechanisms behind peripheral neuropathic pain and chronic mechanical low back pain that could be treated with PNS?

5.1 Chronic Pain Mechanisms

Three broad categories of pain include nociceptive, neuropathic, and nociplastic pain, with mechanisms that overlap and remain incompletely understood (141-143) as shown in Table 5. Nociplastic pain, the newest of the 3 categories, arises from altered nociception without evidence of tissue damage, biomarkers, or pathology involving the somatosensory nervous system (141). Identification of pain mechanisms is critically important for effective management, as it informs treatment decisions at every step (141). It is widely acknowledged that mechanism-based pain treatment is theoretically superior to disease-or etiologic-based treatment, though in clinical practice, this may be difficult to implement (143-145).

Within the pain signaling pathway itself, transduction, transmission, modulation, and perception are the core elements involved in the mechanism of pain physiology (141). Simply put, transduction is the process of converting a noxious stimulation from tissue injury to a nociceptive signal, with transmission involving sending nociceptive information upstream to the CNS. In the CNS, modulation is the process of biological transformation of the signal (with nociplastic pain always, and neuropathic and nociceptive pain sometimes), resulting in central sensitization and signal amplification. Finally, perception is the interpretation of the signals through cognitive and emotional responses in the brain, which considers context, past experiences, and expectations (141). However, all 4 components may not be involved in all pain pathways; specifically, neuropathic pain is unique in that it bypasses the first step of converting a stimulus to an electrical impulse, as the stimulus involves direct injury to the nerve. In general, the peripheral nerve system is the site for transduction and transmission, whereas the CNS is where modulation, i.e., transformation, and perception occur.

IASP defined chronic pain to include the involvement of the somatosensory system, including peripheral fibers (A beta, A delta, and C fibers) and central

Table 5. *Categorization of pain states*.

CLINICAL CHARACTERISTIC	NEUROPATHIC PAIN	NOCICEPTIVE PAIN	NOCIPLASTIC PAIN
Etiology	Disease or injury affecting the nervous system	Tissue or potential tissue damage	Maladaptive changes that affect nociceptive processing
Descriptors	Lancinating, shooting, electrical-like	Throbbing, aching, pressure-like	Similar to neuropathic pain. Visceral pain (irritable bowel syndrome, bladder pain syndrome) may be diffuse, aching, gnawing, or sharp
Sensory deficits	Frequent (e.g., numbness, tingling, pricking)	Infrequent and in non-dermatomal or non-nerve distribution	Common, in non-dermatomal or non-nerve distribution
Motor deficits	Neurological weakness may be present	May have pain-induced weakness	Generalized fatigue common, weakness due to deconditioning
Hypersensitivity	Pain frequently evoked with non-painful (allodynia)	Uncommon except for hypersensitivity in the immediate area of an acute injury	Very common and diffuse
Pain pattern	Distal radiation common	Distal radiation less common; proximal non-dermatomal or nerve radiation frequent around anatomical structure	Diffuse spread not following anatomical referral pattern; patients often have multiple nociplastic conditions
Paroxysms	Exacerbations common and unpredictable	Exacerbations less common and associated with activity	Common, often related to psychosocial stressors
Autonomic signs	Can occur in 1/3 to 1/2 of patients	Uncommon	Sympathetic nervous

Reproduced from: Christiansen S, Cohen SP. Chronic pain: Pathophysiology and mechanisms. In: Manchikanti L, Singh V, Falco FJE, Kaye AD, Soin A, Hirsch JA (eds). *Essentials of Interventional Techniques in Managing Chronic Pain*, 2nd ed. Springer Nature Switzerland, 2024, pp 15-25 (141).

neurons as a direct consequence of a lesion or disease (6-8). In addition, IASP has also defined central sensitization as an amplification of neural signaling in the CNS, and central sensitization commonly underlying chronic pain of both neuropathic and non-neuropathic origin (146,147). Central sensitization is an amplification of neural signaling within the CNS that elicits pain hypersensitivity (148); specifically, it is marked by lasting changes in the excitability of second-order neurons within the spinal cord, induced by increased afferent activity, resulting in significant alterations to the somatosensory system itself (149). Central sensitization has been postulated to contribute to several chronic pain states, including neuropathic pain, complex regional pain syndrome (CRPS), fibromyalgia, musculoskeletal disorders, rheumatoid arthritis, osteoarthritis, and headache (148,150,151).

Further, IASP described peripheral sensitization as a state of "increased responsiveness and diminished threshold of nociceptive neurons in the periphery to the stimulation of the receptive fields" (146,147). This phenomenon occurs because of the chemical mediators released by nociceptors and various non-neuronal cells, such as mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts, at the site of tissue injury or inflammation. A plethora of signaling molecules is involved in this process including protons, adenosine triphosphate, prostaglandins (PGE2), thromboxanes, leukotrienes, endocannabinoids, growth factors (neurotrophins, granulocyte- or granulocyte-macrophage colony-stimulating factors), cytokines (IL6, IL1β, TNFα), chemokines, neuropeptides (calcitonin gene-related protein, substance P, bradykinin, histamine), lipids, and various proteases (150,152-159).

Nociceptive pain may arise from disruption of the stabilizing systems of the lumbar spine comprising the passive structures of the spinal column, as well as the spinal muscles on the neural systems controlling these muscles (48,102-105,160-164). In regard to spinal musculature, the lumbar multifidus is the largest of the back muscles to traverse the lumbosacral junction and plays an important role in stability and support of the lumbar spine (48,161). Further, the CNS, specifically the motor cortex, also facilitates dynamic stability of the multifidus and lumbar spine. Central processing changes in the primary motor cortex may contribute to sustained impaired control and loss of functional stability of the lumbar spine in patients with chronic low back pain (102).

5.2 Neurostimulation Techniques

The use of electricity in medicine for pain management dates back thousands of years BCE, when humans began utilizing the electrical charges from certain fish to treat headaches and gout-related pain (57,164,165). Over the years, advancements in this field led to the development of electrodes, implantable receivers, implantable pulse generators (IPGs), and numerous studies demonstrating the effectiveness of peripheral neurostimulation (164-170).

The mechanism of neurostimulation is based on the gate control theory proposed by Melzack and Wall in 1965 (12,13). This theory hypothesizes that applying non-painful stimuli to the low-threshold, non-nociceptive, large-diameter A delta fibers activates inhibitory interneurons, which then inhibit the nociceptive A delta and C fiber conduction and discharge in the dorsal horn, thereby preventing pain transmission to the central cortex (171). The first reported use of peripheral nerve stimulation (PNS) occurred in the mid-1960s (171). Since then, there have been significant advancements in the techniques, equipment, and devices used. Once the electrode is positioned near the targeted peripheral nerve, it is connected to a power source that delivers electrical pulses, generally resulting in a sensation of paresthesia (172), motor contraction, or both.

5.3 Mechanism of Action of Peripheral Nerve Stimulation

The concept of peripheral and central sensitization following nerve injury is essential for understanding the development of chronic neuropathic pain. Nerve injury initiates an inflammatory cascade that releases various proinflammatory cytokines and neuropeptides, leading to the heightened excitability of nociceptive afferents. This sensitization affects not only nociceptive-specific and wide dynamic range second-order neurons in the dorsal horn of the spinal cord but also reduces inhibitory GABAergic and glycinergic transmission. Although still under discussion and research, alternative theories to the gate control theory have been proposed to explain the mechanism of peripheral stimulation. These include stimulation-induced blockade of cell membrane depolarization, reduce excitation of C fiber nociceptors, suppressed dorsal horn activity to reduce hyperexcitability, long-term potentiation of dorsal horn neurons, depletion of excitatory amino acids like glutamate and aspartate, and the release of inhibitory neurotransmitters such as gamma-aminobutyric

acid (GABA) (57). Researchers continue to explore the mechanisms of PNS through both basic science and clinical studies.

5.3.1 Peripheral Pathway

Chronic pain originating from the peripheral nerves increases the local concentration of mediators such as endorphins and prostaglandins, which enhances blood flow. Research has shown that peripheral nerve stimulation (PNS) can downregulate neurotransmitters, endorphins, local inflammatory mediators, and blood flow at the peripheral level (173). Additionally, electrophysiological studies have demonstrated decreased ectopic discharges, resulting in reduced transmission of afferent nociception (59). Observations by Swett and Law (174) indicated that the analgesic effect of PNS occurs at stimulus intensities above the threshold of perception but below the threshold for pain, suggesting a central mechanism for PNS rather than the gate control theory. Other studies have shown that the excitability and conduction velocity of nerves are subnormal following tetanic stimulation (175). High-frequency stimulation has been noted to cause an exponential decline in conduction velocity of both myelinated and unmyelinated nerve fibers (176). Additionally, repeated electrical stimulation of intact radial and saphenous nerves has resulted in the excitation failure of A and C fibers (177). Furthermore, sciatic nerve stimulation at low to medium frequencies in rats with sciatic nerve injury demonstrated nerve regrowth and changes in the local chemical environment (178).

5.3.2 Central Pathway

Although consistent with the gate control theory, peripheral nerve stimulation (PNS) activates A-delta fibers in the periphery, which then stimulate inhibitory interneurons in the dorsal horn, suppressing nociceptive signals from A-delta and C fibers. Additionally, literature suggests that PNS may modulate higher CNS centers, including the dorsolateral prefrontal cortex, somatosensory cortex, anterior cingulate cortex, and parahippocampal areas (179-181).

The effects on GABAergic and glycinergic transmission, along with increases in serotonin and dopamine metabolites, can also occur at the spinal level (182,183). Changes in the levels of substance P and calcitonin gene-related protein (CGRP) may also play a role (184). Additionally, as previously described, PNS enhances the inhibition of dorsal wide-dynamic range neurons (180), reduces A delta fiber activation in the medial lemniscus pathway (180,185,186), and affects the spinothalamic tract (187).

The trigeminocervical complex, extending from C2-C3 to the trigeminal nucleus caudalis, receives convergent input from various afferent sources. Nociceptive inflow to second-order neurons in the spinal cord and the trigeminocervical complex is modulated by descending inhibitory projections from brainstem structures such as the periaqueductal gray, nucleus raphe magnus, and rostroventral medulla. Stimulation of these regions produces significant antinociception (188). Consequently, it has been suggested that thalamic activation with PNS can occur without altering the underlying brainstem activation (189).

5.4 Results in Analgesia

Research has demonstrated that PNS, combined with transcranial magnetic stimulation (paired associative stimulation), can induce long-term changes in cortical excitability, potentially aiding motor recovery in post-stroke patients and those with amyotrophic lateral sclerosis (ALS) (190,191).

In contrast, studies on suboccipital PNS for migraines have demonstrated significant changes in cerebral blood flow in positron emission tomography (PET) imaging studies, suggesting alternative mechanisms such as central neuromodulation (192). Similar findings have been observed in other studies, with increased blood flow noted in the anterior cingulate and insular cortices, anteroventral insula, and thalamus (193).

Thus, the mechanism of PNS likely involves a combination of peripheral and central pathways. While large-diameter sensory fibers may directly engage the gate mechanism to decrease pain signals, activation of large motor fibers may generate physiological neural afferent signals that help gate or reduce pain. By decreasing pain signals over time, PNS therapy may disrupt the cycle of centrally mediated pain, promoting activity-dependent neuroplasticity and sustaining reduced pain levels long after active stimulation periods have ended (56,194-196).

Clinical evidence suggests clinically significant and sustained reductions in pain can persist well beyond the PNS treatment period, outcomes that have not previously been observed with conventional, permanently implanted neurostimulation devices (56). Mechanistically, it is theorized that these results may be the result of a widened therapeutic window for stimulation that enables robust and selective activation of $A\alpha/\beta$ fibers at frequencies (such as 5-150 Hz) that produce com-

fortable sensations in the region of pain, leading to multiple analgesic mechanisms from the periphery to the dorsal horn and cortex. These diverse effects may be explained in a new theory of pain management, peripherally induced reconditioning of the CNS, involving stimulation-evoked reversal of the central sensitized state that contributes to chronic pain (56).

6.0 Diagnosis Of Peripheral Nerve And/Or Neuropathic Pain And Neuromuscular Impairment

Key Question 4. What evidence supports the accuracy and value of diagnostic methods for conditions amenable to peripheral nerve stimulation?

Peripheral nerve injuries are defined as injuries to a nerve along any segment outside the CNS, namely involving the spinal root, plexus, and/or terminal nerves. These injuries can occur due to trauma, metabolic conditions and inflammation or idiopathically. Such injuries result in decreased sensation, strength and autonomic function. The cardinal symptom of peripheral nerve injury is neuropathic pain. Diagnosis is based on complete neurologic examination and complemented with imaging and electrodiagnostic testing, followed by diagnostic injections. Diagnosis can help determine the location, cause, severity and potential treatment.

6.1 History

Peripheral nerve pathology can be a diagnostic dilemma because of the varied etiology. These patients can have pain that is burning, aching, lancinating that result in hyperalgesia, allodynia and even false sense of numbness (nulliness) in the area supplied by that nerve (197). Mechanical injuries result from compression, stretching, inflammation, and partial or complete transection of the nerve (198-200).

Diabetes predisposes the patient to inflammatory neuropathy and makes the patient susceptible to entrapment neuropathy because of increased sorbitol concentration, abnormal axoplasmic transport and intraneural collagen glucose complex (201-203).

Post-traumatic neuropathy can be due to external trauma, radiotherapy or surgical intervention (201,202,204-207).

Patients with history of diabetes, nicotine use, hypertension, high triglycerides and obesity may be more prone to peripheral nerve injuries (208).

It is important to question the patient about the onset, triggering event, site and character of initial pain, referral pattern and exacerbating and relieving factors.

6.2 Physical Examination

The physical examination for nerve entrapments and neuropathic pain starts with the patient pointing to where it hurts, followed by examination of known nerve entrapment sites. Normal nerves are almost insensate to palpation, and "can be rolled underneath a thumbnail at will" (209), but the inflamed or entrapped nerve will be extremely sensitive to even light pressure, causing the patient to "literally jump out of the chair with pain" (210). There may be tenderness both proximal and distal to the site of entrapment (Valleix phenomenon) (211) and alteration in sensitivity (212).

Diagnostic injections should be performed to confirm the diagnosis of peripheral nerve involvement. However, rarely (or perhaps as an underrecognized phenomena) there will be the patient who has a history and physical exam consistent with a particular pathology but notes no temporary relief from the local anesthetic injection. The patient should be questioned as to numbness; if the patient denies anesthesia as well as analgesia, they may be resistant to that local anesthetic, and a different local anesthetic might provide pain relief as well as a definitive diagnosis (213,214).

Multifidus dysfunction is diagnosed mainly based on physical examination, which includes well-reported provocative maneuvers: the Prone Instability Test and Multifidus Lift Test (161).

6.2.1 Prone Instability Test

The Prone Instability Test aims to identify chronic low back pain due to lumbar segmental instability related to multifidus muscle dysfunction (161,215-217). The presence or absence of pain during the Prone Instability Test highlights the role of multifidus stabilization.

6.2.2 Multifidus Lift Test

The Multifidus Lift Test is designed to identify multifidus muscle dysfunction through palpation. At the lower levels of the lumbar spine, the multifidus muscle can be felt just lateral to the spinous process, in a slight depression between the spinous process and the longissimus muscle. The electromyography (EMG) activity in the muscle during this lift is related to changes in muscle thickness, which can be measured by ultrasound imaging or by simple palpation. Reduced or absent thickness change during the extremity lift procedure is thought to indicate multifidus muscle dysfunction in patients with chronic low back pain. The contraction felt during the Multifidus Lift Test is a summation of all multifidus fascicles at that level, with the deep multifidus expected to contribute the least. The intermediate and superficial muscles associated with voluntary movements may still activate even if the deep fascicles are completely inhibited (161,218). Compared to the Prone Instability Test, the Multifidus Lift Test is less

specific in targeting the deep multifidus fascicles and therefore less precise in detecting functional instability (219,220).

6.3 Imaging

There exist numerous imaging modalities used to diagnose peripheral nerve injuries, each with its varying strengths and limitations. These tests complement clinical and electrodiagnostic testing to provide a comprehensive assessment of various neuropathic pathologies. While magnetic resonance imaging (MRI) and ultrasonography are most utilized in current clinical paradigms, other modalities have evolved with a growing evidence base.

6.3.1 Diagnostic Imaging Criteria for Selective Medial Branch Stimulation

Both ultrasound and MRI can be used to assess multifidus atrophy. Ultrasound measures the muscle's cross-sectional area (221), while MRI can measure both the cross-sectional area and the grade of fatty infiltration in the multifidus muscle (222). Specifically, Grade 0 indicates a normal muscle with up to 10% of the cross-sectional area affected, Grade 1 involves 10–50% and is considered mild-to-moderate atrophy, and Grade 2 involves more than 50%, indicating moderate-to-severe atrophy (222). There is some debate about the correlation between multifidus atrophy and pain, disability or function (221,223-227).

6.3.2 Ultrasound Elastography

Conventional ultrasound has been increasingly used as an accessory diagnostic test in patients with suspected peripheral nerve injury (228). Initially, conventional ultrasound was used to detect morphological changes, including the cross-sectional areas and shapes of nerves, to determine whether a peripheral nerve was affected. However, such approaches had numerous limitations, largely due to the substantial heterogeneity of normal versus affected peripheral nerves as observed with ultrasound. Therefore, ultrasound was associated with poor sensitivity and specificity for the diagnosis of peripheral nerve injury (229,230), though ultrasound may show structural impingements and entrapments..

6.3.3 Magnetic Resonance Neurography

With focal neuropathies, whether traumatic or due to nerve entrapment, magnetic resonance neurography (MRN) has improved diagnostic accuracy by directly visualizing underlying nerve lesions and providing information on the exact lesion localization, extension, and spatial distribution (231). By using heavily T2-weighted sequencing, axonal disruptions as early as 24-48 hours post-injury may be identified in areas with increased intraneural T2-weighted signals. Experiments with this technique showed increased intensity distal to a lesion, which may correlate with Wallerian degeneration secondary to axonal injury. Further observations showed normalization of T2 weighted signals indicating nerve regeneration, which starts proximally and progresses distally. Despite its clinical applications, magnetic resonance neurography does have limitations: price, availability (as 3-Tesla MRI machines are required), and over or under diagnosing of neuropathic conditions (231,232).

6.3.4 Computed Tomography (CT)

Computed tomography (CT) studies produce incredibly detailed images of bones and joints but have limited utility in the diagnosis of peripheral nerve injuries, since nerves are largely radiolucent. However, CT can be particularly useful for peripheral nerve injury diagnosis when nerve compression is suspected to occur in the context of bony fragments secondary to trauma, bone spurs, or hardware. Similarly, CT can be very valuable in cancer patients by helping to identify the size and growth of tumors, along with the associated compression of adjacent nerves. Further, CT myelography, a specialized CT scan following intrathecal contrast injection, can be utilized to visualize spinal nerves more clearly (233-235). Given these indications and limitations, CT for nerve pathology should be used judiciously.

6.3.5 Positron Emission Tomography (PET)

Allodynia, often a cardinal symptom of peripheral nerve injury, can result from altered glucose metabolism in injured nerves. Such metabolic changes can be accurately detected by PET by using glucose molecules modified with fluorine-18 (18F-FDG) (236-238). This compound decays by emitting positrons that collide with electrons, ultimately producing photons. PET imaging precisely localizes photon emissions to map areas of high glucose uptake. Differences between photon emissions from injured and healthy nerves can therefore to help identify the location as well as the severity of peripheral nerve injuries.

6.3.6 Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a novel,

high resolution imaging modality with emerging evidence. Using infrared light, OCT produces cross-sectional images on a micrometer scale. It is an in-vivo imaging technique that can depict detailed nerve structure at the fascicular and axonal level. It is a complementary tool for ultrasound, and is often likened to an "optical biopsy" (239). OCT also has the potential to assist in intraoperative diagnosis, and aid in microsurgical interventions for peripheral nerve injuries.

6.4 Neurophysiologic Testing

Electrodiagnostic studies, which consist of nerve conduction study (NCS) and electromyography (EMG) testing, help to differentiate neuropathic from myopathic or neuromuscular junction pathologies. Additionally, NCS and EMG testing can further characterize peripheral nerve injuries based on the axonal and/or myelin pathologies implicated, as well as identify the temporal course (hyperacute, acute, subacute, or chronic) and severity of a neuropathic lesion. Differentiating axonal loss from demyelination lesions requires an understanding of the patterns of changes that occur over time in each pathological condition. Localizing the peripheral nerve injury is determined from the distribution of electrodiagnostic abnormalities, and a final diagnosis can be reached after analyzing overall patterns of NCS and EMG findings in the appropriate clinical context (Table 6) (240).

With EMG, decreased recruitment of motor unit action potential (MUAP) occurs in weak muscles immediately following a peripheral nerve injury. Because some axons and their motor units have been lost, the only means of increasing contractile force is to fire the remaining available motor units faster, resulting in a pattern of decreased recruitment. No abnormal spontaneous activity or change in MUAP morphology is seen at the onset of the lesion because those changes occur in time (240).

Electrodiagnostic studies can play a crucial role in aiding the diagnosis and prognosis of peripheral nerve injuries throughout the body. However, to enhance the sensitivity and specificity of these studies, they must be evaluated within the specific clinical context. Electrodiagnostic studies are highly operator and interpreter dependent, leading to a wide range of sensitivity and specificity values, as discussed in the following paragraph (241).

6.5 Neuropathic Pain Testing

It is important to distinguish neuropathic pain, which arises from actual or threatened damage to nonneural peripheral tissue, from other forms of pain. Neuropathic pain is generally unresponsive to analgesics such as opioids. To identify neuropathic pain with screenings, multiple self-administered tests are available. Of these, the PainDETECT questionnaire is commonly used (242). The other tests include Douleur Neuropathique 4 Questions (DN4) (243), and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (244). These tests rely on typical symptoms seen with neuropathic pain, including burning, electric shocks, pins and needles, and tingling. Estimates of neuropathic pain in the general population suggest a prevalence of 7% to 10% (5) increasing around 20% to 30% in people with diabetes (245-248). However, it is crucial that history and physical examination, imaging, neurophysiologic testing, and other tests are applied properly before the diagnosis of peripheral nerve or neuropathic pain, specifically prior to selection for implantable PNS.

6.6 Diagnostic Nerve Injections

In interventional pain management, diagnostic injections have become an integral part of the diagnosis, prior to application of more interventional techniques. The reason behind this is that a painful structure will

Table 6. *Time-related changes in axonal loss.*

	Immediate	Hyperacute	Acute	Subacute	Subacute– Chronic	Chronic
		< 3 Days	> 1 Week < 3–6 Weeks	> 3–6 Weeks < 2–3 Months	> 2–3 Months < Many Months/ Years	> Several Months/ Years
Clinical findings	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Normal/ abnormal
Nerve conductions	Normal	Normal	Abnormal	Abnormal	Abnormal	Normal/ abnormal
MUAP recruitment	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Spontaneous activity	Normal	Normal	Normal	Abnormal	Abnormal	Normal
MUAP morphology	Normal	Normal	Normal	Normal	Reinnervated	Reinnervated

MUAP: Motor unit action potential

cease being painful for at least the duration of action of the local anesthetic, whereas anesthetic injection of a non-painful structure will not alter the pain report. Often, as in the case of the diagnosis of facet joint pain as well as sacroiliac joint pain, by repeating the injection with an anesthetic agent that has different duration of action reproducing analgesic response, is felt to it increase the probability that the injected joint is the actual source of pain. Thus, to ensure accuracy and validity, these injections should be controlled and verified for delivery of analgesic agents and to eliminate placebo response. The value and validity of diagnostic injections in facet joint pain as well as sacroiliac joint pain, have been published in multiple studies, as well as in the ASIPP guidelines (40,129,249-253). The ASIPP guidelines (40) showed Level of Evidence I to II with moderate to strong strength of recommendation in the diagnosis of lumbar facet joint pain. For cervical and thoracic spinal pain, the Level of Evidence was II with moderate strength of recommendation. The evidence was Level III with recommendation for diagnostic sacroiliac joint injections. However, the same level of evidence is not available for diagnosis of peripheral nerve pathology.

7.0 Evidence Review And Synthesis

Key Question 5. How effective are peripheral nerve stimulation interventions in managing chronic pain, and what evidence supports their effectiveness?

Peripheral nerve stimulation (PNS) is a rapidly evolving neuromodulation technology in interventional pain management that provides analgesic effects for chronic pain patients. The prevalence, economic impact, pathophysiology, and diagnostic modalities have been described. With advancement of image guidance, improved surgical techniques, and further development of PNS devices, many peripheral nerves from different body regions can be targeted for treatment. Current research has broadened the application of PNS to treat peripheral nerves in the craniofacial, upper and lower extremities, abdomen, back, and pelvis (Table 7) (57). PNS implants are increasingly being used to treat intractable pain, based on their minimally invasive nature, FDA clearance, and the emerging evidence.

As described in the methodology section: literature search, search strategy, methodologic quality or bias assessment, data collection, analysis, and evidence synthesis were performed. Following these systematic steps, recommendations were made. Two review authors independently established appropriate criteria and completed the methodology for each section. Any disagreements between the 2 review authors were resolved by a third author. When an issue of conflict of interest was raised in reviewing the studies (regarding authorship), the involved authors were not allowed to review those studies for quality assessment.

7.1 Literature Search

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

1. PubMed from 2010
   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. FDA-cleared reported evidence
9. Communication with investigators active in the field.
10. Bibliographies of reviewed papers were also examined.

The search period was from 2010 through August 2024.

7.1.1 Search Strategy

The following search terminology was used.

(((((peripheral nerve stimulation) AND ((systematic review OR 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)

7.1.2. Study Selection Criteria

All appropriately performed RCTs and observational studies after 2010 with at least 6-months follow-up were considered for inclusion. Furthermore, for the observational studies, the requirements were that at least 25 patients were studied.

7.2 Results

The results of literature search are shown in Fig. 6. Our comprehensive literature search criteria led to multiple publications considered for inclusion (60,19-27,45-73,75,76,254-361) with 8 systematic reviews (19-26), 26 RCTs (45-54,254-269), and 100 observational studies (either retrospective or case series or reports) (55-65,73,76,268,271-297,299-301,304-356,358,360,361). In addition, we also identified one guideline (27) and multiple narrative reviews.

7.2.1 Systematic Reviews and/or Meta-Analysis

We identified 8 systematic reviews and/or meta-analysis, all of which were performed since 2020 (19-26). One systematic review was excluded (26). Quality assessment of systematic reviews and/or meta-analysis based on Cochrane Review criteria for systematic reviews showed 5 fair quality (20,22-24) and 3 good quality publications (19,21,25) as shown in Table 8. The majority of the systematic reviews suffered with one or more deficiencies with inclusion of non-randomized studies, observational studies with no sample size

Table 7. *Peripheral nerves commonly used for PNS.*

Head/Neck	Occipital nerves Craniofacial nerves Sphenopalatine ganglion Trigeminal nerve and branches Vagus nerve Phrenic nerve
Upper Extremities	Brachial plexus Suprascapular nerve Axillary nerve Radial nerve Median nerve Ulnar nerve
Lower Extremities	Sciatic nerve Obturator nerve Femoral nerve Lateral femoral cutaneous nerve Genicular nerves Saphenous nerve Infrapatellar saphenous nerve Common peroneal nerve Superficial peroneal nerve Deep peroneal nerve Tibial nerve Sural nerve
Abdomen/Trunk/ Back/Pelvis	Intercostal nerve Medial branch nerve Ilioinguinal nerve Iliohypogastric nerve Genitofemoral nerve Superior gluteal nerve Superior cluneal nerve Middle cluneal nerve Pudendal nerve Proximal peripheral nerve root

Modified from: Ong Sio LC, Hom B, Garg S, Abd-Elsayed A. Mechanism of action of peripheral nerve stimulation for chronic pain: A narrative review. *Int J Mol Sci* 2023; 24:4540 (57).

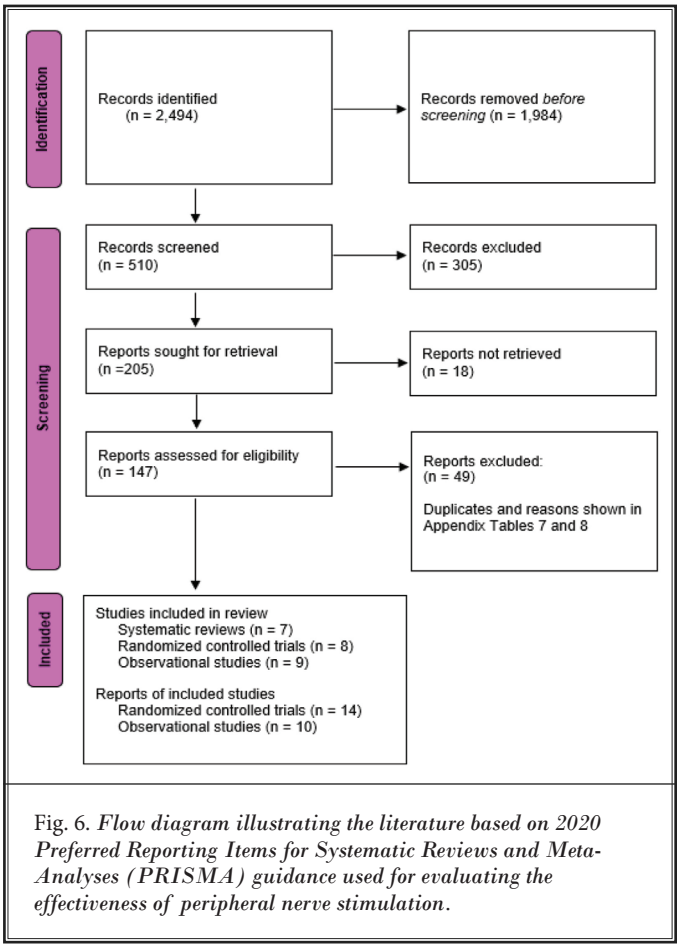


Fig. 6. *Flow diagram illustrating the literature based on 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance used for evaluating the effectiveness of peripheral nerve stimulation.*

requirement, case reports, and short-term follow-up; inclusion of studies which did not include implantable peripheral nerve stimulation; and lack of appropriate methodologic quality assessment; and finally, lack of GRADE assessment.

Among the 7 systematic reviews meeting the inclusion criteria, Deer et al (20) published in 2020, categorized the evidence as Level I for occipital nerve stimulation and for chronic low back pain targeting the cluneal nerve and its branches; Level II for sphenopalatine ganglion stimulation, poststroke shoulder pain, and neuropathic pain of extremities; and Level III for posterior tibial nerve stimulation.

Helm et al (22) also published a systematic review of effectiveness and safety of PNS for chronic pain in 2021, similar to Deer et al (20) with various levels of evidence. They found Level II evidence supporting the use of PNS to treat refractory peripheral nerve injury, with Level III evidence for tibial nerve stimulation for pelvic pain and surgically placed cylindrical leads or sphenopalatine ganglion stimulation for cluster headaches.

Xu et al (23) published a systematic review in 2021 presenting Level I and II evidence of PNS in chronic migraine headache; Level II evidence in cluster headaches, post-amputation pain, chronic pelvic pain, chronic low back pain, and lower extremity pain; and Level IV evidence of peripheral neuropathic pain and post-surgical pain.

Amirianfar et al (24) provided a systematic review of peripheral nerve stimulation for chronic knee pain following total knee arthroplasty, published in 2023, with low level of evidence.

Among the good quality publications, Barad et al (19) performed a systematic review and provided practice guidelines for percutaneous interventional strategies for migraine prevention in 2022, which included implantable peripheral neurostimulation strategies. Their recom-

Table 8. *Criteria used in quality assessment of systematic reviews.*

	Amirianfar et al, 2023 (24)	D'Souza et al, 2023 (25)	Char et al, 2022 (21)	Barad et al, 2022 (19)	Helm et al, 2021 (22)	Xu et al, 2021 (23)	Deer et al, 2020 (20)
1. Is a focused clinical question clearly stated?	Y	Y	Y	Y	Y	Y	Y
2. Are the search methods used to identify relevant studies clearly described?	Y	Y	Y	Y	Y	Y	Y
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	Y	Y	Y
4. Was selection bias avoided?	Y	Y	Y	Y	Y	Y	Y
5. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	Y	Y	Y
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	Y	Y	Y	Y
8. Were the methods used to combine the findings of studies appropriate?	N	Y	Y	Y	N	N	N
9. Was the scientific quality of the included studies used appropriately in formulating conclusions?	N	N	Y	Y	N	N	N
10. Was publication bias assessed?	N	N	N	N	N	N	N
11. Was the conflict of interest stated?	Y	Y	Y	Y	Y	Y	Y
12. Are the stated conclusions supported by the data presented?	Y	Y	Y	Y	Y	Y	Y
TOTAL	9	10	11	11	9	9	9

Y = yes; N = No; C/T = can't tell; N/A = not applicable
Adapted from:
Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7:10 (91).
Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896-1900 (92).
Marinopoulos SS, Dorman T, Ratanawongsa N, et al. Effectiveness of continuing medical education. *Evid Rep Technol Assess (Full Rep)* 2007; 149:1-69 (93).

mendation was that overall strength for the certainty of evidence was moderate with a moderate effect size.

Char et al (21) published a good quality systematic review of implantable peripheral nerve stimulation for peripheral neuropathic pain in 2022, with the results showing poor results with very low quality or low quality of evidence supporting modest to substantial improvement in pain and neurological function. They also showed that phantom limb pain was the only indication for PNS that had moderate level of evidence.

Finally, D'Souza et al (25), in a good quality 2023 systematic review of peripheral nerve stimulation for low back pain, concluded that neuromuscular stimulation may provide modest to moderate pain relief in patients with low back pain, even though evidence was limited due to risk of bias, clinical and methodological heterogeneity, and inconsistency in data.

7.2.2 Randomized Controlled Trials (RCTs)

Of the 26 publications of RCTs identified in literature search and considered for inclusion (45-54,254-269), with exclusion of duplicates and those not meeting the inclusion criteria, there were 8 RCTs which met criteria for inclusion in this analysis (45-49,51-53), one of which was just submitted for publication, but was used for FDA approval of a new indication (51). There were 2 RCTs (45,48), which resulted in 6 publications (45,48,50,258-260).

Appendix Table 7 shows description of the excluded trials.

Methodologic quality assessment of randomized

trials utilizing Cochrane review criteria and IPM-QRB criteria are shown in Tables 9 and 10, respectively. Based on the Cochrane review criteria, 7 of the 8 RCTs were of high quality (45-49,51,53) and one was of moderate quality (52) as shown in Table 9. Based on utilizing IPM-QRB criteria, as shown in Table 10, of the 8 RCTs, one was of high quality (49) and 7 was of moderate quality (45-48,51-53). Only one trial was of high quality with both Cochrane review and IPM-QRB (49).

Study characteristics of the RCTs assessing the effectiveness of PNS are shown in Table 11.

7.2.3 Nonrandomized or Observational Studies

Of the 100 observational studies or case series identified in literature search and considered for inclusion (55-65,73,76,268,271-297,299-301,304-356,358,360,361), with exclusion of duplicates and those not meeting the inclusion criteria, there were 9 studies meeting the inclusion criteria (60-62,64,270,281,282,311,361)

Appendix Table 8 shows description of the excluded studies.

Table 12 shows assessment of methodologic quality utilizing Newcastle-Ottawa Quality Assessment Scale for cohort studies, with 5 of 9 studies scoring 6 or higher, consistent withhigh quality (60-62,73,71,281,311), whereas 4 studies were of moderate quality (64,270,282,361).

Based on assessments utilizing IPM-QRBNR (Table 13), there were no high-quality studies; however, 6 of the studies were of moderate quality (60,64,270,281,282,361), whereas 3 of them were of low quality (61,62,311).

Study characteristics of the nonrandomized or observational studies are described in Table 14.

Table 9. *Methodological quality assessment of randomized trials of peripheral nerve stimulation utilizing Cochrane review criteria.*

	Goree et al, 2024 (47)	Hatheway et al, 2024 (53)	CFPNS study, 2024 (51)	Gilligan et al, 2021 (48)	Gilmore et al, 2019 (45)	Deer et al, 2016 (46)	Dodick et, al, 2015 (49)	Serra & Marchioretto, 2012 (52)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y	N
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	Y	N
Patient blinded	N	N	N	N	N	N	U	N
Care provider blinded	N	N	N	U	N	N	Y	U
Outcome assessor blinded	Y	N	N	Y	Y	Y	U	U
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	N	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	U
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y
Co-intervention avoided or similar in all groups	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	N	N	N	N	N	N	U	Y
SCORE	10/13	9/13	9/13	10/13	10/13	9/13	10/13	7/13

Y = yes; N = no; U = nuclear

Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (87).

Table 10. *Methodologic quality assessment of randomized trials of peripheral nerve stimulation utilizing IPM – QRB criteria.*

		Goree et al, 2024 (47)	Hatheway et al, 2024 (53)	CFPNS study, 2024 (51)	Gilligan et al, 2021 (48)	Gilmore et al, 2019 (45)	Deer et al, 2016 (46)	Dodick et al, 2015 (49)	Serra & Marchioretto, 2012 (52)
I.	TRIAL DESIGN AND GUIDANCE REPORTING								
1.	CONSORT or SPIRIT	3	3	3	3	3	3	3	1
II.	DESIGN FACTORS								
2.	Type and Design of Trial	2	2	2	2	2	2	3	1
3.	Setting/Physician	2	2	2	2	2	2	2	1
4.	Imaging	1	3	3	1	1	1	3	2
5.	Sample Size	2	2	2	3	1	3	3	1
6.	Statistical Methodology	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS								
7.	Inclusiveness of Population	0	2	2	0	0	0	2	2
	• ≥ 50% response to trial								
8.	Duration of Pain	2	2	2	2	2	2	2	1
9.	Previous Treatments	2	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	1	1	3	2	2	2	2
IV.	OUTCOMES								
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	3	2	2	2	1
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	0	2	1
13.	Description of Drop Out Rate	1	1	1	1	1	1	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	2	2	2
15.	Role of Co-Interventions	1	1	1	1	1	1	1	0
V.	RANDOMIZATION								
16.	Method of Randomization	2	2	2	2	2	2	2	0
VI.	ALLOCATION CONCEALMENT								
17.	Concealed Treatment Allocation	2	2	2	2	2	0	2	0
VII.	BLINDING								
18.	Patient Blinding	0	0	0	0	0	0	0	0
19.	Care Provider Blinding	0	0	0	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	1	0	0
VIII.	CONFLICTS OF INTEREST								
21.	Funding and Sponsorship	-3	-3	-3	-3	-3	-3	-3	2
22.	Conflicts of Interest	-2	-2	-2	-3	-2	-3	-2	2
	TOTAL	24/48	27/48	27/48	26/48	23/48	21/48	30/48	23/48

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (88).

Table 11. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
IMPLANTED PERIPHERAL NERVE STIMULATION								
Hatheway et al, 2024 (53) P, RA, AC Quality Scores: Cochrane = 9/13 IPM-QRB = 27/48	Randomized = 89 Intervention group with PNS permanent implant = 48 Control arm with conventional medical management = 31	After successful trial stimulation, 48 of 58 patients were included The stimulation was according to the protocol	Conventional medical management	NRS, ODI, PGIC, BPI-SF, quality-of-life metric (EQ-5D-5L), and BDI 3 months for control group and 6 months for intervention group Ongoing study for follow-up for 3 years for intervention group	At 6 months, 88% response rate with a 70% average reduction in pain in the intervention group Control group, 3% responder rate with 6% pain reduction Pain relief significantly different $P < 0.001$. No major adverse events	RCT comparing with conventional medical management with a 6-month follow-up with ongoing follow-up for 3 years	Not a blinded study The follow-up for conventional medical management was only 3 months	Positive trial Data appears to be reliable showing successful treatment with PNS
CFPNS study, 2024 (51) RA, patient as their own control Quality Scores: Cochrane = 9/13 IPM-QRB = 27/48	60 patients with permanent implantation 56 of 58 returning patients noted > 50% relief with stimulation during 7 day trial Responder rate 93% Patients were then randomized to continue stimulation (activated group) or have the transmitter removed for 3 months (deactivated) When the transmitter was returned, pain scores decreased to the same value as the active group (at least 50% relief) Patients were followed for 1 year	Occipital or trigeminal branch targets Implanted electrode array and separate receiver placed using fluoro External transmitter 7 days of active stimulation in both groups, transmitter was removed in the deactivated group Activated group continued with stimulation on	Deactivated group Stimulation off	Proportion of patients who experienced significant pain relief (at least 50%) 3 months after permanent implant VAS, BPIF, and MPQ-SF-2 were used to measure changes in pain Additional functional outcome measures included the PGIC and the SF-36 Follow-up: 3, 6, 12 months	At 3 months, 69% of the Active stimulation group experienced significant pain relief, while only 11% of the Deactivated group reported significant pain relief The mean VAS reduced by 62% and 8.5% in the Active and Deactivated groups, respectively When patients within the Deactivated group crossed over after 3 months, the cross-over patients reported similar reduced pain scores compared to those reported by the Active arm patients Similar results were found for the functional outcome measures After the cross-over, pain relief was maintained through the 12-month follow-up period for all patients While device-related complications occurred, no SAEs were reported throughout the study for any patients	RCT with appropriate sample size First study studying craniofacial pain and utilizing peripheral nerve stimulation leads rather than spinal cord stimulation leads for occipital stimulation Large number of implanted patients	No patient or observer blinding; patients served as their own control	Positive trial Data appears to provide reliable and reproducible, successful PNS treatment

Table 11 cont. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Gilligan et al, 2021 (48) RA Quality Scores: Cochrane = 10/13 IPM-QRB = 26/48	N=204 176 included in the 1-year analysis 156 included in the 2-year analysis 133 included in the 3-year analysis 119 included in the 4-year analysis 126 included in the 5-year analysis Adults with refractory, mechanical chronic low back pain associated with impaired neuromuscular control of the lumbar multifidus muscle were evaluated in a 5-year longitudinal follow-up of the Reactiv8-B randomized controlled clinical trial	The implant procedure was performed with placement of the leads bilaterally An intraoperative trial confirmed contraction of the multifidi in response to the electrical stimulation of the medial branch Therapeutic stimulation (102 patients)	The implant procedure was performed with placement of the leads bilaterally An intraoperative trial confirmed contraction of the multifidi in response to the electrical stimulation of the medial branch Sham stimulation=102 patients	The difference in proportion of responders in the treatment and sham control group at 120 days post randomization A responder was defined as a participant who responded with > 30% reduction from baseline LBP, VAS, ODI, EQ-5D-5L index, PPR, SGIC, LBP resolution (VAS ≤ 2.5 cm)	Primary endpoint with improvement of 30% was not statistically significant at 120 days (57.1% vs. 46.6%) The mean group difference in VAS improvement (-3.3 vs. -2.4) was significant in favor of the treatment Cumulative proportion of responders analysis of the primary outcome data showed that across all possible response threshold, treatment was superior to sham control Adverse events were seen in 3.9% at the end of 12 months At 5 years (n=126) low back pain VAS had improved from 7.3 to 2.4 cm and 71.8% of participants had a reduction of > 50% ODI improved from 39.1 to 16.5 Opioid intake was reduced or discontinued	RCT of selective lumbar media branch stimulation with large population	Lack of improvement at the end of 12 months despite a low bar of 30% improvement Not placebo-controlled	Positive trial Very well designed with an extensive long-term follow-up provided clinically substantial and durable benefit with a favorable safe profile in patients with refractory chronic low back pain associated with multifidus muscle dysfunction Due to the nature of the muscle dysfunction, we may not see appropriate results until well after 1 year in reference to the improvements

Table 11 cont. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Deer et al, 2016 (46) RA Quality Scores: Cochrane = 9/13 IPM-QRB = 21/48	94 patients were implanted and then randomized to the treatment (45) or the control group (49) Anatomical location of the implant lead was: Upper extremities = 26 Lower extremities = 27 Trunk = 41 Total = 94	All patients had Bioness StimRouter® systems placed. Active stimulation vs. no stimulation with crossover allowed at 90 days. Percutaneously implanted with external generator. 10 minutes to 12 hours of stimulation per day, mean 6 hours, for 3 months,	Received no therapeutic stimulation and a stable dose of pain medication was given	NRS, BPI, QoLSF-12v2, PGIC 3 months for pain relief; 1 year for safety	Mean reduction of pain at 3 months was 27%	RCT with appropriate sample size	There was no trial stimulation 30% decrease in pain was considered as the outcome criteria, which is inferior to 50% relief usually required. Further, the results showed 27.2% improvement in the treatment group compared to 2.3% in the control group, which is significantly less than expected 50% improvement Sample size is too small once the numbers were divided to subgroups variable with 26 for upper extremities, 27 for lower extremities, and 41 for trunk	Negative trial Overall, appropriately designed trial; however, the outcomes criteria were with a low bar. Finally, the response rate was 38% in the treatment group and 10% in the control group Pain reduction was even worse with 27.2% reduction from baseline in the treatment group Overall, this study does not add any evidence to peripheral nerve stimulation

Table 11 cont. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Dodick et al, 2015 (49) RA, DB Quality Scores: Cochrane = 10/13 IPM-QRB = 30/48	Headache A total of 268 patients were enrolled from 15 investigational sites between June 30, 2005, and August 20, 2010, with permanent implants applied in 157 patients	N=102 ONS device was permanently implanted following a successful trial to treat occipital neuralgia Patients were randomized either into an active n = 102 or control group n = 52 in a 2 to 1 ratio Patients in active group were programmed for appropriate stimulation	Patients were randomized either into an active n = 102 or control group n = 52, in a 2 to 1 ratio Patients in the control group were given a sham programmer and did communicate with the IPG	1. Number of headache days 2. Pre- and post-VAS 3. MIDAS 4. Zung PAD 5. QoL, satisfaction 6. Adverse events 4 weeks before the start of the study, and again between 48 and 52 weeks Questionnaires at 24 and 52 weeks	Headache significantly reduced by 6.7 (68.4) days (ITT group) and 7.7 (68.7) days (ICM cohorts) 59.5% had 30% reduction in end points All subjects with improved MIDAS and Zung PAD scores 65.4% ITT and 67.9% ICM reported good to excellent response 70% adverse event rate (183 total), of whom 8.6% were hospitalized and 40.7% required surgical revision	Randomized, multicenter, double-blind, controlled study with a large sample size. Implantation procedure was performed after a successful trial defined as at least 50% reduction in pain or adequate paresthesia coverage in the painful areas Multiple outcome parameters were utilized to assess the effectiveness Over 65% of the patients reported good to excellent report and weaknesses, significant adverse effects rate with 183 total of whom 8.6% were hospitalized and 40.7% required surgical revision	Weak outcome measures with 30% reduction in 59.5% of the patients The percentage of patients who achieved a 30% and 50% reduction in headache days and/or pain intensity were 59.5% and 47.8% respectively The control group had programming changes with the sham programming which may or may not be considered as placebo	Positive trial They performed randomized, double-blind, controlled study with reasonable size population and follow-ups The results showed moderate evidence with 50% reduction in headache of 47.8% of the patients

Table 11 cont. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Serra & Marchioretto, 2012 (52) RA Quality Scores: Cochrane = 7/13 IPM-QRB = 23/48	Chronic migraine headache 30 patients were randomized to "stimulation on" and "stimulation off" arms Patients crossed over after one month or when their headache worsened	n = 30 Patients underwent trial stimulation with 2 leads to stimulate the contralateral nerves Patients were randomized to "stimulation on" or "stimulation off" groups In the treatment group, it was "stimulation on"	n = 30 Patients underwent trial stimulation with 2 leads to stimulate the contralateral nerves Patients were randomized to "stimulation on" or stimulation off groups In the treatment group, it was "stimulation on"	MIDAS, SF-36, NRS-11 1-mo crossover 1-y follow- up	On arm significantly better than off arm ($P < 0.05$) Quality of life significantly improved ($P < 0.05$) during study Decreased medication use	A randomized trial with multiple outcome parameters with implantation after trial stimulation	A single center study with a relatively small number of patients and without a control group Two groups with stimulator on and off were compared after randomization	Positive trial Relatively small study with appropriate follow-up with moderate methodologic quality providing limited evidence for occipital nerve stimulation in the treatment of chronic migraine
60-DAY TEMPORARY STIMULATION								
Goree et al, 2024 (47) RA, PC Quality Scores: Cochrane = 10/13 IPM-QRB = 24/48	n = 40 Patients with postoperative pain after knee replacement were included	Percutaneous PNS implant utilizing SPR Therapeutics leads was performed in all patients Subjects in the treatment group received stimulation	Subjects in the placebo group received sham stimulation and underwent simulated testing, but no stimulation output from the pulse generator	≥ 50% reduction in average pain from baseline Functional outcomes: 6MWT, WOMAC, QoL	60% (12 of 20) subjects in the PNS group responded with >50% pain relief relative to baseline during the primary endpoint of weeks 5-8 compared to 24% (5 of 21) in the sham group PNS group also walked a significantly greater distance at EOT than did those in the placebo sham group (6MWT; + 47% vs -9% change from baseline)	RCT	Small number of patients Comparisons were not performed between the groups, rather they were performed from baseline	Positive trial Reasonably designed RCT showing evidence compared to baseline parameters rather than comparison to placebo group

Table 11 cont. *Study characteristics of randomized controlled trials assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Comparator/ Control**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Gilmore et al, 2019 (45) RA, DB Quality Scores: Cochrane = 10/13 IPM-QRB = 23/48	28 patients Traumatic lower extremity amputees with residual and/or phantom limb pain 28 randomized with 15 followed for 1 year Ultrasound placed SPR PNS placed over the sciatic and femoral nerves.	Group I had 8 weeks of stimulation Group 2 had 4 weeks of sham stimulation then crossed over to stimulation for 4 weeks Leads were removed at 8 weeks.	8 weeks of PNS, SPR Sprint®, vs 4 weeks of placebo followed by 4 weeks of crossover PNS	≥ 50% reduction in NRS, BPI, PGIC 12 months	67% of treated group had ≥ 50% reduction in pain at 12 months 0% of sham group had ≥ %50% relief of pain 17% of sham group had ≥ 50% relief of pain after cross over.	Randomized, double-blind, controlled trial with a 12-month follow-up funded by the Department of Defense. Desired outcomes were appropriate with 50% reduction in average pain Significantly more participants in Group I reported > 50% reduction in average weekly pain at 12 months (67%) or 6 of 9 patients compared with Group II at the end of the placebo period (0%) or 0 of 14 The study also showed reductions in depression, which were significantly greater at 12 months in Group I compared Group II at crossover	There is no demonstration of placebo effect with 0% relief	Positive trial Well-designed RCT with funding from the Department of Defense. However, senior author, JW, is from SPR Therapeutics.

AC = active control; BDI = Beck Depression Inventory; = Brief Pain Inventory; BPIF = Brief Pain Inventory Facial; BPI-SF = Brief Pain Inventory Short Form; DB = double-blind; EOT = end of treatment; EQ-5D-5L = EuroQol-5 Dimension-5 Levels; ICM = Intractable chronic migraine; IPG = implantable pulse generator; IPM-QRB = Interventional Pain Management techniques–Quality Appraisal of Reliability and Risk of Bias Assessment; ITT = Intent-to-Treat; LBP = low back pain; MIDAS = Migraine Disability Assessment Scale; MPQ-SF-2 = Short-Form McGill Pain Questionnaire-2; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; ONS = occipital nerve stimulation; PAD = Pain and Distress; PGIC = Patient Global Impression of Change; PNS = Peripheral nerve stimulation; PPR = Percent of pain relief ; QoL = Quality of Life; QoLSF-12v2= Quality of Life SF-12v2 Health Survey; RA = randomized; RCT = randomized controlled trial; SAEs = serious adverse events; SF-36 = 36-Item Short Form Survey Instrument; SGIC = Subject global impression of change; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 6MWT = 6-minute walk test

Table 12. *Newcastle-Ottawa quality assessment scale for cohort studies of PNS.*

	Aman et al, 2024 (62)	Lin, 2024 (64)	Abd-Elsayed & Moghim, 2023 (270)	Früh et al, 2023 (311)	Gilmore et al, 2023 (60)	Huntoon et al, 2023 (61)	Oswald et al, 2019 (361)	Bouche et al, 2017 (281)	Colini Baldeschi et al, 2017 (282)
SELECTION									
1. Representativeness of the exposed cohort	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Selection of the nonexposed cohort	N	N	N	N	N	N	N	N	N
3. Ascertainment of exposure	Y	Y	Y	Y	Y	Y	N	Y	Y
4. Demonstration that outcome of interest was not present at start of study	Y	Y	Y	Y	Y	Y	Y	Y	Y
COMPARABILITY									
1. Comparability of cohorts on the basis of the design or analysis	N	N	N	N	N	Y	N	N	N
OUTCOME									
1. Assessment of outcome	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was follow-up long enough for outcomes to occur	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Adequacy of follow up of cohorts	Y	N	N	Y	Y	Y	N	Y	N
TOTAL	6/8	5/8	5/8	6/8	6/8	7/8	4/8	6/8	5/8

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (89).

7.3 Assessment of Evidence by GRADE Criteria

GRADE assessment criteria were applied to RCTs of PNS interventions for the same outcome and similar certainty of evidence as shown in Table 15. In this analysis, we developed certainty of assessment with study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Based on the above analysis, 6 (45,47-49,51,53) of the 8 RCTs (45-49,51-53) showed effectiveness with moderate certainty.

7.4 Qualitative and Quantitative Evidence Synthesis

Due to inability to perform meta-analysis, quantitative synthesis was not performed.

Qualitative evidence is based on randomized (45-49,51-53) and nonrandomized studies (60-62,64,270,281,282,311,361). There was moderate or Level II evidence. With incorporation of GRADE evidence with moderate impact and certainty, overall evidence was downgraded to fair or Level III with moderate recommendation.

Among the RCTs, 2 recent publications in 2024 by Hatheway et al (53) and CFPNS study (51) showed positive results with reliable and reproducible data. Hatheway et al (53) included 89 patients with 31 randomized to control arm with conventional medical management. At 6-month follow-up, they showed 88% response rate in the treatment group with significant difference compared to the control group. Similarly, CFPNS study (51) evaluated 60 patients in an FDA evaluation study with stimulation on and off stimulating occipital or trigeminal branch nerves. Results were positive with 69% of the active stimulation group experiencing significant pain relief, while only 11% of the deactivated group reported significant pain relief. The relief patterns were sustained at 12-month follow-up.

Another important study was by Gilligan et al in 2021 (48,258-260) evaluating selective medial branch stimulation in 204 patients with long-term follow-up and overall positive results. There were multiple issues related to this study in understanding and measuring the improvement in refractory low back pain.

Among the remaining 2 positive trials, a high-quality study in headache was by Dodick et al (49) that included a total of 102 patients in an active group with 52 patients in the control group. Overall results were

Table 13. *Assessment of nonrandomized or observational studies of peripheral nerve stimulation utilizing IPM-QRBNR.*

		Aman et al, 2024 (62)	Lin, 2024 (64)	Abd-Elsayed & Moghim, 2023 (270)	Früh et al, 2023 (311)	Gilmore et al, 2023, 2021 (60)	Huntoon et al, 2023 (61)	Oswald et al, 2019 (361)	Bouche et al, 2017 (281)	Colini Baldeschi et al, 2017 (282)
I.	STUDY DESIGN AND GUIDANCE REPORTING									
1.	STROBE or TREND GUIDANCE	0	0	1	0	2	0	0	0	0
II.	DESIGN FACTORS									
2.	Study Design and Type	0	0	0	0	2	1	0	0	0
3.	Setting/Physician	1	2	2	2	2	2	2	1	2
4.	Imaging	1	3	3	1	3	1	1	1	3
5.	Sample Size	0	1	1	0	2	0	0	0	0
6.	Statistical Methodology	1	0	1	1	1	1	2	2	2
III.	PATIENT FACTORS									
7.	Inclusiveness of Population	0	2	0	0	0	0	2	2	2
	• ≥ 50% response to trial									
8.	Duration of Pain	2	2	2	2	2	2	2	2	2
9.	Previous Treatments	2	2	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	1	2	1	2	2	2	3	1
IV.	OUTCOMES									
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	2	2	4	2	2	2
12.	Description of Drop Out Rate	1	1	0	1	1	1	0	1	1
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	0	0	0	0	0	0	0	0
14.	Role of Co-Interventions	2	2	2	2	2	2	2	2	2
V.	ASSIGNMENT									
15.	Method of Assignment of Participants	0	0	0	0	1	0	0	0	0
VI.	CONFLICTS OF INTEREST									
16.	Funding and Sponsorship	0	0	-1	0	-3	-3	0	0	2
	TOTAL	15/48	18/48	17/48	14/48	21/48	15/48	17/48	18/48	21/48

Source: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of non-randomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (90).

positive with 60% of the patients having 30% reduction in endpoints.

The other 2 trials were related to 60-day temporary stimulation by Goree et al (47) and Gilmore et al (45,50). Both the studies showed positive results in both groups at 12 months even though the stimulation was terminated after 60 days.

Among the nonrandomized or observational studies, 9 studies met the inclusion criteria (60-62,64,270,281,282,311,361). The studies were heterogeneous and 7 of the 9 included permanent implantable PNS (62,64,270,281,282,311,361), whereas 2 were 60-day temporary stimulations (60,61,73). The first 60-day temporary stimulation study (61) was a secondary retrospective review of 6,160 patients, with the inclusion of various types of pain problems. Overall results were positive in 71% of the patients. The second study by Gilmore et al (60) studied chronic axial back pain with

Table 14. *Study characteristics of nonrandomized or observational studies assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
IMPLANTED PERIPHERAL NERVE STIMULATION							
Aman et al, 2024 (62) Retrospective case series **Quality Scores:** Newcastle-Ottawa = 6/8 IPM-QRBNR = 15/48	N=29 5 patients with leads in different dermatomes (n = 29) Total number of patients = 24	5 patients had 2 leads in 2 different dermatomes 15 leads were placed for primarily neuropathic pain 14 leads were placed for nociceptive pain Peripheral nerve stimulators were from Bioness	NRS Change in opioid intake Proportion of pain relief	At 12-month follow-up, 70% reported >50% pain relief 93% of patients reported achieving their personal functional goal 86% of patients for primary nociceptive pain and 93% of patients for neuropathic pain achieved 50% or greater relief at 6 months At 12 months, > 50% of patients provided sustained relief Opioid reductions were reported	Overall good relief and reduction in opioid use	Selection criteria was based on a diagnostic nerve block without trial stimulation	Positive study Retrospective evaluation with good pain relief of > 50% at 6 months; however, by 12 months, only 50% of the patients reported pain relief at 12 months
Lin et al, 2024 (64) Retrospective evaluation **Quality Scores:** Newcastle-Ottawa = 5/8 IPM-QRBNR = 18/48	63 consecutive patients with peripheral neuropathy originating from the shoulder, hip, knee, ankle, and groin	Freedom PNS System (Curonix) 63 patients trialed, with 55 out of 63 (87%) having a successful trial 48 patients received a permanent implant Permanent implant was performed after positive trial results PNS treatment nerves: Suprascapular (n = 21), cluneal (n = 9), femoral/obturator (N = 2), genicular (n = 23), sural/deep peroneal (n = 8).	NRS, 1-to-2-year follow-up Mean follow up=763 days	At long-term follow-up of 24 months (50% of the total implants): 19 patients (79%) experienced > 50% improvement in pain The average NRS pain score decreased significantly ($P = 0.001$)	Permanent implant after trial stimulation and inclusion of various peripheral neuropathic conditions and nerve targets	The long-term follow-up was feasible only in 50% of the patients, even though the results were good in this 50% of the patients	Borderline positive study Long-term follow-up was feasible only in 50% of the patients, though results in these patients were good

Table 14 cont. *Study characteristics of nonrandomized or observational studies assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Abd-Elsayed & Moghim, 2023 (270) Retrospective chart review Single center **Quality Scores:** Newcastle-Ottawa = 5/8 IPM-QRBNR = 17/48	57 patients	Retrospective review of charts Freedom PNS System (Curonix)	Pain and opioid use AEs 24 month follow up	70% improvement maintained at 24 months 47% decrease in medications Pain scores changed from 7.41 ± 1.58 to 1.76 ± 1.63 at 12 months At 24 months, pain scores changed from 7.5 ± 1.7 to 1.45 ± 1.57 ($P \leq 0.001$) Patients also reported significant reduction in MME: At 12-month follow-up pre-procedure MME 42.72 ± 43.19 to 30.38 ± 41.62 ($P = 0.003$, N = 42) At 24-month follow-up pre-procedure MME 41.2 ± 46.12 to 21.19 ± 40.88 at 24 months ($P \leq 0.001$, n = 27)	No SAEs	Retrospective chart review Limited outcome measurements Retrospective analysis with some missing follow up pain scores as in any other retrospective study	Positive study Potential durable effect over 24 months
Früh et al, 2023 (311) Retrospective, multicenter study Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 14/48	N=33 Subjects suffering from chronic intractable post-surgical knee pain, refractory to a multimodal pain management paradigm	Patients underwent diagnostic nerve injections Freedom PNS System (Curonix LLC)	Pain relief, quality of life with SF-36, quality of sleep index, mood states, and general depression scale Follow-up of 6 months For 9 patients, (18-month) follow-up	25 patients reported significant improvements related to pain, quality of life, mood quality, and quality of sleep They also reduced opioid intake 2 subjects were explanted due to wound infections	Well conducted multi-center retrospective study Significant improvement in significant proportion of patients with multiple outcome parameters "Direct to perm"; patients explanted if ineffective (8/33)	Retrospective evaluation, There was no trial stimulation but direct to permanent in that market is standard of care	Positive study Moderate sized, well-conducted, retrospective study from multiple centers with improvement with appropriate parameters

Table 14 cont. *Study characteristics of nonrandomized or observational studies assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Oswald et al, 2019 (361) Prospective **Quality Scores:** Newcastle-Ottawa = 4/8 IPM-QRBNR = 17/48	n = 39 Mononeuropathies Multicenter	PNS Bioness StimRouter®	VAS, activity, opioid consumption 3-6 months	Of 39 patients studied, 78% of the participants noticed an improvement in their pain by a 71% reduction in pain scores with the average pre-procedure score of 8, improving to 2 post-implant An average of 72% improvement in activity was observed Greatest improvement with activity was reported in brachial plexus (80%) and suprascapular nerve (80%), and smallest in the intercostal nerve (40%) Overall, 89% of those implanted with a peripheral nerve stimulator experienced greater than 50% reduction in opioid consumption	Good outcomes in a retrospective evaluation Majority of the patients underwent a diagnostic nerve block	Retrospective evaluation No trial stimulation.	Positive study A small prospective case series from various centers with overall good results and the best results noted with brachial plexus stimulation and suprascapular nerve stimulation
Bouche et al, 2017 (281) Case series **Quality Scores:** Newcastle-Ottawa = 6/8 IPM-QRBNR = 18/48	26 patients with upper extremity neuropathic pain CRPS = 10 Direct peripheral nerve injury = 10 Upper extremity neuropathic pain	Ultrasound guided brachial plexus or suprascapular nerve placement	NRS, opioid intake, return to work Mean 27.5 months ≥ 50% relief All patients had >1 year follow up 14 patients had >2 year follow up	20 of 26 patients used the PNS at last follow up Mean pain relief was 67%; all had >40% relief; 65% had ≥50% relief Results were similar in CRPS and peripheral nerve injury groups	Long-term follow up Homogenous population	Moderate quality small, retrospective pilot study No control group	Positive study Pilot case-series study showing the PNS is safe and effective PNS is effective in relieving upper extremity neuropathic pain

Table 14 cont. *Study characteristics of nonrandomized or observational studies assessing the effectiveness of peripheral nerve stimulation.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients**	**Interventions/ Treatment**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Colini Baldeschi et al, 2017 (282) Case series **Quality Scores:** Newcastle-Ottawa = 5/8 IPM-QRBNR = 21/48	74 patients with peripheral nerve injury from trauma, compression, ischemic or iatrogenic origin. 0f the 74 trialed, 58 were implanted 29 of 58 had CRPS Refractory peripheral nerve injury with or without loss of motor function, of at least 6 months' duration Cranial, upper extremity, truncal, lower extremity nerves and spinal roots were stimulated	Ultrasound guided placement of a peripheral nerve lead with a generator implanted adjacent to the lead and nerve Quadripolar percutaneous leads (Lightline or Fixline, Neurimpluse)	NRS relief of ≥ 50%, drug use, work status, PGIC, SF-36 1, 3 and 6 months	Mean relief at 6 months was 61% 69% had ≥ 50% relief at 6 months	Large, multicenter study with robust outcomes and diverse peripheral nerve pathologies	Moderate quality study with no control group. Relatively short follow up.	Positive study Large scale observational study evaluating the effectiveness of PNS with an IPG implanted close to the target nerve PNS is effective, reliable, and safe Over half the patients had CRPS
IMPLANTED TEMPORARY 60-DAY PERIPHERAL NERVE STIMULATION							
Gilmore et al, 2023 (60) Prospective, multicenter study **Quality Scores:** Newcastle-Ottawa = 6/8 IPM-QRBNR = 21/48	74 patients with chronic axial low back pain	All participants were implanted with percutaneous PNS leads targeting the lumbar medial branch nerves for up to 60-days, after which the leads were removed	18 months Average pain intensity, analgesic medication usage Primary endpoint: Clinically significant reductions in chronic low back pain, as defined by ≥ 30%, reduction in average pain intensity at the end of 2-month treatment	2-month follow-up 73% of the patients showed success rate with significant (> 30% reduction) in the back pain intensity Average pain intensity decreased from baseline of 6.08 to 3.87 at 14 months ($P < 0.0001$) ODI decreased from 38.33 at baseline to 28.86 at 14 months (P 0.002) Proportion of patients experiencing clinically meaningful improvement was: 79% at 5 months 73% at 8 months 77% at 14 months There were no serious or unanticipated study related adverse events	Prospective, multicenter study clinical study demonstrating the clinical utility of percutaneous PNS with 60-day stimulation improvement lasting 14 months	Outcome parameters are improvement of 30% which is a weak measure	Positive study Results though utilized a lower proportion of relief, overall pain relief, function, and pain interference improved significantly from baseline

Table 14 cont. *Study characteristics of nonrandomized or observational studies assessing the effectiveness of peripheral nerve stimulation.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients	Interventions/ Treatment	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Huntoon et al, 2023 (61) Retrospective review **Quality Scores:** Newcastle-Ottawa = 7/8 IPM-QRBNR = 15/48	6,160 Secondary retrospective review with the inclusion of various types of pain problems	Records of 6,160 patients were implanted with a Sprint PNS system from August 2019 through August 2022 were reviewed	> 50% pain relief > 50% improvement in quality of life PGIC	Overall, 71% of patients were responders with > 50% pain relief and/or improvement in quality of life Average pain relief among responders was 63% The responder rate was largely consistent across nerve targets throughout the back and trunk, upper and lower extremities, and posterior head and neck	Real world data with a large population of 6,160 patients	Retrospective data collection	Positive study This large retrospective review of real-world outcome following 60-day PNS for the treatment of chronic pain confirms the evidence for PNS derived by RCTs

AEs = adverse events; ADLs= activities of daily living; CRPS = complex regional pain syndrome; HIT-6 = Headache Impact Test; IPG = implantable pulse generator; IPM-QRBNR = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; MIDAS = Migraine Disability Assessment; MME = Morphine milligram equivalents; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; PGIC = Patient Global Impression of Change; PNS = Peripheral nerve stimulation; SF-36 = 36-Item Short Form Health Survey; VAS = Visual Analog Scale

60-day percutaneous medial branch PNS in a prospective, multicenter study showing positive results.

7.5 Recommendations and Statements

A total of 31 authors participated in the development of these guidelines. Of these, 21 participated in the voting process. A total of 8 recommendations were developed. Overall, 100% acceptance was obtained for 8 of 8 items. Thus, with appropriate literature review, consensus-based statements were developed for implantable peripheral nerve stimulation in chronic pain management.

Table 15. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
IMPLANTED PERIPHERAL NERVE STIMULATION									
Hatheway et al, 2024 (53)	RA	Low	NS	NS	NS	Low	Randomized = 89 Intervention group with PNS permanent implant = 48 Control arm with conventional medical management = 31	RCT comparing with conventional medical management, well designed, applicable to clinical practice	Moderate
CFPNS study, 2024 (51)	RA	Low	NS	NS	NS	NA*	60 permanent implants Treatment group = 58 Randomized = 56 Activated = 28 Deactivated and then reactivated = 28	Multicenter RCT resulting in first FDA 510K clearance full body indication, including craniofacial indication A moderate sized study, with moderate methodologic quality and minimal risk of bias. Applicable to clinical practice	Moderate
Deer et al, 2016 (46)	RA	Low/ Moderate	NS	NS	NS	Low	94 Treatment group = 45 Control group = 49 With no stimulation: 152	A moderate sized multicenter RCT with moderate methodologic quality or risk of bias. There was no trial stimulation and 30% decrease was considered as criterion standard instead of standard 50%. The results showed only 27.2% showing improvement.	Low
Dodick et al, 2015 (49)	RA, DB	Low	NS	NS	NS	Low	152 Treatment group = 102 Control group = 52	The study was multicenter and a large number of patients were included. The percentage of patients who achieved a 50% reduction in headache days was 47.8% and 30% reduction in headache days was 59.5%	Moderate
Serra & Marchioretto, 2012 (52)	RA	Low/ Moderate	NS	NS	NS	Low	30	Small number of patients	Low
Gilligan et al, 2012 (48)	RA	Low	NS	NS	NS	Low	204 Stimulation on = 102 Stimulation off = 102	RCT of selective medial branch stimulation with large population. Well-designed trial with an extensive long-term follow up showing clinically substantial and durable benefit with a favorable safe profile. Results were superior as time passed on based on the mechanism of the stimulation to cause restoration and reverse muscle dysfunction	Moderate

Table 15 cont. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
60-DAY TEMPORARY STIMULATION									
Goree et al, 2024 (47)	RA, PC	Low/ Moderate	NS	NS	NS	Low	40 No control	Small number of patients with appropriate outcome parameters of 50% reduction of average pain from baseline with multiple functional outcomes showing positive results in 60% of the patients	Moderate
Gilmore et al, 2019 (45)	RA, DB	Low/ Moderate	NS	NS	NS	Low	28	Desired outcomes were achieved initially and on long-term follow-up. The major drawback was there was no placebo effect	Moderate

DB = double blind; NS = Not serious; NA = Not available; RA = randomized

8.0 Complications and Side Effects of Peripheral Nerve Stimulation

Key Question 6. What are the adverse consequences and harms, and related precautions in providing peripheral nerve stimulation interventions?

Complications can stem from hardware-related issues, biological factors like infections, and nerve injuries. A thorough understanding of these complexities is essential for healthcare providers to manage and minimize risks effectively.

8.1 Hardware Related Complications

8.1.1 Lead Migration

Migration rates vary widely across studies due to differences in implanter experience, migration definitions, clinical contexts, migration mitigations, and practices. The extent to which recent hardware advancements impact migration incidence remains uncertain.

8.1.2 Lead Fracture

The incidence of lead fracture for PNS is unknown. In principle, this can occur due to mechanical stress movement, or repetitive bending of the lead overtime. This is due to certain factors such as the patient's activity level, anatomical location of the lead as well as surgical technique.

8.1.3 Battery Failure (Implanted Pulse Generator-IPG)

While battery failure is relatively rare, this complication may be related to factors such as battery type (rechargeable vs non-rechargeable), device longevity, and patient usage pattern. The internal battery of an IPG powers the device, and its replacement necessitates surgical intervention. The majority of reports concerning battery failure pertain to spinal cord stimulators (342). Notably, there are a dearth of reports on battery replacement for PNS (23).

8.2 Biological Complications

Although hardware-related complications are more common, there are several biological complications that can occur as a result of PNS (342). This includes pain related to device components, hematoma or hemorrhage, wound dehiscence and infection, skin erosion, and neurological injury (342-346). Although these can be major complications, they are usually easily reversible with minor surgery or explantation of the device (342).

Wound infection is one of the major complications of PNS. However, PNS has lower infection rates than spinal cord stimulation and deep brain stimulation (347). Current literature suggests Staphylococcus aureus and Staph epidermis are the most commonly involved bacteria. Infections with Candida albicans and Streptococcus species are less common. It has been previously suggested that intraoperative antibiotics can prevent these wound infections (346). However, in a study by Warner et al (339), where almost all the patients received preoperative antibiotics, there was no difference in the surgical site infection rates between patients who were given prophylactic postoperative antibiotics and those who were not. In this study, 99% of patients were given preoperative intravenous antibiotics, either cefazolin, vancomycin, or clindamycin. The patients who did receive postoperative antibiotics received cephalexin therapy (250 to 500 mg dosed bid, tid, or qid), clindamycin (150 to 300 mg bid), ciprofloxacin (300 mg bid), or cefadroxil (1,000 mg bid) for median antibiotic duration of 7 days (339). This raises the question as to whether antibiotic therapy might only be necessary during the pre-operative period. Current research has not addressed the timing of antibiotics (pre-operative, intraoperative, or post-operative) and its effect on wound infection rate.

Despite antibiotic therapy likely being the primary consideration among clinicians in preventing wound infections, a recent study suggests that the design of the percutaneous leads is associated with infection rate. As it relates to temporary peripheral nerve stimulation systems, it was found that the risk of infection with non-coiled leads was found to be about 25 times greater than with coiled leads (360). In addition to the type of percutaneous leads, wound infections could also be a result of poor surgical technique or insufficient dissection for the anchors and connectors, with tissue tension not allowing for adequate wound healing (343).

Other less common complications include skin erosion, hematoma, seroma, and nerve injury. In a case report by Uppal et al (348), 2 patients experienced lead migration to the skin, ultimately requiring open surgical removal. Another study evaluating the effects of sacral nerve stimulation found that seroma formation at the IPG site was the most common complication; however, these seromas resolved spontaneously (272). Furthermore, another study evaluating sacral and pudendal nerve stimulation found seroma formation in

two patients, which resolved after drainage with aspiration (268).

In conclusion, there are many factors that contribute to the occurrence of complications in PNS. Special care and attention should be placed on the technique of the procedure to minimize the occurrence of complications.

9.0 Peripheral Nerve Stimulation

Key Question 7. What are the various types of peripheral nerve systems available in the United States?

PNS is a rapidly evolving neuromodulation technology in interventional pain management that provides analgesic effects to chronic pain patients (10,30).

With the advancement of guided imaging, improved surgical techniques, and the further development of temporary and permanent PNS devices, many peripheral nerves from different body regions can be targeted for treatment. For example, current research has broadened the application of PNS devices to treat regions of peripheral nerves in the face and head, upper and lower extremities, abdomen, back, and pelvis (57). The number of FDA-cleared devices have also been increasing.

9.1 Types of Systems

The field of peripheral stimulation has witnessed significant expansion in recent years, offering interventional pain physicians multiple options facilitated by external transmitters ("wireless systems") with no implanted battery. These advancements enable peripheral stimulation closer to the pathology, in all regions of the body.

Presently, there are 5 distinct types of peripheral nerve stimulation with implanted receivers or pulse generators on the market:

- Curonix LLC, 2017, Pompano Beach, FL, USA, Freedom® Peripheral Nerve Stimulator (PNS) System
- Bioness, now Bioventus, 2015, Durham, NC, USA, StimRouter® Neuromodulation System
- SPR Therapeutics, Inc., 2016, Cleveland, OH, USA, SPRINT® PNS System
- Nalu Medical, Inc., 2019, Carlsbad, CA, USA, Nalu™ Neurostimulation System
- Mainstay Medical Limited, 2020, San Diego, CA, USA, ReActiv8® Implantable Neurostimulation System

Table 16 shows an overview of percutaneous PNS systems.

9.1.1 Freedom Peripheral Nerve Stimulator (PNS) System (Curonix LLC, 2017)

The Freedom Peripheral Nerve Stimulator (PNS) System, manufactured and distributed by Curonix, is designed for adults experiencing intractable pain of peripheral nerve origin throughout the entire body (362). The system includes a 2-component implantable neurostimulator (comprised of an electrode array and a separate receiver) and an external transmitter assembly. Before the permanent device is implanted, patients typically undergo a trial using a temporary electrode array to assess whether the patient is a good candidate for the therapy.

Through a first incision, the distal end of the PNS electrode array (which houses the electrodes) is positioned next to the targeted peripheral nerve, using ultrasound or fluoroscopic guidance. The PNS STQ4 model electrode array is equipped with tines to mitigate migration. Through a second incision and pocket creation, the separate receiver is connected to the electrode array, and the receiver is anchored to the fascia within the pocket. The transmitter assembly is then placed over the implant to communicate with the receiver and power the device. Electronic analysis is performed. The system offers multiple programming options, using a wide range of waveforms, with stimulation frequencies reaching up to 1499 Hz. Additionally, the permanent FR4A and STQ4 model neurostimulators are full-body MR conditional (excluding the craniofacial region), allowing for MRI scans.

9.1.2 StimRouter Neuromodulation System (Bioness, now Bioventus, 2015)

The Bioness StimRouter device, developed by Bioventus/Bioness Inc. in Durham, NC, is designed to treat peripheral nerve pain in the lower and upper extremities, pelvis, and trunk (363). The system involves the implantation of a peripheral lead, which is powered by a rechargeable lithium battery within an external pulse transmitter. The implanted lead is 15 cm long and 1.2 mm in diameter, containing a receiver coil and three stimulation electrodes.

The external pulse transmitter powers the system by being positioned directly over the receiver of the implanted lead, attaching to a disposable electrode patch on the skin for daily wear and programming. Once programmed, the patient can power the device on or off, select different settings, and adjust the amplitude using a separate patient programmer. The StimRouter® system is MRI conditional for the head and extremities under specific conditions (364).

9.1.3 Sprint PNS System (SPR Therapeutics, Inc., 2016)

The SPRINT PNS System, developed by SPR Therapeutics in Cleveland, OH, is designed for use up to 60 days to

Table 16. *Overview of percutaneous PNS systems.**

PNS DEVICE (MANUFACTURER)	FDA CLEARED INDICATION	PERMANENT VS TEMPORARY	DEVICE CHARACTERISTICS	MRI CAPABILITY
Freedom Peripheral Nerve Stimulator (PNS) System (Curonix LLC)	The Freedom Peripheral Nerve Stimulator (PNS) System is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin throughout the body, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach. The trial devices are solely used for a trial stimulation period (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device. *Not intended to treat pain in the region innervated by the cranial and facial nerves.	Permanent with trial system Trial – up to 30 days	4 and 8 electrode neurostimulators – tined and un-tined Trial kit available Multiple waveforms Frequency: 5-1499 Hz Amplitude: 0-13.5 mA per electrode pair Pulse Width: 30-1000 mSec Implanted electrode array with separate receiver requiring connection and pocket creation	1.5T MR conditional, full body with permanent 4-electrode neurostimulator
StimRouter Neuromodulation System (Bioness, now Bioventus)	Severe, intractable chronic pain of peripheral nerve origin. *Not intended to treat pain in the region innervated by the cranial and facial nerves.	Permanent without trial system	3 electrodes; each 1 mm long Frequency: 1-200 Hz Amplitude: 0-30 mA Pulse width: 140-2500 mSec Minimum pulse duration is 70msec positive plus 70 msec negative (symmetric) Maximum pulse duration is 500 mSec positive plus 2000 mSec negative (asymmetric) The pulse generator and battery are external.	MR conditional for both 1.5T and 3T, under specific conditions
SPRINT PNS System (SPR Therapeutics)	Up to 60 days in the back, extremities, head, neck, and/ or torso for: Symptomatic relief of chronic, intractable pain, postsurgical and posttraumatic acute pain Symptomatic relief of posttraumatic pain Symptomatic relief of postoperative pain *Not intended to treat pain in the region innervated by the cranial and facial nerves.	Temporary	Open-coil, externalized lead(s) Option for 1- or 2-lead configurations Tonic stimulation Frequency: 12 to 100 Hz Amplitude: 0 30 mA Pulse Width: 10-200 mSec Bimodal stimulation enables the use of different frequencies on each lead; 12 Hz is typical for motor activation and 96 Hz for sensory stimulation	Not compatible (leads must be withdrawn prior to MRI); any retained fragments are conditional MR Unsafe
Nalu Neurostimulation System (Nalu Medical, Inc.)	Severe, intractable chronic pain of peripheral nerve origin. *Not intended to treat pain in the region innervated by the cranial and facial nerves.	Permanent with trial system Trial – up to 30 days	4 and 8 contact leads- tined and un-tined Option for 1- or 2-lead configurations Implantable IPG with external power source Trial kit available – FDA approved for 30-day use Multiple waveforms Frequency: 2 to 1,500 Hz Amplitude: 0 to 10.2 mA Pulse Width: 12 mSec	MR conditional for head & extremity only
ReActiv8 Implantable Neurostimulation System (Mainstay Medical Limited)	To aid in treatment of intractable chronic low back pain associated with multifidus muscle dysfunction *Not intended to treat pain in the region innervated by the cranial and facial nerves.	Permanent without trial system	Tined, 4 contact leads Leads are implanted bilaterally at the transverse processes of L3 Implanted non-rechargeable IPG Handheld activator to start and stop stimulation Stimulation activates lumbar multifidus muscles	Not compatible

*For updated information, check manuals published and updated by manufacturers. FDA – Food and Drug Administration; IPG = implantable pulse generator

alleviate chronic intractable pain in the back and extremities, as well as acute post-surgical and post-traumatic pain (365). In 2021, the FDA expanded its clearance to include use in the head, neck, and front of the torso, with the exception of areas innervated by facial or cranial nerves.

At the end of the 60-day therapy period, or sooner if needed, the lead is withdrawn from the subcutaneous tissues and the EPG is removed from the skin surface. The SPRINT® PNS System is MRI unsafe while implanted and must be removed prior to undergoing an MRI. If any lead fragments are retained after removal, they are considered MRI conditional (363).

9.1.4 Nalu Neurostimulation System (Nalu Medical, Inc., 2019)

The Nalu Neurostimulation System, developed by Nalu Medical Inc. in Carlsbad, CA, offers both central and peripheral nervous system stimulation using battery-free microstimulation technology (366). The system is indicated for intractable chronic pain of peripheral nerve origin. It utilizes tined four-contact leads, available in lengths of 25 cm or 40 cm, which are implanted subcutaneously near the targeted nerve. The IPG is battery-free and powered externally by a therapy disc worn over the IPG site.

The therapy disc allows the patient to power the device on or off, change programs, and adjust stimulation intensity. The Nalu PNS system is MRI conditional for the head and extremities under specific conditions (363).

9.1.5 ReActiv8 Implantable Neurostimulation System (Mainstay Medical Limited, 2020)

The ReActiv8 Implantable Neurostimulation System, developed by Mainstay Medical Limited in San Diego, CA, formerly, Dublin, Ireland, is intended for patients suffering from intractable low back pain associated with multifidus muscle dysfunction, as indicated by multifidus atrophy on advanced imaging (367). The ReActiv8® system includes an IPG and stimulation leads. The non-rechargeable IPG can accommodate two to four electrode leads, which are equipped with bi-directional tines at the distal end to anchor the lead in place by engaging with the surrounding soft tissues. Patients can control the stimulation using a hand-held activator, which starts and stops the stimulation. The IPG is programmed to deliver episodic electrical stimulation, with varying durations and frequencies throughout the day, aimed at eliciting contractions of the lumbar multifidus muscles.

10.0 Medical Necessity Criteria

Key Question 8. What are medical necessity criteria and indications for PNS?

Establishment of medical necessity and indications are crucial in performing any medical intervention, including peripheral nerve blocks and PNS. PNS trials or implants are required to meet the following:

1. Documented function-limiting moderate to severe pain for at least 3 months, with average pain scores of 5 or above
2. Documented failure of less invasive treatment modalities and medication of at least 4 weeks
3. Lack of surgical contraindications including infections and medical risks
4. Appropriate proper patient education, discussion and disclosure of risks and benefits
5. There is no active substance abuse
6. Formal psychological screening by a qualified mental health professional
7. Successful stimulation trial with ≥ 50% reduction in pain intensity before permanent implantation

These medical necessity criteria have been established in LCDs (368). Further, the only reliable predictor of PNS effectiveness is a trial stimulation with implanted PNS electrodes. If a trial fails, a repeat trial is usually not appropriate unless there are extenuating circumstances that led to the trial failure, including equipment malfunction, early lead migration, etc., technological advances or an alternative neuromodulatory technique that may lead to a more successful second trial. Documentation must explain these unusual situations. It is expected that accurate patient selection will lead to most patients going on to receive permanent implants. All trials that proceed to permanent implant must have adequate documentation to support the decision. A successful trial should be associated with at least 50% reduction of the target pain or 50% reduction of analgesic medications, and should show some element of functional improvement (368).

In fact, while the NCD is less restrictive, guidance from one Medicare Administrative Contractor (MAC), Noridian, shows that physicians with a low trial to permanent implant rate of less than 50% will be subject to post payment review and may be asked to submit documentation as to the patient selection criteria, the imaging demonstrating proper lead placement, and the medical necessity of the trials. Present approved indications by Noridian are as follows (368):

- PNS of occipital nerves for occipital neuralgia, post-surgical neuropathic pain, cervicogenic headaches and treatment resistant migraines.
- PNS of trigeminal nerves (and branches) for post-traumatic and post-surgical neuropathic pain in the face related to the trigeminal nerves.
- PNS of nerves in upper and lower extremities of complex regional pain syndromes (Type 1 and 2), pain due to peripheral nerve injury, post-surgical scar formation, nerve entrapment, painful mononeuropathy, and painful amputation neuromas.
- PNS of intercostal and ilioinguinal nerves for post-surgical and post-traumatic neuropathic pain involving these nerve distributions.

Thus far, LCD data does not support PNS for fibromyalgia, phantom limb pain, diffuse polyneuropathy, nociceptive pain in the trunk or lower back, or angina pectoris.

Based on emerging evidence with assessment of appropriate evidence in these guidelines, utilizing RCTs, observational studies, and systematic reviews, with application of appropriate methodologic quality or risk of bias assessment, GRADE criteria or certainty of evidence, and qualitative evidence synthesis based on best evidence synthesis, the summary of evidence is as follows:

- For implantable peripheral nerve stimulation systems following a trial, including selective lumbar medial branch stimulation without a trial, the evidence is Level III or fair, with moderate certainty.
  Evidence Level: Fair; Strength of Recommendation: Moderate
- For temporary peripheral nerve stimulation for 60 days, the evidence is Level III or fair, with moderate certainty.
  Evidence Level: Fair; Strength of Recommendation: Moderate

Based on this, it is our recommendation to expand the CMS guidance to include phantom limb pain and nociceptive pain in the lower back as present evidence shows Level III or fair with moderate certainty.

11.0 Patient Education

Key Question 9. What is the importance of patient education in peripheral nerve stimulation implants?

The education needed for patients undergoing PNS encompasses several key aspects:

- Understanding of the Procedure: Patients should receive comprehensive education about the PNS procedure itself, including how the device works, its potential benefits, and any associated risks or complications.
- Preoperative Preparation: Patients should understand the preoperative preparations required for PNS, which may include discontinuing certain medications, fasting prior to the procedure, and arranging transportation to and from the medical facility. Clear instructions from the healthcare team help ensure that patients are adequately prepared.
- Informed Consent: Patients must provide informed consent before undergoing PNS. This involves understanding the purpose of the procedure, its potential benefits and risks, alternative treatment options, and the expected outcomes. Healthcare providers should take the time to address any questions or concerns the patient may have before obtaining consent.
- Device Operation: Patients need education on how to operate the PNS device, including turning it on and off, adjusting stimulation settings (such as frequency and amplitude), and charging or replacing the device's batteries if applicable.
- Managing Expectations: It is important for patients to have realistic expectations about the outcomes of PNS therapy. While many patients experience significant pain relief, it may not eliminate pain in all cases. Patients should understand that individual responses to treatment can vary and that it may take time to optimize the stimulation settings for optimal pain control.
- Postoperative Care: Patients require guidance on postoperative care following PNS implantation, including wound care instructions, activity restrictions, and guidelines for managing discomfort or pain during the initial recovery period. Regular follow-up appointments with the healthcare team are essential to monitor progress and make any necessary adjustments to the treatment plan.
- Lifestyle Considerations: Patients should be educated about lifestyle modifications that can complement PNS therapy, such as maintaining a healthy diet, engaging in appropriate exercise or physical therapy, and managing stress. These factors can influence the overall effectiveness of treatment and contribute to long-term success.
- Potential Complications: While PNS is generally safe, patients should be made aware of potential complications associated with the procedure, such as infection, lead migration, or device malfunction. They should know the signs and symptoms of these complications and when to seek medical attention promptly.
- Resources and Support: Patients benefit from access to educational materials, support groups, and resources that provide additional information and emotional support throughout their treatment journey. These resources can help patients feel empowered and better equipped to manage their pain effectively.

12.0 Perioperative Anticoagulant And Antiplatelet Therapy

Key Question 10. What are the precautions in patients on antiplatelet and anticoagulant therapy implanting PNS?

PNS techniques performed in patients receiving anticoagulant and antiplatelet therapy are increasingly common (369). The frequency of these combinations continues to rise, necessitating a multidisciplinary approach to understand the importance of anticoagulant therapy and the need for interventional techniques and to determine the duration and discontinuation or temporary interruption of anticoagulation (369). Anticoagulants and antiplatelets are commonly prescribed to reduce the risk of thromboembolism in patients with a history of angina, atherosclerosis, atrial fibrillation, cerebrovascular accidents, ischemic heart disease, myocardial infarction, pulmonary embolism, and peripheral vascular disease, thereby preventing the incidence of life-threatening events. Among the multiple therapeutic options reported, continuation of oral anticoagulant therapy, switching to another oral anticoagulant, adding antiplatelet therapy, performing left atrial appendage closure or a combination of the above strategies have been recommended (370). The 2024 updated guidelines from ASIPP on perioperative management of antiplatelet and anticoagulant therapy in patients undergoing interventional techniques are consensus-based guidelines on best evidence synthesis, included review of the literature on bleeding risks during interventional pain procedures, practice patterns, and perioperative management of anticoagulant and antiplatelet therapy (369). This guideline development included extensive evaluation of bleeding patterns and risk stratification of interventional techniques.

The risk stratification for interventional techniques was developed based on the available literature in reference to the adverse consequences of anticoagulant and antiplatelet therapy, thromboembolic risk, and risks related to interventional techniques. Risk stratification of each procedure included for the majority of interventional techniques was based on:

- Anatomic risk factors
- Procedural risk factors
- Bleeding risk factors
- Anticoagulant/antiplatelet therapy related risk factors
- Medical or physiological risk factors

Table 17 shows factors associated with increased bleeding risk (371).

Table 17. *Factors associated with increased bleeding risk.*

Need for oral anticoagulation in addition to dual antiplatelet therapy
Advanced age (older than 75 years)
Frailty
Anemia with hemoglobin < 110 g/L
Chronic renal failure (creatinine clearance < 40 mL/min)
Low body weight (<60 kg)
Hospitalization for bleeding within past year
Previous stroke/intracranial bleed
Regular need for NSAIDs or prednisone

NSAIDs: nonsteroidal anti-inflammatory drugs
Source: Mehta SR, Bainey KR, Cantor WJ et al; members of the Secondary Panel. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. Can J Cardiol 2018; 34:214-233 (371).

12.1 Determination of Timing of Anticoagulant Interruption

Determination of timing of anticoagulant use and its interruption is an extremely important aspect and variable among the specialties and authors. Table 18 shows a sample recommended preoperative withholding times of oral antiplatelet and anticoagulant drugs in the literature (372). Figure 7 shows an algorithm for anticoagulant and antiplatelet discontinuation in individuals undergoing interventional procedures.

Figure 8 shows recommended perioperative withholding times of antiplatelet or anticoagulant drugs for interventional procedures, similar to recommendations by various authorities.

These recommendations show that for high-risk procedures, aspirin, clopidogrel (Plavix), and prasugrel (Effient) are discontinued 6 days prior to the procedures and resumed after one day. In reference to ticagrelor (Brilinta), it is discontinued for 5 days and resumed after one day. For intermediate or moderate-risk procedures, aspirin is stopped for 3 days, clopidogrel (Plavix) for 5 days, prasugrel (Effient) for 5 days, and ticagrelor (Brilinta) for 3 days. For low-risk procedures, recommendations are highly variable based on our evidence and previous recommendations and the literature. For low-risk procedures, all of the drugs may be continued or stopped as in intermediate or moderate risk procedures.

Figure 9 shows perioperative management of patients receiving direct oral anticoagulants during interventional procedures.

For patients in the high-risk category, direct oral anticoagulants interruption is 2 days prior to the procedure, the day of the procedure, and one day following the procedure, leading to a total cessation of 4 days unless creatinine clearance is ≤ 50 mL per minute, in which case dabigatran (Pradaxa), is stopped for 4 days with resuming it on day 2 with a total cessation of 6 days. For intermediate or moderate risk category, preprocedural cessation of direct oral anticoagulants is a total of 2 days, the day before and the day of the procedure, and they can be resumed on the next day. Similar to the high-risk category for dabigatran (Pradaxa), the cessation for moderate or intermediate category is 2 days and resumption on the first day, totaling cessation of 3 days.

For low-risk category, the recommendation is that there is no need of cessation; however, based on other variables, it may be changed to moderate or intermediate category and follow the recommendations for intermediate risk category.

In reference to warfarin (Coumadin), Douketis et

Table 18. *Recommended preoperative withholding times of oral antiplatelet and anticoagulant drugs.*

Drug	Half-life	Time to withhold prior to		Time to restart after	
		Minor surgery	Major surgery	Minor surgery	Major surgery
Warfarin (Coumadin)	20–60 h	3–5 days*	3–5 days	24 h, overlapping therapy with heparin	48–72 h; overlapping therapy with heparin
Apixaban (Eliquis)	8–15 h	24 h**	48 h**	24 h	24–48 h
Rivaroxaban (Xarelto)	5–9 h (Elderly: 11–13 h)	24 h**	48 h**	24 h	24–48 h
Edoxaban (Savaysa, Lixiana)	10–14 h	24 h**	48 h**	24 h	24–48 h
Betrixaban (Bevyxxa)	19–27 h	≥ 4 days	≥4 days	24 h	24–48 h
Dabigatran (Pradaxa)	12–17 h	CrCl > 50 mL: 24 h CrCl < 50 mL: 72 h	CrCl > 50 mL: 72 h CrCl < 50 mL: 120 h	24 h	24–48 h
Aspirin	7–10 days	usually continued	usually continued	usually continued	usually continued
Clopidgrel (Plavix)	7–10 days	5–7 days	5–7 days	24 h	24–48 h
Prasugrel (Effient)	7–10 days	5–7 days	5–7 days	24 h	24–48 h
Ticagrelor (Brilinta)	5–7 days	3–5 days	3–5 days	24 h	24–48 h

*In some cases, continued drug administration is feasible
**In case of impaired renal function, withholding interval should be prolonged and/or drug level should be evaluated by laboratory tests
CrCl: creatinine clearance

Adapted and modified: Moster M, Bolliger D. Perioperative guidelines on antiplatelet and anticoagulant agents: 2022 update. *Curr Anesthiol Rep* 2022; 12:286-296 (372).

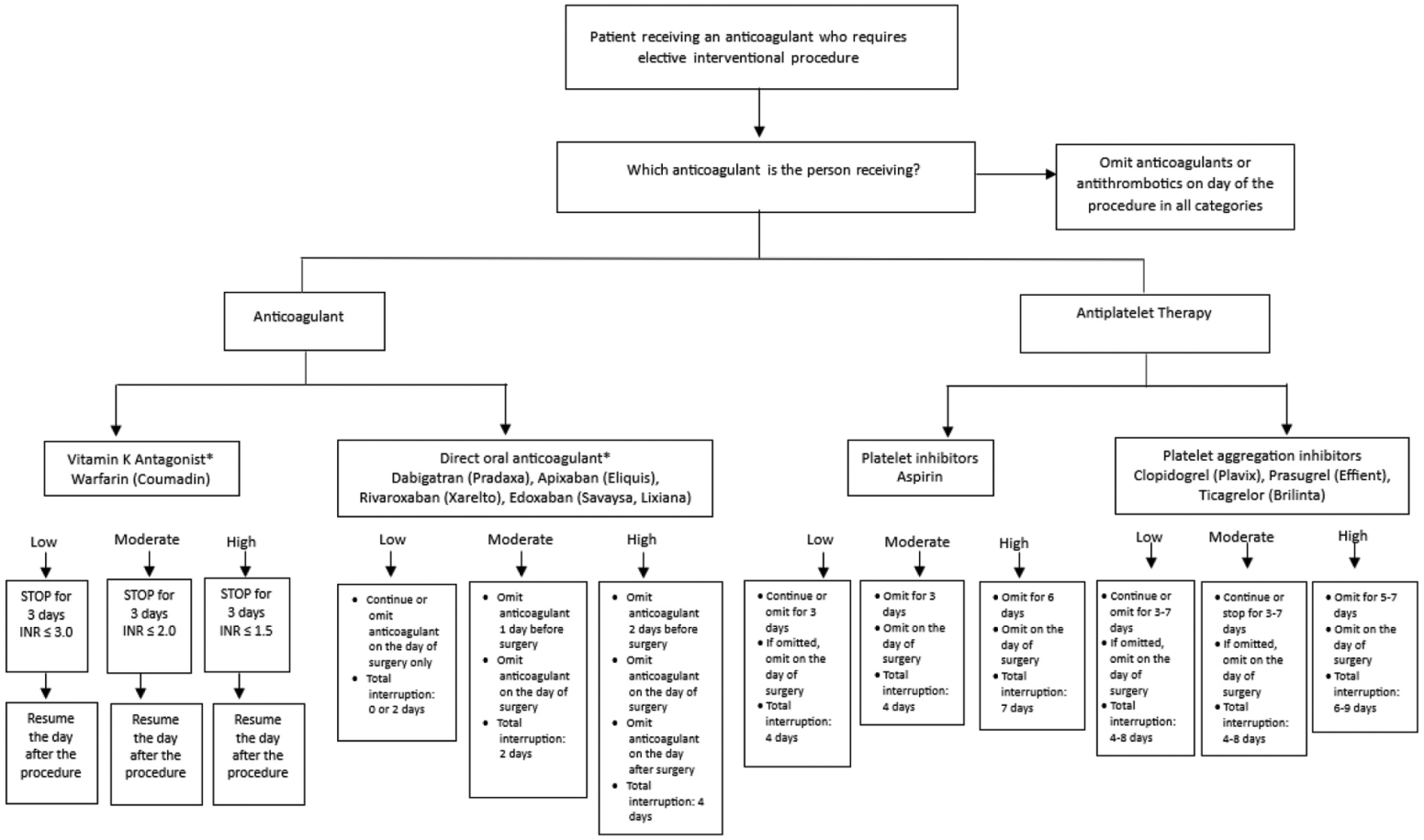
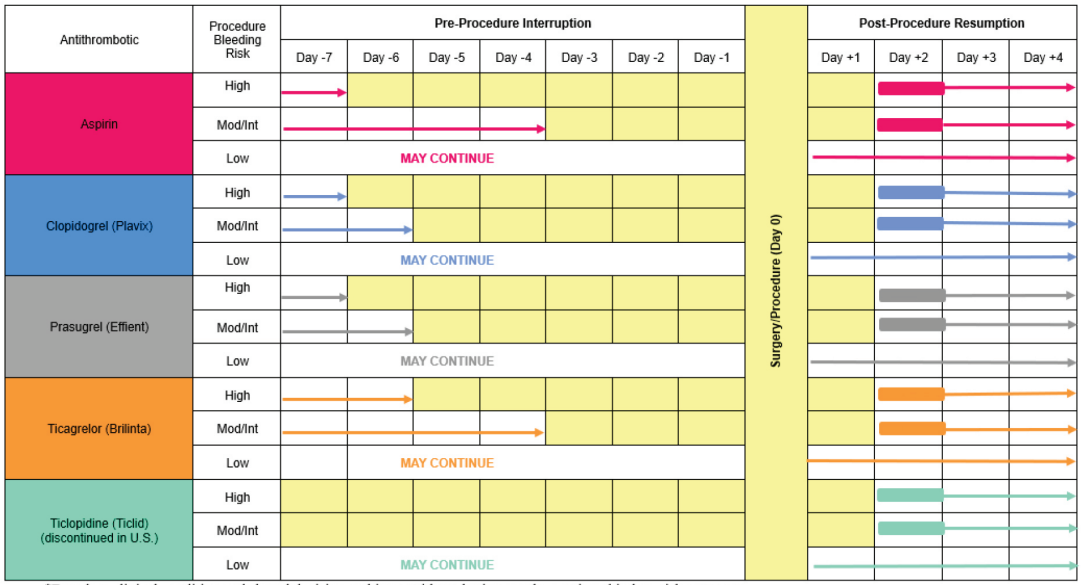


Fig. 7. *An algorithm for anticoagulant and antiplatelet discontinuation in individuals undergoing interventional procedures.*

**Anticoagulants:*

- *Vitamin K antagonists include warfarin (Coumadin)*
- *Direct oral anticoagulants (DOACs) include dabigatran (Pradaxa), apixaban (Eliquis), rivaroxaban (Xarelto), and edoxaban (Savaysa, Lixiana)*
- *Platelet inhibitors include aspirin*
- *Platelet aggregation inhibitors include clopidogrel (Plavix), Prasugrel (Effient), and Ticagrelor (Brilinta)*

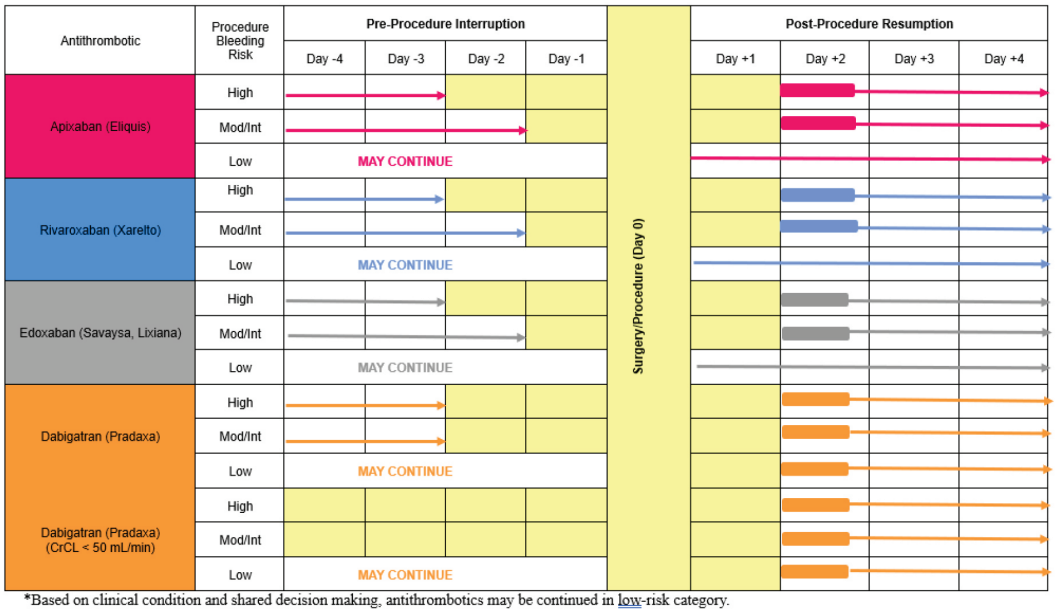


*Based on clinical condition and shared decision making, antithrombotics may be continued in low-risk category.

No antithrombotic administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Fig. 8. *Perioperative management of antiplatelet or anticoagulant drugs for interventional procedures.*



*Based on clinical condition and shared decision making, antithrombotics may be continued in low-risk category.

CrCl = creatinine clearance

No DOAC administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Fig. 9. *Perioperative management of interventional techniques in patients on direct oral anticoagulants (DOACs).*

al (373,374) recommended continuing for minimal bleed risk. For low to moderate bleed risk, they recommend warfarin to be withheld for 5 days with bridging, even though the guidance states lack of value of bridging.

However, for interventional procedures, a 1-to-3-day interruption is recommended to achieve an optimal INR of ≤ 3.0 for low-risk procedures, 2-to-3-day interruption with an optimal INR of ≤ 2.0 for intermediate risk or moderate risk procedures and 3-to-5-day interruption with an optimal INR of ≤ 1.5 for high-risk procedures.

Low molecular weight heparin bridging may be considered for high-risk surgical procedures such as SCS and intrathecal implantables. The trial may also be shortened. Bridging may be performed by a cardiologist, or, if a cardiologist recommends, an interventional pain physician may perform.

Based on the above, ASIPP guidance has developed an algorithmic approach for interventional techniques as shown in Fig. 7 for patients on anticoagulant or antiplatelet therapy.

12.2 Guidelines for Managing Anticoagulant and Antiplatelet Therapy During Interventional Techniques

ASIPP guidelines with recommendations and statements are developed based on a comprehensive review of the literature of thromboembolic risk, bleeding risk, anatomical factors, procedural factors and medical or physiologic status. Further, we also utilized review of previous guidelines for interventional pain management, as well as for general surgery, endoscopy and ophthalmic surgery as developed by various organizations.

Table 19 shows guidelines for antiplatelet and anticoagulation medication management for interventional procedures (369).

Table 20 shows a procedural checklist for managing anticoagulant and antiplatelet therapy during interventional techniques.

Table 19. *ASIPP guidelines for antithrombotic medication management and interventional techniques.*

MEDICATION	Time to Wait After Last Dose of Medication Before Interventional Techniques Are Performed			Timing of Therapy Restoration or Restarting
	LOW RISK PROCEDURES	MODERATE OR INTERMEDIATE RISK PROCEDURES	HIGH-RISK PROCEDURES	
	• Trigger point and intramuscular injections • Peripheral nerve blocks • Sacroiliac joint injections • All facet joint interventions (intra-articular injections, medial branch and L5 dorsal ramus nerve blocks and radiofrequency neurotomy) • Intraarticular injections of extremities • Pocket revision and implantable pulse generator/intrathecal pump replacement • Peripheral nerve stimulation trial and implantation of extremities and other superficial nerves • Lumbar transforaminal epidural injections at L3, L4, L5, and S1 • Ganglion impar blocks • Sacroiliac joint nerve radiofrequency • Trigeminal branch nerve blocks (mandibular, maxillary, and other branches)	• Caudal epidural injections • Caudal epidural adhesiolysis • Lumbar interlaminar epidural at L5, S1 • Cervical, thoracic, and lumbar transforaminal at L1 and L2 • Peripheral nerve stimulation trial and implantation of lumbar medial branches	• Cervical, thoracic, and lumbar (above L5) interlaminar epidurals • Peripheral nerve stimulation trial and implantation of thoracic and cervical medial branches • Trigeminal ganglion, ophthalmic division, and sphenopalatine ganglion blocks • Discography and intradiscal procedures • Dorsal column and dorsal root ganglion stimulator trial and implantation • Intrathecal catheter and pump implant • Vertebral augmentation • Percutaneous and endoscopic disc decompression procedures • Minimally invasive lumbar decompression (MILD) • Trigeminal and cranial nerve blocks and stimulation • Sympathetic blocks (stellate ganglion, thoracic sympathetic, splanchnic, celiac plexus, lumbar sympathetic, hypogastric plexus) • Percutaneous adhesiolysis with interlaminar or transforaminal approach (cervical, thoracic, and lumbar) • Intervertebral spinous prosthesis including lateral fusion • SI joint fusion • Intracept procedure	

Table 19 cont. *ASIPP guidelines for antithrombotic medication management and interventional techniques.*

MEDICATION	Time to Wait After Last Dose of Medication Before Interventional Techniques Are Performed			Timing of Therapy Restoration or Restarting
	LOW RISK PROCEDURES	MODERATE OR INTERMEDIATE RISK PROCEDURES	HIGH-RISK PROCEDURES	
NSAIDS (COX 1) (COX 2)	May continue or stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	24 hours
THC/CBD	May continue or stop 1-10 days	May continue or stop 1-10 days	Stop for 5 days	24 hours
Garlic	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Vitamin E	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Fish Oil	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Aspirin				
Low-Dose Aspirin	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
High Dose Aspirin	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Antiplatelet Agents (Phosphodiesterase Inhibitors)				
Dipyridamole (Persantine)	May continue	May continue	May continue or stop for 2 days	12 hours
Cilostazol (Pletal)	May continue	May continue	May continue or stop for 2 days	12 hours
Aggrenox (dipyridamole plus aspirin)	May continue	May continue	Stop for 6 days	24 hours
Platelet Aggregation Inhibitors				
Clopidogrel (Plavix)	May continue	May continue or stop for 5 days	Stop for 6 days	12 hours
Prasugrel (Effient)	May continue	May continue or stop for 5 days	Stop for 6 days	24 hours
Ticagrelor (Brilinta)	May continue	May continue or stop for 3 days	Stop for 5 days	24 hours
Vitamin K Antagonists				
Warfarin	May continue or stop for 1-2 days INR ≤ 3.0	May continue or stop for 2-3 days INR ≤ 2.0	Stop for 3-5 days INR ≤ 1.5	12-24 hours
Direct Oral Anticoagulants (DOACs)				
Dabigatran (Pradaxa)	May continue or stop for 1 day	Stop for 2 days	Stop for 2 days	24 hours
Dabigatran (Pradaxa) (CrCl ≤ 50 ml/min)	May continue or stop for 1 day	Stop for 3-4 days	Stop for 3-4 days	24 hours
Apixaban (Eliquis)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Rivaroxaban (Xarelto)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Edoxaban (Savaysa, Lixiana)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Heparins				
Heparin (treatment) - IV	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	24 hours
Heparin (treatment) - SC	Discontinue for 6 hours	Discontinue for 6 hours	Discontinue for 24 hours	24 hours
Low Molecular Weight Heparin	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	24 hours

Adapted and modified from: Manchikanti L, Sanapati MR, Nampiaparampil D, et al. Perioperative management of antiplatelet and anticoagulant therapy in patients undergoing interventional techniques: 2024 updated guidelines from the American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2024; 27:S1-S94 (369).

Table 20. *Procedural checklist for managing anticoagulant and antiplatelet therapy during interventional techniques.*

PROCEDURE:
1.0 Patient evaluation and Identification of Risk Factors ❑ 1.1 Age ❑ 1.2 Diabetes ❑ 1.3 Bleeding disorders ❑ 1.4 Hypertension ❑ 1.5 Obesity ❑ 1.6 Low body weight ❑ 1.7 Renal disease ❑ 1.8 Low creatinine clearance
2.0 Identification of Anticoagulant or Antithrombotic Medication ❑ 2.1 Aspirin Use: • Primary Prophylaxis: Absence of established cardiovascular disease or risk factor • Secondary Prophylaxis: Presence of cardiovascular or cerebrovascular disease ❑ 2.2 Antiplatelets • Clopidogrel (Plavix) • Prasugrel (Effient) • Ticagrelor (Brilinta) ❑ 2.3 Direct oral anticoagulants (DOACs) • Dabigatran (Pradaxa) • Apixaban (Eliquis) • Rivaroxaban (Xarelto) • Edoxaban (Savaysa, Lixiana) ❑ 2.4 Warfarin (Coumadin) ❑ 2.5 Identification of over-the-counter drugs influencing thrombolysis: • Garlic • Vitamin E ❑ 2.6 Fish Oil • Primary Prophylaxis: Absence of established cardiovascular disease or risk factor • Secondary Prophylaxis: Presence of cardiovascular or cerebrovascular disease ❑ 2.7 SSRIs • Citalopram (Celexa) • Fluoxetine (Prozac) • Escitalopram (Lexapro) • Paroxetine (Paxil) • Sertraline (Zoloft) ❑ 2.8 NSAIDs
❑ 3.0 Risk Stratification and Recommendations • Low risk • Moderate or intermediate risk • High risk
❑ 4.0 Informed Decision Making
❑ 5.0 Restarting of Drugs
❑ 6.0 Postoperative Monitoring

13.0 Recommendations And Statements

1. There is evidence supporting the accuracy and value of diagnostic methods for diagnosing conditions amenable to peripheral nerve stimulation.
   Evidence Level: Low; Strength of Recommendation: Moderate

2. The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain, based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable peripheral nerve stimulation systems following a trial or selective lumbar medial branch stimulation without a trial, is Level III or fair with moderate certainty utilizing GRADE criteria.
   Evidence Level: Fair; Strength of Recommendation: Moderate

3. The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable stimulation systems following temporary peripheral nerve stimulation for 60 days is Level III or fair with moderate certainty utilizing GRADE criteria.
   Evidence Level: Fair; Strength of Recommendation: Moderate

4. Based on the evidence and the recommendations, indications may be expanded from present CMS guidance with addition of craniofacial pain, phantom limb pain, and low back pain, either nociceptive or neuropathic, with present evidence showing Level III or fair with moderate certainty utilizing GRADE criteria.
   Evidence Level: Fair; Strength of Recommendation: Moderate

5. It is important to understand each type of peripheral nerve stimulation implant with features of the equipment and technical requirements.
   Evidence Level: Moderate; Strength of Recommendation: Strong

6. Based on the available evidence and all the available guidance, patient education is a crucial aspect of success of peripheral nerve stimulation.
   Evidence Level: Moderate; Strength of Recommendation: Strong

7. Risk stratification of peripheral nerve stimulation, based on ASIPP guidelines: low risk for peripheral nerve stimulation trial and implantation of extremities and other superficial nerves, moderate risk for lumbar medial branches and high risk for thoracic and cervical medial branches, trigeminal and cranial nerve blocks and nerve stimulation.
   Evidence Level: Moderate; Strength of Recommendation: Moderate

8. Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized as per ASIPP guidelines for low- and high-risk procedures.
   Evidence Level: Moderate; Strength of Recommendation: Moderate

14.0 Conclusion

Peripheral nerve stimulation (PNS) systems have undergone remarkable advancements over the past 50 years, evolving from highly invasive open neurosurgical procedures to minimally invasive, FDA- cleared therapies for managing chronic pain. The availability of various peripheral nerve stimulation systems, including those from Curonix LLC, Bioness, SPR Therapeutics, Inc., Nalu Medical Inc., and Mainstay Medical Limited, has expanded the treatment options for patients suffering from chronic intractable pain.

The American Society of Interventional Pain Physicians (ASIPP) has developed evidence-based guidelines to aid clinicians in safe and effective use of PNS technology. These guidelines are built upon a thorough review of existing literature and expert consensus, emphasizing the importance of utilizing both temporary and permanent peripheral nerve stimulation for patients with chronic pain that has not responded to conservative treatments. This guideline provides a comprehensive review and critical analysis regarding the growing body of evidence supporting the use and long-term efficacy of PNS in clinical practice. The integration of PNS technology, guided by these robust guidelines, holds the potential to greatly improve patient outcomes and promote equitable access to innovative pain management solutions.

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Conflict of Interest

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Appendix Table 1. *Sources of risk of bias from Cochrane Review collaboration*.

Bias Domain	Source of Bias		Possible Answers
Selection	(1) Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.	Yes/No/Unsure
		Examples of inadequate methods are: alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors, and it was successful or:	Yes/No/Unsure
		• for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"	
		• for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination	
		• for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome	
		• for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes"	
		• for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data	
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure

Appendix Table 1 cont. ***Sources of risk of bias from Cochrane Review collaboration.***

Bias Domain	**Source of Bias**		**Possible Answers**
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	If there were no cointerventions or they were similar between the index and control groups.	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore, it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Other types of biases. For example: • When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. • Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.	Yes/No/Unsure

Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (87).

Appendix Table 2. *Item checklist for assessment of randomized controlled trials of peripheral nerve stimulation utilizing IPM – QRB.*

		Scoring
I.	TRIAL DESIGN AND GUIDANCE REPORTING	
1.	CONSORT or SPIRIT	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	DESIGN FACTORS	
2.	Type and Design of Trial	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	Statistical Methodology	
	None or inappropriate	0
	Appropriate	1
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
	For peripheral nerve stimulation:	
	No trial stimulation	0
	Selection with trial stimulation	1
	Selection with ≥ 50% relief	2
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2

Appendix Table 2 cont. ***Item checklist for assessment of randomized controlled trials of peripheral nerve stimulation utilizing IPM – QRB.***

		Scoring
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	2
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	3
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High-quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	ALLOCATION CONCEALMENT	
17.	Concealed Treatment Allocation	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1

Appendix Table 2 cont. ***Item checklist for assessment of randomized controlled trials of peripheral nerve stimulation utilizing IPM – QRB.***

		Scoring
	High-quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	BLINDING	
18.	Patient Blinding	
	Patients not blinded	0
	Patients blinded adequately	1
19.	Care Provider Blinding	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	Outcome Assessor Blinding	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	CONFLICTS OF INTEREST	
21.	Funding and Sponsorship	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	Conflicts of Interest	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
TOTAL		48

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (88).

Appendix Table 3. *Newcastle-Ottawa quality assessment scale for case control studies*.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection
1) Is the case definition adequate?
  a) yes, with independent validation ❋
  b) yes, eg record linkage or based on self reports
  c) no description
2) Representativeness of the cases
  a) consecutive or obviously representative series of cases ❋
  b) potential for selection biases or not stated
3) Selection of Controls
  a) community controls ❋
  b) hospital controls
  c) no description
4) Definition of Controls
  a) no history of disease (endpoint) ❋
  b) no description of source

Comparability
1) Comparability of cases and controls on the basis of the design or analysis
  a) study controls for _____ (Select the most important factor.) ❋
  b) study controls for any additional factor ¯ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure
1) Ascertainment of exposure
  a) secure record (eg surgical records) ❋
  b) structured interview where blind to case/control status ❋
  c) interview not blinded to case/control status
  d) written self report or medical record only
  e) no description
2) Same method of ascertainment for cases and controls
  a) yes ¯
  b) no
3) Non-Response rate
  a) same rate for both groups ❋
  b) non respondents described
  c) rate different and no designation

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (89).

Appendix Table 4. ***Newcastle-Ottawa quality assessment scale cohort studies.***

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection
1) Representativeness of the exposed cohort
  a) truly representative of the average _____ (describe) in the community ❋
  b) somewhat representative of the average _____ in the community ❋
  c) selected group of users eg nurses, volunteers
  d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
  a) drawn from the same community as the exposed cohort ❋
  b) drawn from a different source
  c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
  a) secure record (eg surgical records) ❋
  b) structured interview ❋
  c) written self report
  d) no description
4) Demonstration that outcome of interest was not present at start of study
  a) yes ❋
  b) no

Comparability
1) Comparability of cohorts on the basis of the design or analysis
  a) study controls for _____ (select the most important factor) ❋
  b) study controls for any additional factor ❋ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome
1) Assessment of outcome
  a) independent blind assessment ❋
  b) record linkage ❋
  c) self report
  d) no description
2) Was follow-up long enough for outcomes to occur
  a) yes (select an adequate follow up period for outcome of interest) ❋
  b) no
3) Adequacy of follow up of cohorts
  a) complete follow up - all subjects accounted for ❋
  b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ❋
  c) follow up rate < ____% (select an adequate %) and no description of those lost
  d) no statement

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (89).

Appendix Table 5. *Item checklist for assessment of nonrandomized or observational studies of peripheral nerve stimulation utilizing IPM-QRBNR.*

		Scoring
I.	STUDY DESIGN AND GUIDANCE REPORTING	
1.	STROBE or TREND Guidance	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	DESIGN FACTORS	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
	For peripheral nerve stimulation:	
	No trial stimulation	0
	Selection with trial stimulation	1
	Selection with ≥ 50% relief	2
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2

Appendix Table 5 cont. ***Item checklist for assessment of nonrandomized or observational studies of peripheral nerve stimulation utilizing IPM-QRBNR.***

		Scoring
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	1
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	2
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	3
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	4
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1
	No co-interventions or similar co-interventions in majority of the participants	2
V.	ASSIGNMENT	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4

Appendix Table 5. *Item checklist for assessment of nonrandomized or observational studies of peripheral nerve stimulation utilizing IPM-QRBNR.*

		Scoring
VI.	CONFLICTS OF INTEREST	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		48

Appendix Table 6. ***Criteria used in quality assessment of systematic reviews.***

1. Is a focused clinical question clearly stated?
   At a minimum, the question should be developed a priori and should clearly identify population and outcomes. The study question does not have to be in PICO format (Population, Intervention, Comparisons, Outcomes).
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

2. Are the search methods used to identify relevant studies clearly described?
   Search methods described in enough detail to permit replication. (The report must include search date, databases used, and search terms. Keywords and/or MeSH terms must be stated and where feasible the search strategy should be provided.)
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

3. Was a comprehensive literature search performed?
   At least 2 electronic sources should be searched and electronic searches should be supplemented by consulting: reference lists from prior reviews, textbooks, or included studies; specialized registries (eg, Cochrane registries); or queries to experts in the field.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

4. Was selection bias avoided?
   Study reports the number of studies identified through searches, the numbers excluded, and gives appropriate reasons for excluding, based on explicit inclusion/exclusion criteria.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

5. Was there duplicate study selection and data extraction?
   Did two or more raters make inclusion/exclusion decisions, abstract data, and assess study quality – either independently or with one rater over-reading the first raters result? Was an appropriate method used to resolve disagreements (eg, a consensus procedure)?
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

6. Were the characteristics of the included studies provided?
   In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed (eg, age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases) should be reported.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

7. Was the scientific quality of the included studies assessed and documented?
   A priori methods of assessment should be provided and criteria used to assess study quality specified in enough detail to permit replication.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

8. Were the methods used to combine the findings of studies appropriate?
   For pooled results, an accepted quantitative method of pooling should be used (ie, more than simple addition; e.g., random-effects or fixed-effect model). For pooled results, a qualitative and quantitative assessment of homogeneity (Cochran's Q and/or I2) should be performed. If only qualitative analyses are completed, the study should describe the reasons that quantitative analyses were not completed.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

9. Was the scientific quality of the included studies used appropriately in formulating conclusions?
   The results of the methodological rigor and scientific quality should be considered in the analysis (eg, subgroup analyses) and the conclusions of the review, and explicitly stated in formulating recommendations.
   [ ] Yes [ ] No [ ] Can't tell [ ] N/A

10. Was publication bias assessed?
    Publication bias tested using funnel plots, test statistics (eg, Egger's regression test), and/or search of trials registry for unpublished studies.
    [ ] Yes [ ] No [ ] Can't tell [ ] N/A

11. Was the conflict of interest stated?
    Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
    [ ] Yes [ ] No [ ] Can't tell [ ] N/A

12. Are the stated conclusions supported by the data presented?
    Were the conclusions made by the author(s) supported by the data and/or analyses reported in the systematic review?
    [ ] Yes [ ] No [ ] Can't tell [ ] N/A

Adapted from:
Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7:10 (91).
Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896-1900 (92).

Marinopoulos SS, Dorman T, Ratanawongsa N, et al. Effectiveness of continuing medical education. *Evid Rep Technol Assess (Full Rep)* 2007; 149:1-69 (93).

Appendix Table 7. *Randomized controlled trials of PNS excluded for various reasons from inclusion.*

AUTHOR, YEAR	TITLE	EXCLUSION CRITERIA
Kapural et al, 2024 (54)	Primary 3-month outcomes of a double-blind randomized prospective study (The QUEST Study) assessing effectiveness and safety of novel high-frequency electric nerve block system for treatment of post-amputation pain.	3-month follow-up
Liu et al, 2024 (255)	Short-term supraorbital nerve stimulation and pain relief for acute and subacute ophthalmic herpetic neuralgia: A randomized controlled crossover trial.	50 patients 12-week follow-up
Eldabe et al, 2019 (262)	A randomized controlled trial of subcutaneous nerve stimulation for back pain due to failed back surgery syndrome: The SubQStim study.	9-month follow-up Trial 30% relief also successful
Finch et al, 2019 (302)	High-frequency (10 kHz) electrical stimulation of peripheral nerves for treating chronic pain: A double-blind trial of presence vs absence of stimulation.	11 patients
Wilson et al, 2017 (257)	The effect of peripheral nerve stimulation on shoulder biomechanics: A randomized controlled trial in comparison to physical therapy.	The same study with publication of different outcome Intramuscular 3-month follow-up
van Gorp et al, 2016 (263)	Subcutaneous stimulation as ADD-ON therapy to spinal cord stimulation is effective in treating low back pain in patients with failed back surgery syndrome: A multicenter randomized controlled trial.	3-month follow-up
Plazier et al, 2015 (266)	C2 nerve field stimulation for the treatment of fibromyalgia: A prospective, double-blind, randomized, controlled cross-over study.	Fibromyalgia, short-term follow-up of 24 weeks
Slotty et al, 2015 (256)	Occipital nerve stimulation for chronic migraine: A randomized trial on subthreshold stimulation.	119-day follow-up
Istek et al, 2014 (265)	Randomized trial of long-term effects of percutaneous tibial nerve stimulation on chronic pelvic pain.	6-month follow-up
Wilson et al, 2014 (269)	Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: A randomized controlled trial.	Intramuscular 3-month follow-up
McRoberts et al, 2013 (264)	Peripheral nerve field stimulation for the management of localized chronic intractable back pain: Results from a randomized controlled study.	Field stimulation
Schoenen et al, 2013 (261)	Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study.	Blind 4-week follow-up
Gokyildiz et al, 2012 (349)	Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain.	Temporary stimulator

Appendix Table 8. *Non-randomized or observational studies of PNS excluded for various reasons from inclusion.*

AUTHOR, YEAR	TITLE	EXCLUSION CRITERIA
Gutierrez et al, 2024 (65)	Sustained relief of complex regional pain syndrome (CRPS) pain following a 60-day peripheral nerve stimulation: A report of three cases.	3 case reports
Ashkan et al, 2020 (63)	Peripheral nerve stimulation registry for intractable migraine headache (RELIEF): A real-life perspective on the utility of occipital nerve stimulation for chronic migraine.	Registry
Frederico & da Silva Freitas, 2020 (355)	Peripheral nerve stimulation of the brachial plexus for chronic refractory CRPS pain of the upper limb: Description of a new technique and case series.	14 patients 12-month follow-up
Herschkowitz & Kubias, 2019 (290)	A case report of wireless peripheral nerve stimulation for complex regional pain syndrome type-I of the upper extremity: 1 year follow up.	A single case report
Cohen et al, 2019 (292)	Percutaneous peripheral nerve stimulation for the treatment of chronic pain following amputation.	14 patients 4-week follow-up s
Freitas et al, 2018 (273)	Peripheral nerve stimulation for painful mononeuropathy secondary to leprosy: A 12-month follow-up study.	23 patients 12-month follow-up
Wilson et al, 2018 (308)	Fully implantable peripheral nerve stimulation for hemiplegic shoulder pain: A multi-site case series with two year follow-up.	28 patients trialed with 5 patients implanted
Guentchev et al, 2017 (299)	Long-term reduction of sacroiliac joint pain with peripheral nerve stimulation.	16 long-term
Reddy et al, 2017 (288)	Novel technique for trialing peripheral nerve stimulation: Ultrasonography-guided StimuCath trial.	17 patients 14-month follow-up
Sokal et al, 2017 (274)	Tibial nerve stimulation with a miniature, wireless stimulator in chronic peripheral neuropathic pain.	6 patients
Rossi et al, 2016 (294)	A novel mini-invasive approach to the treatment of neuropathic pain: The PENS Study.	Field stimulation 6-month follow-up
Heinze et al, 2015 (295)	Comparative pilot study of implantation techniques for pudendal neuromodulation: Technical and clinical outcome in first 20 patients with chronic pelvic pain.	20 patients
Voorbrood et al, 2015 (275)	An algorithm for assessment and treatment of post-herniorrhaphy pain.	68 patients Short-term follow-up
Rauck et al, 2014 (277)	Treatment of post-amputation pain with peripheral nerve stimulation.	14 patients 4-week follow-up
Stevanato et al, 2014 (276)	Chronic post-traumatic neuropathic pain of brachial plexus and upper limb: A new technique of peripheral nerve stimulation.	7 patients
Wilson et al, 2014 (358)	Percutaneous peripheral nerve stimulation for chronic pain in subacromial impingement syndrome: A case series.	10 patients 12-week follow-up
Burgher et al, 2012 (301)	Subcutaneous peripheral nerve stimulation with inter-lead stimulation for axial neck and low back pain: Case series and review of the literature.	10 patients 2-9 month follow-up
Rauck et al, 2012 (291)	Peripheral nerve stimulation for the treatment of postamputation pain – A case report.	A single case report
Deer et al, 2010 (278)	Prospective clinical study of a new implantable peripheral nerve stimulation device to treat chronic pain.	8 patients
Govaert et al, 2010 (297)	Sacral neuromodulation for the treatment of chronic functional anorectal pain: A single center experience.	9 patients
Falletto et al, 2009 (296)	Is sacral nerve stimulation an effective treatment for chronic idiopathic anal pain?	12 patients
Huntoon & Burgher, 2009 (286)	Ultrasound-guided permanent implantation of peripheral nerve stimulation (PNS) system for neuropathic pain of the extremities: Original cases and outcomes.	8 patients
Jeon et al, 2009 (289)	Median nerve stimulation in a patient with complex regional pain syndrome Type II.	A single case report
Narouze et al, 2009 (287)	Ultrasound-guided placement of a permanent percutaneous femoral nerve stimulator leads for the treatment of intractable femoral neuropathy.	A single case report

Appendix Table 8 cont. *Non-randomized or observational studies of PNS excluded for various reasons from inclusion.*

AUTHOR, YEAR	TITLE	EXCLUSION CRITERIA
Verrills et al, 2009 (300)	Peripheral nerve stimulation: A treatment for chronic low back pain and failed back surgery syndrome?	11 patients 1-year follow-up
Strege et al, 1994 (305)	Chronic peripheral nerve pain treated with direct electrical nerve stimulation.	24 patients 6 implant failures
Waisbrod et al, 1985 (285)	Direct nerve stimulation for painful peripheral neuropathies.	11 patients Not implanted
Law et al, 1980 (284)	Retrospective analysis of 22 patients with chronic pain treated by peripheral nerve stimulation.	22 patients