Systematic Review

Effectiveness of Peripheral Nerve Stimulation in Managing Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Peripheral nerve stimulation (PNS) has been used for over 50 years to treat chronic pain. Since 2015, the Food and Drug Administration (FDA) has approved percutaneously implanted PNS leads and neurostimulators, offering a minimally invasive, non-opioid alternative for managing persistent and refractory chronic pain.

Objective: To evaluate the current evidence on PNS through a systematic review and meta-analysis.

Study Design: A systematic review and meta-analysis of randomized controlled trials (RCTs) on PNS for chronic pain management, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods: Quality was assessed using Cochrane review criteria for risk of bias and the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) for randomized therapeutic trials.

A comprehensive literature search was conducted across multiple databases (1966-February 2025), supplemented by manual searches of bibliographies from relevant review articles. Included studies underwent quality assessment, best evidence synthesis, and grading using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Evidence levels were classified from Level I to Level V.

Outcome Measures: The primary outcome was the proportion of patients achieving significant pain relief and functional improvement (≥ 50%) sustained for at least 12 months.

Results: The present investigation identified 7 high-quality and 2 moderate-quality RCTs based on Cochrane criteria and 9 moderate-quality trials based on IPM-QRB criteria. Utilizing GRADE criteria, 7 of 9 studies demonstrated moderate evidence and clinical applicability, and 2 of 9 showed low evidence and applicability.

Overall, the combined qualitative and quantitative analysis supported a fair (Level III) evidence level, with moderate certainty and moderate strength of recommendation for:

- Implantable PNS systems following a trial or selective lumbar medial branch stimulation without a trial
- Temporary PNS therapy for 60 days

Limitations: A key limitation remains the scarcity of high-quality studies.

Conclusion: The evidence supports a fair (Level III) level of evidence with moderate certainty and recommendation strength, based on qualitative and quantitative analyses and GRADE assessment.

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Chronic pain affects an estimated 24.3% of U.S. adults, with 8.5% experiencing high-impact chronic pain as of 2023, an increase from 20.4% and 7.4%, respectively, in 2019 (1,2). It is more prevalent among older adults, females, and residents of non-metropolitan areas. Low back and neck pain remain the leading causes of disability worldwide (3,4). In contrast, neuropathic pain is recognized as a particularly debilitating form of chronic pain, resulting from lesions or diseases affecting the somatosensory nervous system. Globally, neuropathic pain impacts 7% to 10% of the population, with 20% to 30% of affected individuals experiencing chronicity (5).

The International Association for the Study of Pain (IASP) defines 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" (6,7). Neuropathic pain encompasses diverse clinical conditions and can be classified by etiology, such as degenerative, traumatic, infectious, metabolic, and toxic causes, or by the site of neurological lesions, whether peripheral or central (7). Common associated conditions include complex regional pain syndrome (CRPS), phantom limb pain, traumatic nerve injuries, chemotherapy-induced neuropathy, human immunodeficiency virus (HIV)-related neuropathy, diabetic neuropathy, post-herpetic neuralgia, and post-surgical pain. The widespread prevalence and impact of neuropathic pain on quality of life, healthcare utilization, and health equity are well-documented (8-10).

Peripheral nerve stimulation (PNS) offers a unique neuromodulation strategy for pain management. PNS serves diagnostic and therapeutic roles by targeting peripheral nerves, the potential pain sources, and conduits for pain signals between the central nervous system (CNS) and affected areas. Historically, stimulating peripheral nerves predates spinal cord and brain stimulation. Pioneers such as Wall and Sweet (11) explored PNS within the framework of the "gate-control" theory of pain, and Shelden et al (12) applied high-frequency PNS for neuropathic facial pain.

Despite significant shifts in utilization patterns of interventional pain management techniques (3,4,13-23), PNS adoption remained limited for decades, with only a handful of "off-label" devices available (24). However, the past decade has seen renewed interest and rapid advancements. Several dedicated Food and Drug Administration (FDA)-cleared PNS systems have entered the market (4), leading to an expansion of use and the development of multiple guidelines and comprehensive reviews (4,24-28).

The U.S. FDA has cleared PNS for treating acute and chronic pain in the lower back, upper and lower extremities, trunk, and craniofacial regions (4). Some of the clinical applications now include mononeuropathies, neuropathic limb pain, post-stroke shoulder pain, headaches, facial pain, plexus injuries, phantom limb pain, CRPS, and chronic low back pain.

Since 2020, 8 systematic reviews and meta-analyses have evaluated PNS for chronic pain (29-36). However, many of these reviews were limited by methodological weaknesses, such as inclusion of non-randomized studies, observational designs without sufficient sample sizes, case reports, and short-term follow-ups (37-47).

In 2024, the American Society of Interventional Pain Physicians (ASIPP) released evidence-based guidelines for implantable PNS systems, grounded in FDA clearances (4). These guidelines specifically exclude peripheral field percutaneous electrical and sacral nerve stimulation, instead focusing on integrating PNS into neuromodulation and interventional pain management algorithms. The current evidence is classified as fair, with a moderate strength of recommendation based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Consequently, we sought to evaluate recent literature and conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing PNS in managing chronic pain.

Methods

A systematic review followed the methodological and reporting standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (48). Additionally, methodologies from prior reviews and established guidelines were incorporated to enhance rigor (3,4,37-44,49).

Objectives

This systematic review of RCTs aimed to evaluate PNS's effectiveness in managing chronic pain.

Eligibility Criteria

The review included all RCTs investigating PNS for chronic pain management, with a minimum follow-up duration of 6 months for implanted stimulators and 3 months for temporary stimulation.

Information Sources

A comprehensive literature search was performed to identify RCTs on PNS for chronic pain management. The search encompassed studies published globally, without language or country of origin restrictions. Sources included multiple databases and manual searches of reference lists to ensure a thorough capture of relevant studies.

1. PubMed from 1966 https://pubmed.ncbi.nlm.nih.gov/
2. Cochrane Library https://www.cochranelibrary.com/
3. Google Scholar https://scholar.google.com/
4. US National Guideline Clearinghouse (NGC) https://www.ahrq.gov/gam/index.html
5. Clinical Trials https://www.clinicaltrials.gov/
6. Previous systematic reviews and cross-references
7. All other sources, including non-indexed journals and abstracts

The search period was from 1966 through April 2025.

Search Strategy

The search strategy included PNS in managing chronic pain. The search terms included:

(((((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)

Data Selection

Two reviewers (LM and ADK) independently developed the search criteria, performed the literature search, and extracted data from the included studies. Any disagreements were resolved through consultation with a third reviewer (MRS). To address potential conflicts of interest involving the authors of this review, disputes were referred to independent reviewers not involved in the authorship.

Study of Risk of Bias and Methodological Quality Assessment

RCTs were evaluated for methodological quality and risk of bias using the Cochrane review criteria (Appendix Table 1) (50) and the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) tool (Appendix Table 2) (51).

Trials meeting the inclusion criteria and scoring at least 9 out of 13 on the Cochrane review criteria (50) were classified as high quality. Those scoring between 5 and 8 were considered of moderate quality.

Similarly, all included trials were evaluated using the IPM-QRB criteria (51). Studies scoring 32-48 were rated as high quality, those scoring 16-31 as moderate quality, and studies scoring below 16 were classified as low quality and excluded from further analysis.

Assessment Utilizing Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Criteria

The evidence grading was performed using the GRADE system to evaluate the overall strength and certainty (52,53). The GRADE assessment considered five key factors:

1. Methodological limitations
2. Consistency of results
3. Indirectness of evidence
4. Imprecision
5. Publication bias

Each domain was rated as high, moderate, low, or very low, as outlined in Table 1. Based on the meth-

odological quality of the studies, the grading could remain unchanged, be downgraded, or upgraded.

The certainty of evidence was determined by assessing the risk of bias, imprecision, inconsistency, indirectness, and publication bias. Adjustments to the certainty rating (upward or downward) were made based on these criteria, as detailed in Table 2.

The methodological quality assessment and GRADE appraisal were independently performed by two authors (LM and ADK) unblinded. Any disagreements were resolved through consultation with a third author (MRS). In cases where a potential conflict of interest arose due to authorship, the involved reviewers were excluded from assessing the quality of those studies.

Outcome Measures

An outcome was deemed clinically significant if there was a reduction of 2 points on the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), or if patients experienced at least a 50% reduction in pain along with improvement in functional status. A study was classified as positive, clinically significant, and effective if the primary outcome reached statistical significance at a *P*-value ≤ 0.05.

Table 1. *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/ (53)

Table 2. *Reasons rate certainty in evidence up or down.*

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

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/ (53)

Analysis of Evidence

The evidence was analyzed through both qualitative and quantitative synthesis. Quantitative synthesis included conventional meta-analysis as well as single-arm meta-analysis.

Qualitative Analysis

The qualitative analysis was conducted using a best-evidence synthesis approach, which was modified and collated based on multiple criteria, including the Cochrane Review criteria and the United States Preventive Services Task Force (USPSTF) grading system (Table 3) (54). This analysis categorized evidence into five levels, from strong to opinion- or consensus-based.

Table 4 outlines the strength of recommendations based on the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (55), as adapted by the guideline panel (3,22).

Meta-Analysis

Dual-Arm Meta-Analysis

Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020) was utilized for the dual-

Table 3. *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 (54).

arm meta-analysis. Pain and functional improvement outcomes were reported as standardized mean differences (SMD) with 95% confidence intervals (CI). Forest plots were generated to visualize treatment effects, applying a random-effects model. Heterogeneity was assessed using the I^2 statistic.

Summary of Evidence

The evidence was analyzed using qualitative evidence synthesis combined with GRADE criteria.

At least 2 reviewers (LM and ADK) independently assessed the evidence in a standardized manner. Any disagreements were resolved through consultation with a third reviewer (MRS). In cases of potential conflicts of interest, such as authorship involvement, the reviewers concerned were recused from the assessment and analysis process.

Results

Study Selection

Figure 1, developed by the 2020 PRISMA guidelines (48), illustrates the flow diagram of study selection following the PRISMA process.

Twenty-seven RCT publications were identified based on the search criteria (56-82), of which 9 trials were included in the review (56,58-62,64-66).

Methodological Quality and Risk of Bias Assessment

The methodological quality of the 9 included trials was evaluated using the Cochrane review criteria (Table 5) (50) and the IPM-QRB criteria (Table 6) (51). According to the Cochrane review criteria, 7 of the 9 RCTs were rated high quality (56,58-62,66), while 2 trials were rated as moderate quality (64,65). In contrast, the IPM-QRB criteria assessment classified all 9 trials as moderate quality (56,58-62,64-66).

Study Characteristics

The characteristics of the included RCTs evaluating the effectiveness of PNS are summarized in Table 7.

Analysis of Evidence

The evidence was analyzed using both qualitative and quantitative approaches.

Table 4. *Guide for strength of recommendations as modified for American Society of Interventional Pain Physicians (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 (55).

Quantitative Analysis

Quantitative analysis was conducted using conventional dual-arm meta-analysis with RevMan 5.4. A detailed examination of the included studies revealed significant heterogeneity in outcome measurement tools across trials. The variability in pain relief and functional outcome scales posed significant challenges to the feasibility and validity of pooled quantitative synthesis.

Pain assessments utilized diverse instruments, including the NRS, VAS, Brief Pain Inventory (BPI), Oswestry Disability Index (ODI), and the 36-Item Short Form Survey (SF-36) physical function subscale. These tools differed considerably in scaling systems, psychometric properties, and interpretation thresholds. Additionally, pain reduction was reported variably, as change scores, final scores, or responder analyses (e.g., percentage of patients achieving ≥ 30% or ≥ 50% pain reduction), making standardization across studies infeasible. Similar inconsistencies were noted in functional outcome measures.

This heterogeneity in outcome measures introduces a high risk of measurement bias and undermines the internal validity of any pooled mean difference (MD) or SMD calculations.

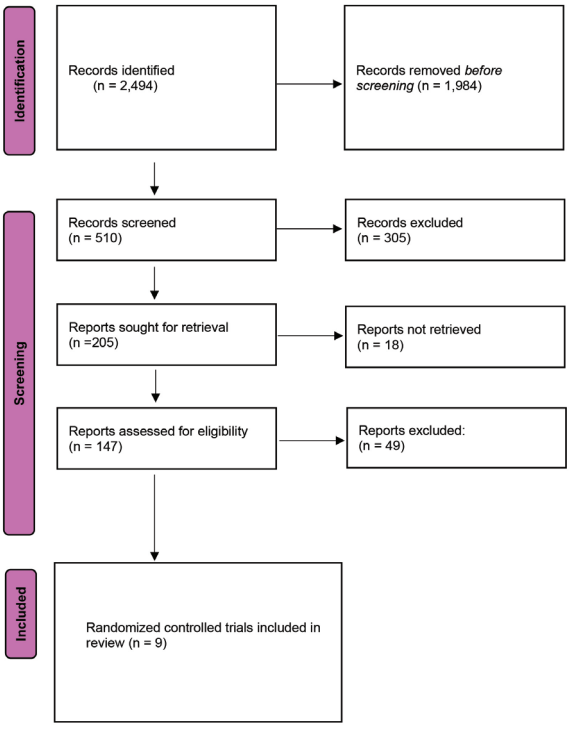

Fig. 1. *Flow diagram illustrating the literature based on 2020 PRISMA guidance used for evaluating PNS in managing chronic pain.*

Furthermore, temporal variability in follow-up intervals added another layer of complexity. While the analysis focused on outcomes at 1, 3, 6, and 12 months, not all studies reported results at these exact time points. Some studies presented ranges (e.g., 4–6 weeks, 120 days) or only assessed specific time points for the treatment group, limiting direct comparability.

To address these challenges, we prioritized data on pain relief, reflecting the number of patients reporting no improvement or relief in pain and function. Where possible, studies using consistent measurement tools, such as NRS for pain and ODI for function, were included in the meta-analysis. A random-effects model was applied using RevMan 5.4, with statistical significance set at $P \leq 0.05$.

Pain Relief – 1 Month Follow-Up

Seven studies met the inclusion criteria. (56,58-61,64,66). After treatment, the pooled effect size was 0.35 odds ratio (OR) (95% CI, 0.14-0.85), with a significant difference ($P = 0.02$). This indicated that the stimulation group had fewer patients with pain than the control group and substantially improved the patients' pain. However, a moderate heterogeneity ($I^2 = 60\%$, $P = 0.03$) was observed among the studies (Fig. 2).

Functionality – 1 Month Follow-Up

Only 2 studies met inclusion criteria (61,66). After treatment, the pooled effect size was 0.19 OR (95% CI, 0.05-0.70), with a significant difference ($P = 0.01$). This indicated that the stimulation group had fewer patients with disabilities than the control group and substantially improved patient functionality. However, a moderate heterogeneity ($I^2 = 50\%$, $P = 0.16$) was observed among the studies (Fig. 3).

Pain Relief – 3-Month Follow-Up

Two studies met inclusion criteria (58,66). At the 3-month follow-up, the pooled effect size for pain relief using NRS for pain was -3.81 MD (95% CI, -3.81 to -2.41), with a significant difference ($P < 0.00001$). This indicated that the intervention had a substantial positive effect on the patient's pain. However, a high heterogeneity ($I^2 = 99\%$, $P < 0.00001$) was observed among the studies (Fig. 4).

Subgroup Analysis for Functionality after 3 and 12 months' Follow-Up

In the subgroup analysis, after 3 months, with

2 studies meeting inclusion criteria (58,66), the pooled effect size for functionality using the ODI was -13.10 MD (95% CI, -17.31 to -8.89), with a significant difference ($P < 0.00001$). A moderate heterogeneity was observed across the studies ($I^2 = 41\%$). Likewise, after a 12-month follow-up, the pooled effect size was -15.80 MD (95% CI, -17.35 to -16.24), with significant difference ($P < 0.00001$) and moderate heterogeneity ($I^2 = 5\%$). Meanwhile, the overall pooled effect size was -15.35 MD (95% CI, -18.42 to -12.28), with a significant difference ($P < 0.00001$). These negative values indicate a meaningful reduction in the disability scores, reflecting improved functional status in the stimulation group. However, a high heterogeneity ($I^2 = 98\%$) was observed among the studies (Fig. 5).

Assessment of Evidence by GRADE Criteria

Table 8 presents the assessment of GRADE criteria, applying 5 levels of evidence and evaluating 5 key factors: methodological limitations, consistency, indirectness, imprecision, and publication bias. Each study was graded as high, moderate, low, or very low. Overall, 7 studies demonstrated a moderate level of evidence according to the GRADE assessment (56,58,59,61,62,64,66), while 2 studies were graded as low (60,65).

The GRADE framework was applied to the RCTs to evaluate PNS interventions for comparable outcomes and determine the certainty of evidence. This assessment incorporated factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on this evaluation, seven of the nine RCTs (56,58,59,61,62,64,66) were found effective, with an overall moderate certainty of evidence.

Overall, this analysis included 7 trials investigating implanted PNS

Table 5. *Methodological quality assessment of randomized trials of peripheral nerve stimulation utilizing Cochrane review criteria.*

	Goree et al, 2024 (61)	Hatheway et al, 2024 (66)	Hayek et al, 2025 (64)	Gilligan et al, 2021 (56)	Gilmore et al, 2019 (59)	Deer et al, 2016 (60)	Dodick et, al, 2015 (62)	Serra & Marchioretto, 2012 (65)	Schwab et al, 2025 (58)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y	N	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	Y	N	Y
Patient blinded	N	N	N	N	N	N	U	N	N
Care provider blinded	N	N	N	U	N	N	Y	U	N
Outcome assessor blinded	Y	N	N	Y	Y	Y	U	U	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	N	Y	Y	N	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	U	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y	Y
Co-intervention avoided or similar in all groups	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	N	N	N	N	N	N	U	Y	N
SCORE	10/13	9/13	8/13	10/13	10/13	9/13	10/13	7/13	9/13

Y = yes; N = no; U = unclear

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 (51).

Table 6. *Methodologic quality assessment of randomized trials of peripheral nerve stimulation utilizing IPM – QRB criteria.*

		Goree et al, 2024 (61)	Hatheway et al, 2024 (66)	Hayek et al, 2025 (64)	Gilligan et al, 2021 (56)	Gilmore et al, 2019 (59)	Deer et al, 2016 (60)	Dodick et, al, 2015 (62)	Serra & Marchioretto, 2012 (65)	Schwab et al, 2025 (58)
I.	TRIAL DESIGN AND GUIDANCE REPORTING									
1.	CONSORT or SPIRIT	3	3	3	3	3	3	3	1	3
II.	DESIGN FACTORS									
2.	Type and Design of Trial	2	2	2	2	2	2	3	1	2
3.	Setting/Physician	2	2	2	2	2	2	2	1	2
4.	Imaging	1	3	3	1	1	1	3	2	1
5.	Sample Size	2	2	2	3	1	3	3	1	3
6.	Statistical Methodology	1	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS									
7.	Inclusiveness of Population	0	2	2	0	0	0	2	2	0
	• ≥ 50% response to trial									
8.	Duration of Pain	2	2	2	2	2	2	2	1	2
9.	Previous Treatments	2	2	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	1	1	3	2	2	2	2	3
IV.	OUTCOMES									
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	3	2	2	2	1	3
12.	Analysis of all Randomized Participants in the Groups	2	2	1	2	2	0	2	1	2
13.	Description of Drop Out Rate	1	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	2
15.	Role of Co-Interventions	1	1	1	1	1	1	1	0	1
V.	RANDOMIZATION									
16.	Method of Randomization	2	2	2	2	2	2	2	0	2
VI.	ALLOCATION CONCEALMENT									
17.	Concealed Treatment Allocation	2	2	2	2	2	0	2	0	2
VII.	BLINDING									
18.	Patient Blinding	0	0	0	0	0	0	0	0	0
19.	Care Provider Blinding	0	0	0	0	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	1	0	0	0

Table 6 cont. *Methodologic quality assessment of randomized trials of peripheral nerve stimulation utilizing IPM – QRB criteria.*

		Gorce et al, 2024 (61)	Hatheway et al, 2024 (66)	Hayek et al, 2025 (64)	Gilligan et al, 2021 (56)	Gilmore et al, 2019 (59)	Deer et al, 2016 (60)	Dodick et, al, 2015 (62)	Serra & Marchioretto, 2012 (65)	Schwab et al, 2025 (58)
VIII.	CONFLICTS OF INTEREST									
21.	Funding and Sponsorship	-3	-3	-3	-3	-3	-3	-3	2	-3
22.	Conflicts of Interest	-2	-2	-2	-3	-2	-3	-2	2	-3
TOTAL		24/48	27/48	26/48	26/48	23/48	21/48	30/48	23/48	26/48

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 (51).

(56,58,60,62,64–66), 2 trials evaluating medial branch stimulation (56,58), and 2 trials assessing 60-day temporary stimulation (59,61). Among the implanted PNS studies, 2 trials (62,65) utilized spinal cord stimulation (SCS) leads instead of PNS-specific leads developed and approved for PNS applications.

For the 60-day temporary stimulation studies (59,61), both were rated as moderate quality and demonstrated moderate evidence, though limitations such as small sample sizes and methodological drawbacks resulted in only fair overall evidence.

Based on these findings, the overall evidence is classified as Level III (fair) with moderate certainty according to GRADE criteria.

Qualitative Analysis

Table 7 summarizes the study characteristics of the included RCTs. Of the 9 studies, 7 evaluated implanted PNS systems (56,58,60,62,64-66), including 2 studies focused on medial branch stimulation (56,58). Notably, 2 studies employed neuromodulation systems from Abbott (formerly St. Jude Medical) (62) and Medtronic (65), which are not specifically approved for PNS but rather for spinal cord stimulation.

Among the remaining 5 implanted PNS studies, one utilized the Curonix system (64), one the Nalu system (66), one the Bioness system (60), and 2 employed the ReActiv8 system (56,58). Of these 7 studies, 5 demonstrated moderate-quality evidence (56,58,62,64,66), while 2 were rated as low-quality evidence (60,65).

For the 60-day temporary stimulation, 2 studies (59,61) were identified, both showing moderate evidence, but limited by small sample sizes.

Based on qualitative analysis, the overall evidence is considered Level III, fair.

Summary of Evidence

The summary of evidence was determined using qualitative synthesis, quantitative synthesis, and GRADE criteria. Both the qualitative analysis and GRADE assessment yielded consistent findings, indicating similar levels of evidence. In contrast, the quantitative analysis did not provide definitive evidence but demonstrated trends toward improvement in pain and functional outcomes.

As a result, the overall evidence is classified as Level III (fair) with moderate certainty and a moderate strength of recommendation, based on the combined qualitative and quantitative analyses and the GRADE assessment.

Discussion

The present systematic review and meta-analysis of available RCTs included 9 trials (56,58-62,64-66). Of these, 7 trials evaluated permanent implants (56,58,60,62,64-66), including 2 trials focused on medial branch stimulation (56,58). Among the included studies, 5 utilized peripheral neurostimulation systems (56,58,60,64,66), 2 employed SCS leads (62,65), 2 examined medial branch stimulation (56,58), and 2 investigated 60-day temporary stimulation (59,61).

Following rigorous methodological quality assessment and grading of the evidence using both qualitative and quantitative synthesis and applying GRADE criteria, the overall evidence was determined to be Level III (fair), with moderate certainty and a moderate strength of recommendation for implantable PNS systems after a trial or selective lumbar medial branch stimulation without a trial for temporary PNS (60 days).

Table 7. *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								
Hayek et al, 2025 (64) (Freedom® PNS System, Curonix LLC) RA, patient as their own control Quality Scores: Cochrane = 8/13 IPM-QRB = 26/48	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 trial 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 7 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**
Hatheway et al, 2024 (66) (Nalu Neurostimulation System) 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 trial 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 trial The follow-up for conventional medical management was only 3 months	Positive trial Data appears to be reliable showing successful treatment with PNS
Deer et al, 2016 (60) (Bioness StimRouter® System) 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® System 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 trial does not add any evidence to peripheral nerve stimulation

Table 7 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 (62) (St. Jude Medical Neuromodulation) 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 trial 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 trial with reasonable size population and follow-ups The results showed moderate evidence with 50% reduction in headache of 47.8% of the patients
Serra & Marchioretto, 2012 (65) (Medtronic, Inc.) 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 trial Decreased medication use	A randomized trial with multiple outcome parameters with implantation after trial stimulation	A single center trial 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 trial with appropriate follow-up with moderate methodologic quality providing limited evidence for occipital nerve stimulation in the treatment of chronic migraine

Table 7 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**
MEDIAL BRANCH STIMULATION								
Schwab et al, 2025 (58) (ReActiv8) P, RA, AC Quality Scores: Cochrane = 9/13 IPM-QRB = 26/48	n = 203 Restorative neurostimulation = 99 Control (optimal medical management) = 104 Patients with chronic low back pain associated with multifidus dysfunction, with no indication for or history of lumbar spine surgery	Restorative neurostimulation	Optimal medical management	The primary endpoint was a comparison of the mean change in the ODI between the treatment and control arms at 1 year The secondary endpoints included pain (NRS) and health-related quality of life (EQ-5D-5L) 1 year	Primary endpoint showed statistically significant difference with mean improvement in the ODI in favor of restorative neurostimulation ($P < 0.001$) Secondary endpoints with NRS ($P < 0.001$) and EQ-5D-5L ($P < 0.001$) were statistically and clinically significant improvement in neurostimulation arm compared to optimal medical management arm	RCT of selective medial branch stimulation with relatively large participants Significant improvement at 1 year follow up with primary and secondary outcomes compared to previous trial by Gilligan et al, 2021	No placebo control Active control	Positive trial Well-designed trial with better outcomes than the original trial
Gilligan et al, 2021 (56) (ReActiv8-B) 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) 1, 2, 3, & 5 years	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 7 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**
60-DAY TEMPORARY STIMULATION								
Goree et al, 2024 (61) (SPRINT PNS System; SPR Therapeutics) 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
Gilmore et al, 2019 (59) (SPRINT PNS System; SPR Therapeutics) 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 trial 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; MPQ-SF-2 = Short-Form McGill Pain Questionnaire-2; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; ONS = occipital nerve stimulation; P = Prospective; 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

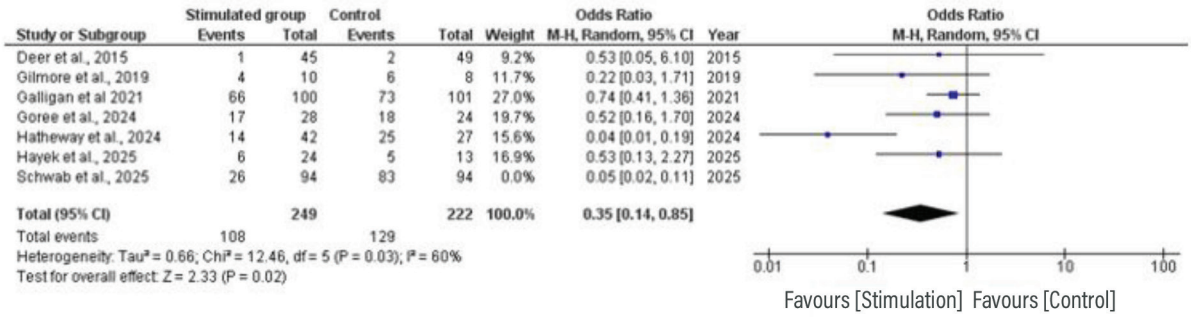

Fig. 2. *The forest plot for the pain was not resolved after treatment.*

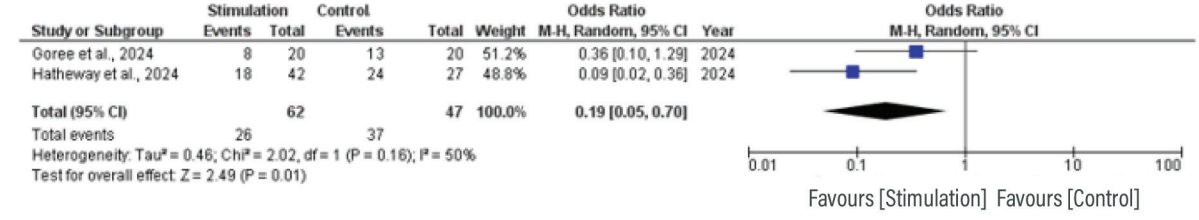

Fig. 3. *The forest plot for functionality did not improve after treatment.*

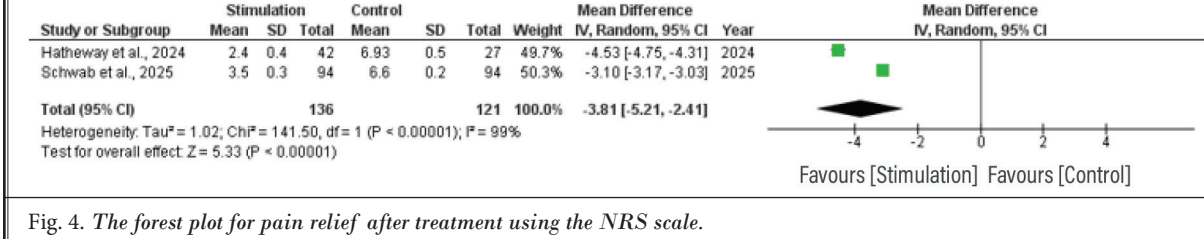

Fig. 4. *The forest plot for pain relief after treatment using the NRS scale.*

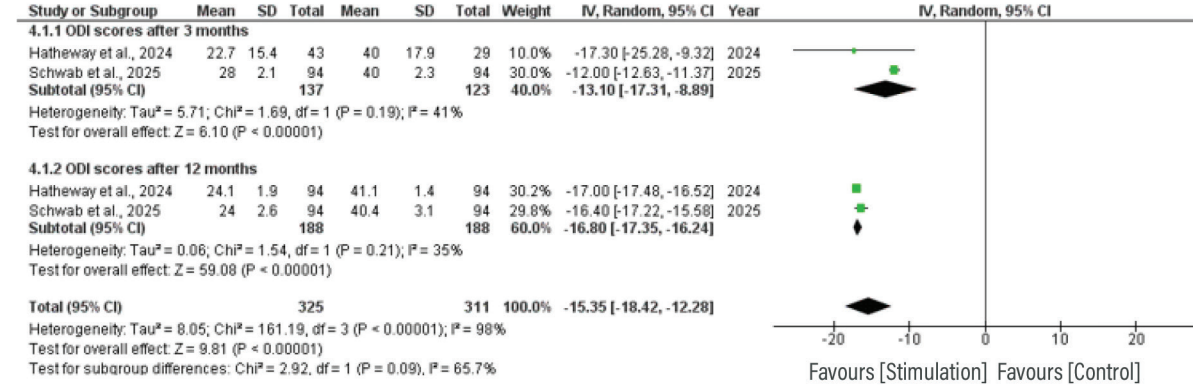

Fig. 5. *The forest plot for the functionality at 3 and 12-month follow-up using the Oswestry disability index scale.*

Table 8. *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									
Hayek et al, 2025 (64)	RA	Low	NS	NS	NS	Low	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 trial with moderate methodologic quality and minimal risk of bias. Applicable to clinical practice	Moderate
Hatheway et al, 2024 (66)	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
Deer et al, 2016 (60)	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 (62)	RA, DB	Low	NS	NS	NS	Low	152 Treatment group = 102 Control group = 52	The trial 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 (65)	RA	Low/ Moderate	NS	NS	NS	Low	30	Small number of patients	Low
MEDIAL BRANCH STIMULATION									
Schwab et al, 2025 (58)	P, RA, AC	Low	NS	NS	NS	Low	203 Restorative neurostimulation = 99 Control (optimal medical management) = 104	The trial was performed in a relatively large population comparing to optimal medical management (OMM). Well designed trial with appropriate outcomes. In fact, outcomes were better than the original trial by Gilligan et al (37).	Moderate

Table 8 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			
Gilligan et al, 2021 (56)	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
60-DAY TEMPORARY STIMULATION									
Goree et al, 2024 (61)	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 (59)	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

AC = active control; DB = double blind; NS = Not serious; NA = Not available; P = Prospective; PC = placebo control; RA = randomized

This review aligns with several previous systematic reviews but also incorporates more recent studies published subsequently. It differs from earlier reviews by exclusively including RCTs, focusing solely on implantable temporary or permanent systems.

Notably, among higher-quality publications, Barad et al (29) conducted a systematic review in 2022 and developed practice guidelines for percutaneous interventional migraine prevention strategies, including implantable PNS approaches. Their findings reported a moderate strength of evidence with a moderate effect size for these interventions.

Char et al (31) published a high-quality systematic review in 2022 on implantable PNS for peripheral neuropathic pain. Their analysis found that the overall evidence was generally of very low or low quality. However, they reported modest to substantial improvements in pain and neurological function, with phantom limb pain being the only indication supported by moderate-level evidence for PNS.

D'Souza et al (35), in a 2023 systematic review on PNS for low back pain, concluded that neuromuscular stimulation may offer modest to moderate pain relief in patients with low back pain. Nevertheless, they emphasized that the evidence was limited due to risks of bias, clinical and methodological heterogeneity, and inconsistencies in the available data.

Among earlier reviews, Deer et al (30) published a systematic review in 2020 in which the evidence was categorized as Level I for occipital nerve stimulation and for chronic low back pain targeting the cluneal nerve and its branches. They assigned Level II evidence for sphenopalatine ganglion stimulation, poststroke shoulder pain, and neuropathic pain in the extremities, and Level III evidence for posterior tibial nerve stimulation.

Helm et al (32) published a systematic review in 2021 on the effectiveness and safety of PNS for chronic pain, paralleling the findings of Deer et al (30) but reporting varying levels of evidence. They identified Level II evidence supporting PNS for refractory peripheral nerve injury and Level III evidence for tibial nerve stimulation in pelvic pain, as well as surgically placed cylindrical leads or sphenopalatine ganglion stimulation for cluster headaches.

Xu et al (33), in a 2021 systematic review, reported Level I and II evidence for the use of PNS in chronic migraine headache. They also found Level II evidence for cluster headaches, post-amputation pain, chronic pelvic pain, chronic low back pain, and lower extremity pain, with Level IV evidence for peripheral neuropathic pain and post-surgical pain.

Amirianfar et al (34), in their 2023 review, evaluated the use of PNS for chronic knee pain following total knee arthroplasty, concluding that the evidence was of low quality.

A recent trial by Hayek et al (64) demonstrated positive outcomes among RCTs assessing the effectiveness of permanent implantable systems. Their findings supported an expanded indication for PNS in treating craniofacial pain. They confirmed that High Frequency-Electromagnetic Coupling (HF-EMC)-powered permanent PNS is an effective and safe intervention for refractory chronic craniofacial neuropathic pain.

This was a prospective, randomized, controlled clinical trial performed in 7 clinical sites in the United States under an investigational device exemption (IDE). The study included 60 randomized patients implanted with the Freedom® PNS system, 30 in the active group, and 30 in the deactivated group, after the initial 7-day assessment period. The trial included multiple outcome parameters with VAS, Brief Pain Inventory Facial (BPIF), Patient Global Impression of Change (PGIC), 36-Item Short-Form Survey Instrument (SF-36), quality of life with Physical Component Score (PCS), and pain rating index with the Short-Form McGill Pain Questionnaire (MPQ-SF-2). Initially, 58 of the 60 subjects completed the 7-day assessment period, whereas 2 patients withdraw consent without completing the first post-treatment visit, 56 out of 60 respondents, or 93%, experienced greater than 50% improvement in VAS scores, 28 of whom had been randomized to active permanent PNS and 28 to deactivated permanent PNS for 3 months. Fifty-two subjects completed the primary 3-month endpoint. After the deactivated group was reactivated, 43 subjects in total completed the 6-month follow-up, and 37 completed the 12-month endpoint. As predetermined, the primary effectiveness endpoint, the proportion of patients experiencing at least 50% overall relief on a VAS scale, was compared at 3 months between the active and deactivated groups. The responder rate in the deactivated arm was 11% and in the active group was 69%. The primary effectiveness endpoint passed the inequality test, demonstrating that the proportion of responders was significantly larger within the active arm than in the deactivated arm. The estimated difference in responder rate was 58%, signifying that 58% more subjects experienced clinically important relief with stimulation than the deactivated arm. Further, active arm patients experienced a mean VAS reduction of 62% compared to a mean reduction of 8.5% in the deactivated arm 3 months after the initial 7-day assessment period. The differences between the treatment groups were no longer significant at 6 and 12 months after the initial 7-day therapy assessment period due to the initial deactivated group's reactivation. Similar results were also noted with the BPIF, PGIC, PCS, Mental Component Score (MCS), and MPQ-SF-2 at 3 months after the initial. Interestingly enough, after the 3-month hiatus for the deactivated arm, when stimulation was resumed, these patients reported the same degree of improvement that they did during the initial 7-day assessment period after the initial permanent implant procedures.

The limitations of this trial include the absence of a true placebo group, as patients served as their controls, and a relatively high withdrawal rate. Despite these limitations, the trial provided encouraging and positive data.

In a second trial, Hatheway et al (66) reported findings from the first large, postmarket, multicenter RCT evaluating PNS for chronic peripheral pain using a micro-implantable pulse generator (micro-IPG). Subjects were randomized to either the active arm, receiving PNS in combination with conventional medical management (CMM), or the control arm, receiving CMM alone.

At the 3-month primary endpoint, the active arm achieved an 84% responder rate with an average pain reduction of 67%, compared to the control arm's 3% responder rate and 6% average pain reduction. By 6 months, the active arm demonstrated an 88% responder rate and a 70% average reduction in pain. Both responder rate and pain reduction were significantly greater in the active arm than in the control arm ($P < 0.001$).

Additionally, most patient-reported outcomes (PROs) reached statistical significance. The authors concluded that treatment with the micro-IPG resulted in statistically significant improvements in pain and other PROs relative to baseline, and between the active and control arms. These outcomes were consistent with, in some cases superior to, results reported in previous PNS literature for treating chronic peripheral neuropathy or neuralgia. The trial also demonstrated a favorable

safety profile, with no serious adverse device effects or reported pocket pain cases.

The limitations of this study include the absence of long-term follow-up, the lack of a placebo group, and a high proportion of patients lost to follow-up, with only 16 patients remaining in the active arm at 12 months. Additionally, the relatively small sample size further limits the generalizability of the findings. Despite these limitations, the study was conducted with appropriate parameters, and the results were clinically significant.

The third trial in this group, published in 2016 by Deer et al (60), evaluated PNS for severe intractable pain of peripheral nerve origin over a minimum of 3 months. Following device implantation and a 14-24-day healing period, 94 participants were randomized to either an active treatment group (n = 45) or a no-stimulation control group (n = 49) for 3 months. Both groups were permitted to maintain stable doses of their medications throughout the study.

The primary efficacy outcome was pain reduction measured on a 10-point NRS. Responders were defined as participants achieving at least a 30% reduction in NRS scores without any increase in their pain medication regimen. At 3 months, the treatment group achieved a mean pain reduction of 27.2%, compared to 2.3% in the control group ($P < 0.0001$). However, specific NRS scores at 3 months were not reported. A total of 17 out of 45 participants in the treatment group (38%) and 5 out of 49 in the control group (10%) met the responder criteria ($P = 0.0048$).

After the initial 3-month period, participants in the control group were offered the option to cross over to active treatment. Of these, 30 out of 45 (67%) consented. Three months after crossing over, 9 of 30 participants (30%) were classified as responders. No data was provided for the 15 participants who declined crossover. Participants were monitored for safety outcomes for an average of 320 days. A total of 51 device-related adverse events were reported, none of which were classified as serious. Most adverse events were localized to the surgical or stimulation sites, with skin irritation being the most commonly reported (13 participants). Two participants discontinued the study due to prolonged skin sensitivity near the electrode patch. Additionally, 7 participants had the device explanted: 5 due to insufficient pain relief, one due to chronic sensitivity to the electrode patch, and one due to lead rejection.

This trial exhibited several limitations, including the absence of trial stimulation and using a 30% pain reduction threshold for defining responders instead of the more clinically meaningful 50%. Even with this lower threshold, only 27.2% of patients in the treatment group showed improvement, compared to 2.3% in the control group. When the various conditions evaluated in the study are separated, the resulting sample sizes become very small. The overall response rate was low, with 38% of the treatment group (17 of 45 participants) and 10% of the control group (5 of 49 participants) meeting responder criteria, despite statistical significance ($P = 0.0048$). This suggests limited clinical significance. Furthermore, the high attrition rate, with 33 patients lacking data at the 12-month follow-up, raises concerns about long-term efficacy. Of the 94 participants implanted, 7 (7.4%) required device explantation.

Among the permanent implantable stimulation studies, 2 RCTs evaluated headache treatment using implantable stimulators (62,65), specifically utilizing SCS systems from Abbott (formerly St. Jude Medical) (62) and Medtronic Neuromodulation Systems (65), rather than peripheral nerve systems.

Dodick et al (62), in a 2015 multicenter, double-blind RCT, assessed the safety and efficacy of occipital nerve stimulation for managing chronic migraine. Patients who responded positively to a trial stimulation (achieving ≥ 50% pain reduction or adequate paresthesia coverage of the painful area) were implanted with a neuromodulation system (Quattrode, St. Jude Medical, Plano, TX, USA). Following implantation, participants were randomized in a 2:1 ratio to an active treatment group (n = 102) or a control group (n = 52) for a 12-week blinded phase. Patients in the active group received programmed stimulation, while those in the control group were assigned a sham program that did not communicate with the implantable pulse generator (IPG). After the 12-week blinded phase, all patients received open-label active stimulation for an additional 40 weeks.

Outcomes measured included the number of headache days, pain intensity, Migraine Disability Assessment (MIDAS), Zung Pain and Distress (PAD) scores, direct patient reports of headache relief, quality of life assessments, patient satisfaction, and adverse events. The study's inclusion and exclusion criteria were robust, and lead placement was optimized during trial stimulation to ensure appropriate paresthesia coverage.

In their systematic review, Barad et al (29) extensively discussed the trial by Dodick et al (62), as reported in an earlier publication. One notable issue

is that the 2015 publication (62) indicated no funding, while an earlier publication of 12-week outcomes (72) from the same study reported funding from St. Jude Medical Systems. Despite this, no significant concerns were identified regarding inconsistency, imprecision, or publication bias.

The second study on chronic migraine headache was conducted by Serra and Marchioretto (65) in 2012. This non-industry-funded, randomized crossover study evaluated occipital nerve stimulation for chronic migraine refractory to preventive treatments, utilizing implanted bilateral percutaneous quadripolar leads (Medtronic Inc., Minneapolis, MN). The inclusion criteria encompassed patients with chronic migraine and medication overuse headaches; however, participants in the overuse group had been off medication for 2 months prior to enrollment. This contrasts with Dodick et al (62), who excluded patients with medication overuse headaches.

Before randomization, all participants underwent a successful trial period, defined as achieving > 50% pain reduction. Participants were then randomized to Group A (stimulation on) or Group B (stimulation off). Group B participants could transition to "stimulation on" if their headache frequency increased by more than 30%. On average, patients in Group B remained in the "stimulation off" condition for 4.9 ± 3.8 days (range: 1–12 days) before transitioning. After one month, the groups crossed over.

Results showed that Group A had a median of 2.1 headache days per week with "stimulation on" compared to 6.3 headache days in Group B with "stimulation off" ($P = 0.001$). After crossover, Group A experienced a median of 6 headache days per week versus 2.3 days per week in Group B ($P < 0.001$). Following the crossover phase, all participants received active stimulation.

The study also reported significant reductions in the monthly use of triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) at one-year follow-up ($P = 0.001$). Functional outcomes, assessed with the MIDAS and SF-36, demonstrated statistically significant improvements compared with baseline at each follow-up visit, with continued improvement throughout the trial duration.

Our analysis of methodological quality indicated moderate quality based on Cochrane reviews and IPM-QRB assessments, suggesting a potential risk of bias. Similarly, Barad et al (29) identified a high risk of bias in their evaluation. A major concern was the study population, which combined patients with chronic migraine and medication-overuse headache. Notably, in the medication overuse group, overused medications had been discontinued for 2 months. However, it was unclear whether all patients in this group carried a formal diagnosis of migraine.

Additionally, the study design allowed early crossover if headache severity or frequency increased by 30%. As a result, the average duration spent in the "stimulation off" condition before crossover was 4.9 ± 3.8 days (range: 1–12 days) in the first group and 4.4 ± 2.8 days (range: 2–10 days) in the second group. Barad et al (29) noted that this short duration limited the ability to evaluate a whole month of headache data. Outcomes were reported as headache days per week rather than per month, further complicating interpretation. Moreover, it was unclear whether the investigators performed an intention-to-treat (ITT) analysis or a per-protocol analysis (29). For these reasons, the study data were excluded from the meta-analysis (29).

Regarding selective medial branch stimulation, Gilligan et al (56) reported multiple publications from a single RCT, providing follow-up data at 1, 2, 3, and 5 years. The initial study, published in 2021, was a prospective, parallel-group, randomized, double-blind, sham-controlled clinical trial conducted across 26 multidisciplinary centers in the United States, Australia, and Europe.

Inclusion criteria encompassed adults with disabling, mechanical chronic low back pain persisting despite > 90 days of medical management (including medications prescribed for chronic low back pain) and at least one previous or new attempt at physical therapy, though no specific program or duration was required. Additional criteria included average low back pain > 6 and ≤ 9 cm on a 10 cm VAS, an ODI score between 21 and 50 (on a 0–100 scale), and a positive Prone Instability Test, suggesting impaired multifidus muscle motor control and lumbar segmental instability. Exclusion criteria included previous lumbar surgery below T8, spinal fusion at any level, eligibility for surgical intervention, leg pain worse than back pain or radiculopathy below the knee, and sacroiliac joint pain.

Participants were randomized 1:1 to receive either optimized therapeutic stimulation (treatment group) or low-level sham stimulation (control group). All participants were permanently implanted with the neuromuscular selective medial branch stimulation system, with electrodes placed at the junction of the L3 transverse process and the base of the L3 superior articular

process, targeting the L2 medial branch of the dorsal ramus of the spinal nerve. Therapeutic stimulation was administered for 120 days in the treatment group, after which all participants received active stimulation.

The primary endpoint was the proportion of participants achieving a ≥ 30% reduction from baseline in the 7-day recall of average low back pain (VAS score) without an increase in baseline pain medications. Secondary outcomes included improvements in ODI, EuroQol quality-of-life survey (EQ-5D-5L) index, percent-of-pain-relief (PPR), Subject Global Impression of Change (SGIC), and resolution of low back pain (VAS ≤ 2.5 cm).

The primary endpoint at 120 days did not demonstrate a statistically significant difference between groups (57.1% vs 46.6%); however, four of five secondary endpoints showed statistically significant improvements favoring the treatment group. At the one-year follow-up, with 176 patients remaining after the double-blind phase, efficacy outcomes consistently demonstrated significant and clinically meaningful improvements compared with baseline and the combined control group ($P < 0.0001$).

Mean average low back pain improved by –4.3 ± 2.6 cm, with 74% of participants achieving ≥ 30% pain reduction, 64% achieving ≥ 50% reduction, and 52% reporting complete resolution of low back pain (VAS ≤ 2.5 cm). Functional outcomes also improved substantially: the ODI decreased by –19.9 ± 15.8 points ($P < 0.0001$), and the EQ-5D-5L index showed significant gains.

At five-year longitudinal follow-up (70), low back pain VAS scores improved from 7.3 cm to 2.4 cm ($P < 0.001$; 95% CI, –5.32 to –4.5 cm), with 71.8% of participants achieving ≥ 50% pain reduction. ODI scores improved from 39.1 to 16.5 (95% CI, –25.4 to –20.8; $P < 0.0001$). Among the 52 participants on opioids at baseline who attended the five-year visit, 46% discontinued opioid use, and 23% reduced their intake. The safety profile was favorable, comparable to other neuromuscular neurostimulator treatments for back pain. Notably, no lead migrations were observed.

Regarding safety outcomes at one year, 8 device- or procedure-related adverse events were reported in 8 participants (4%), all occurring prior to the 120-day follow-up. Six participants developed pocket infections, all of which were resolved after system explantation and antibiotic treatment. In one case, a new system was successfully implanted prior to the 120-day visit. One participant experienced an intraoperative open airway obstruction that was resolved without lasting effects, and another reported a persistent non-radicular numb patch on the thigh.

Overall, 27 participants (13%) underwent a total of 30 surgical interventions during the study. These included 19 system explants (9%), 1 system reimplantation (< 1%), 4 pulse generator re-positionings (2%), and 6 lead replacements (3%). The primary reasons for explantation were lack of effectiveness (n = 9), infection (n = 6), and safety precautions before MRI scanning.

This large, multicenter trial included a long-term follow-up of 5 years.

In a 2025 RCT, Schwab et al (58) reported outcomes from a cohort of patients with chronic low back pain associated with multifidus dysfunction. Participants were randomized to receive either restorative neurostimulation with the ReActiv8 system or optimal medical management (OMM) over a one-year period. The primary endpoint was the mean change in the ODI between the treatment and control groups at one year. Secondary endpoints included pain intensity measured by the NRS and health-related quality of life assessed using the EQ-5D-5L.

The authors concluded that restorative neurostimulation is a safe, reversible, clinically effective, and highly durable treatment option for patients with nonoperative chronic low back pain associated with multifidus dysfunction. The demonstration of treatment superiority over OMM at one year represents a significant milestone in addressing this major health burden and unmet clinical need.

Sixty-day temporary stimulation with the Sprint PNS system has been evaluated in 2 RCTs (59,61). In 2019, Gilmore et al (59) published results from a study investigating percutaneous PNS for the treatment of chronic neuropathic post-amputation pain, initially reporting 8-week outcomes, which were later followed by 12-month follow-up results (63).

The study, funded by the U.S. Department of Defense and SPR Therapeutics, was a multicenter, randomized, placebo-controlled trial (59). Inclusion criteria required participants to have a traumatic lower extremity amputation with a healed and healthy residual limb and residual and/or phantom limb pain with a pain score ≥ 4. The femoral and sciatic nerves were targeted, and PNS leads were implanted and connected to an external wearable pulse generator mounted on the body.

Subjects in the PNS group received stimulation programmed to evoke comfortable sensations in the regions of residual and phantom limb pain. Stimulation parameters matched those used during test stimula-

tion, and participants were permitted to adjust intensity within predefined ranges set by study staff. The placebo group received sham stimulation; although the stimulator user interface was identical to that of the active group, no stimulation was delivered. All participants were instructed to use the device continuously.

Twenty-eight lower extremity amputees with post-amputation pain were enrolled and followed weekly over the 8-week treatment period. At week 4, participants in the placebo group crossed over to receive active treatment.

The primary efficacy endpoint was the proportion of subjects reporting ≥ 50% reduction in pain during weeks 1-4. Results showed a significantly greater proportion of PNS-treated subjects (n = 7/12, 58%; *P* = 0.037) achieved ≥50% pain reduction compared to placebo-treated subjects (n = 2/14, 14%). Two participants were excluded from efficacy analysis due to eligibility changes.

At week 8, a significantly greater proportion of PNS-treated subjects reported ≥ 50% reductions in pain (n = 8/12, 67%; *P* = 0.014) and pain interference (n = 8/10, 80%; *P* = 0.003), compared to placebo subjects (pain: n = 2/14, 14%; pain interference: n = 2/13, 15%).

The subsequent follow-up study, reporting 12-month outcomes, was published in 2020 (63). Results showed that significantly more participants in Group 1 achieved ≥ 50% reductions in average weekly pain at 12 months (67%, 6/9) compared to Group 2 at the end of the placebo period (0%, 0/14; *P* = 0.001). Similarly, 56% (5/9) of participants in Group 1 reported ≥50% reductions in pain interference at 12 months, versus 15% (2/13; *P* = 0.074) in Group 2 at crossover. Reductions in depression were also statistically significantly greater in Group 1 at 12 months compared to Group 2 at crossover.

While this study was randomized and partially funded by the Department of Defense, the results present challenges for interpretation. Both groups received stimulation for at least 4 weeks; however, the placebo group demonstrated no placebo response and substantially lower effectiveness. Additionally, there was significant attrition, with only 9 of 12 patients in the treatment group and 6 of 14 patients in the control group completing the 12-month follow-up. All outcomes were assessed from baseline through the follow-up period, yet even with stimulation, the placebo group's response was 0%.

In the same category of 60-day temporary stimulation, Goree et al (61) investigated persistent post-operative pain following knee replacement surgery. This study, also partially funded by the Department of Defense and SPR Therapeutics, included patients with prior knee replacement surgery experiencing moderate to severe pain (≥ 5/10). Forty patients were enrolled and randomized after implantation of temporary 60-day leads to receive either active PNS or placebo (sham stimulation). Group assignments were determined by a designated evaluator. Leads remained in place for 8 weeks. The primary efficacy outcome was the proportion of participants in each group reporting ≥ 50% reduction in average pain during weeks 5 to 8 compared to baseline. Secondary outcomes included functional assessments, such as the 6-minute walk test and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and quality of life measured by the PGIC at the end of treatment.

Results demonstrated that a significantly greater proportion of subjects in the PNS group (60%, 12/20) achieved ≥ 50% pain relief relative to baseline during the primary endpoint period (weeks 5–8) compared to the placebo (sham) group (24%, 5/21; *P* = 0.028). Additionally, subjects in the PNS group exhibited a significantly greater improvement in functional capacity, as measured by the 6-minute walk test (6MWT), showing a +47% change from baseline versus a –9% change in the placebo group (*P* = 0.048; n = 18 vs. n = 20 completed the test, respectively). A 12-month follow-up is ongoing.

This study shares several limitations with the trial by Gilmore et al (59). While the differences between groups are statistically significant, the clinical relevance remains uncertain. Specifically, 60% of the stimulation group achieved pain relief, compared to only 24% in the placebo group, which had received stimulation for 4 weeks rather than the full 8-week period. Despite moderate methodological quality, potential risks of bias and inconsistent effects should be considered. Furthermore, the present meta-analysis for pain relief included only two studies, which may affect the generalizability of the results. These studies also demonstrated moderate to high heterogeneity. As such, the findings should be interpreted with caution, as the inclusion of only two studies can limit both the strength and generalizability of the conclusions. A small sample size may reduce statistical power and affect the reliability of pooled estimates. Nevertheless, conducting a meta-analysis with two studies is methodologically acceptable, particularly when both studies evaluate the same outcome using comparable methodologies, as supported by recent literature (86).

Additionally, concerning the type of data used for various outcomes, continuous data, such as mean and standard deviation, are required to calculate mean differences. This is illustrated in Fig. 5, where the included studies reported such metrics, allowing for mean difference calculations. In contrast, Figs. 2 and 3 are based on dichotomous data, specifically the total number of patients and those who reported no pain. This type of data is generally analyzed using odds ratios.

PNS represents a rapidly evolving neuromodulation technology within interventional pain management, offering analgesic benefits for patients with chronic pain (9,83). Advances in imaging guidance, surgical techniques, and the development of both temporary and permanent PNS devices have expanded the ability to target peripheral nerves in various regions of the body. Current research highlights applications of PNS for peripheral nerves in the face and head, upper and lower extremities, abdomen, back, and pelvis (84). Moreover, the number of FDA-cleared PNS devices continues to grow, further supporting its integration into clinical practice.

The field of PNS has experienced remarkable growth in recent years, providing interventional pain physicians with multiple options. These advancements include systems with external transmitters ("wireless systems") that eliminate the need for an implanted battery, enabling stimulation closer to the site of pathology in virtually all regions of the body.

Currently, there are five distinct types of PNS systems with implanted receivers or pulse generators available 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

The establishment of medical necessity and appropriate indications is essential when performing any medical intervention, including peripheral nerve blocks and PNS implantation. To ensure appropriate use, PNS trials or permanent implants should meet the following criteria:

1. Documented function-limiting moderate to severe pain persisting for at least 3 months, with average pain scores ≥ 5.
2. Documented failure of less invasive treatment modalities and pharmacologic therapies for a minimum of 4 weeks.
3. Absence of surgical contraindications, including active infections or significant medical risks.
4. Completion of patient education with thorough discussion and disclosure of potential risks and benefits.
5. No evidence of active substance abuse.
6. Formal psychological evaluation by a qualified mental health professional to assess suitability for neuromodulation.
7. Successful stimulation trial demonstrating ≥ 50% reduction in pain intensity prior to permanent implantation.

These medical necessity criteria have been established in local coverage determinations (LCDs) (85). Importantly, the only reliable predictor of PNS effectiveness is a trial stimulation with implanted PNS electrodes. If a trial fails, repeating it is generally not appropriate unless extenuating circumstances are present—such as equipment malfunction, early lead migration, technological advancements, or alternative neuromodulatory techniques, that could improve the likelihood of success. Any such situation must be thoroughly documented. Accurate patient selection is expected to result in most patients progressing to permanent implantation. All trials leading to permanent implants must include adequate documentation to justify the decision. A successful trial is typically defined as achieving at least a 50% reduction in target pain or analgesic medication use, along with evidence of functional improvement (85).

Although the National Coverage Determination (NCD) is less restrictive, guidance from Medicare Administrative Contractor (MAC) Noridian specifies that physicians with a trial-to-permanent implant conversion rate below 50% may be subject to post-payment review. These physicians may be required to submit documentation demonstrating patient selection criteria, imaging confirming proper lead placement, and the medical necessity of the trials.

Currently, Noridian-approved indications for PNS include (85):

- PNS of the occipital nerves for occipital neuralgia, postsurgical neuropathic pain, cervicogenic headaches, and treatment-resistant migraines.

- PNS of the trigeminal nerves (and branches) for posttraumatic and postsurgical neuropathic pain in the face related to trigeminal nerve distributions.
- PNS of upper and lower extremity nerves for CRPS (Types I and II), pain from peripheral nerve injuries, post-surgical scar formation, nerve entrapments, painful mononeuropathies, and painful amputation neuromas.
- PNS of intercostal and ilioinguinal nerves for postsurgical and posttraumatic neuropathic pain in these nerve distributions.

To date, LCDs do not support PNS for fibromyalgia, phantom limb pain, diffuse polyneuropathy, nociceptive pain of the trunk or lower back, or angina pectoris.

Based on the emerging evidence assessed in these guidelines, incorporating data from RCTs, observational studies, and systematic reviews, and applying rigorous methodologic quality and risk of bias assessments, GRADE criteria for certainty of evidence, and qualitative evidence synthesis following best evidence synthesis principles, 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 these findings, we recommend expanding CMS guidance to include phantom limb pain and nociceptive pain in the lower back, as current evidence supports these indications at Level III (fair) with moderate certainty.

Conclusion

Peripheral nerve stimulation (PNS) systems have seen remarkable advancements over the past 50 years, transitioning from highly invasive open neurosurgical procedures to minimally invasive, FDA-cleared therapies for the management of chronic pain. The introduction of various PNS systems—including those developed by Curonix LLC, Bioness (now Bioventus), SPR Therapeutics, Inc., Nalu Medical Inc., and Mainstay Medical Limited—has significantly expanded treatment options for patients with chronic intractable pain.

ASIPP has developed evidence-based guidelines to assist clinicians in the safe and effective use of PNS technology. These guidelines are grounded in a comprehensive review of the literature and expert consensus, highlighting the role of both temporary and permanent PNS in patients whose chronic pain has not responded to conservative therapies.

This guideline offers an in-depth review and critical analysis of the growing body of evidence supporting PNS use and its long-term efficacy in clinical practice. The integration of PNS technology, guided by these robust recommendations, has the potential to substantially improve patient outcomes and promote equitable access to innovative pain management solutions.

Author Contributions

The article was designed by LM, MRS, ADK, and AS. Statistical analysis was performed by MBK.

All authors contributed to the preparation of this article, reviewed, and approved the content with the final version.

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References

1. Lucas JW, Sohi I. Chronic pain and high-impact chronic pain in U.S. adults, 2023. NCHS Data Brief, No. 518. Hyattsville, MD: National Center for Health Statistics. November 2024. Accessed 12/4/2024. https://www.cdc.gov/nchs/data/databriefs/db518.pdf
2. Rikard SM, Strahan AE, Schmit KM, Guy GP Jr. Chronic pain among adults - United States, 2019-2021. *MMWR Morb Mortal Wkly Rep* 2023; 72:379-385.
3. Manchikanti L, Kaye AM, Knezevic NN, et al. Comprehensive, evidence-based, consensus guidelines for prescription of opioids for chronic non-cancer pain from the American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2023; 26:S7-S126.
4. Manchikanti L, Sanapati MR, Soin A, et al. 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). *Pain Physician* 2024; 27:S115-S191.

5. Van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain* 2014; 155:654-662.
6. International Association for the Study of Pain (IASP). Pain Terms. Accessed 7/17/2024. https://www.iasp-pain.org/resources/terminology/
7. Scholz J, Finnerup NB, Attal N, et al; Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: Chronic neuropathic pain. *Pain* 2019; 160:53-59.
8. Liedgens H, Obradovic M, De Courcy J, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *Clinicoecon Outcomes Res* 2016; 8:113-126.
9. Li AH, Bhatia A, Gulati A, Ottestad E. Role of peripheral nerve stimulation in treating chronic neuropathic pain: An international focused survey of pain medicine experts. *Reg Anesth Pain Med* 2023; 48:312-318. Erratum in: *Reg Anesth Pain Med* 2023; 48:e1.
10. Sadosky A, Schaefer C, Mann R, et al. Economic burden of neuropathic pain in the United States: BEAT neuropathic pain observational study. *J Pain* 2013; 14:S13.
11. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science* 1967; 155:108-109.
12. Shelden CH, Pudenz RH, Doyle J. Electrical control of facial pain. *Am J Surg* 1967; 114:209-212.
13. Manchikanti L, Sanapati MR, Pampati V, et al. A 24% decline in the utilization of epidural procedure visits for chronic spinal pain management in the Medicare population from 2019 to 2022: Updated analysis of the effect of multiple factors. *Pain Physician* 2024; 27:E983-E994.
14. Manchikanti L, Abd-Elsayed A, Kaye AD, et al. Escalating growth to rapid decline of utilization patterns of facet joint interventions in managing spinal pain in the Medicare population: Updated analysis of the effect of multiple factors from 2000 to 2022. *Pain Physician* 2024; 27:E979-E982.
15. Manchikanti L, Simopoulos TT, Pampati V, et al. Impact of COVID-19 pandemic and updated utilization patterns of sacroiliac joint injections from 2000 to 2020 in the fee-for-service (FFS) Medicare population. *Pain Physician* 2022; 25:239-250.
16. Manchikanti L, Pampati V, Knezevic NN, et al. The influence of COVID-19 on utilization of epidural procedures in managing chronic spinal pain in the Medicare population. *Spine (Phila Pa 1976)* 2023; 48:950-961.
17. Lown Institute Hospital Index. Unnecessary Back Surgery: Older Americans put at Risk While Billions in Medicare Funds Wasted. November 14, 2024. Accessed 11/25/2024. https://lownhospitalsindex.org/unnecessary-back-surgery/
18. Ezeonu T, Narayanan R, Huang R, et al. Higher socioeconomic status is associated with greater rates of surgical resource utilization prior to spine fusion surgery. *Spine J* 2025; 25:631-639.
19. Oh TK, Song IA. Prevalence and risk factors for persistent spinal pain syndrome Type II following spinal surgery: A nationwide retrospective cohort study. *Pain Physician* 2024; 27:555-563.
20. Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician* 2021; 24:S27-S208.
21. Manchikanti L, Kaye AD, Soin A, et al. Comprehensive evidence-based guidelines for facet joint interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2020; 23:S1-S127.
22. 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.
23. Manchikanti L, Pampati V, Vangala BP, et al. Spinal cord stimulation trends of utilization and expenditures in fee-for-service (FFS) Medicare population from 2009 to 2018. *Pain Physician* 2021; 24:293-308.
24. Slavin KV. History of peripheral nerve stimulation. *Prog Neurol Surg* 2011; 24:1-15.
25. Abd-Elsayed A, Trescot AM. *Peripheral Nerve Stimulation: A Comprehensive Guide*. Elsevier, Philadelphia, PA, 2023.
26. Slavin KV, Carayannopoulos AG, Plazier M, Vanneste S, De Ridder D. Peripheral nerve stimulation. In: Knotkova H, Rasche D (eds.) *Textbook of Neuromodulation*. Springer, New York, NY, 2015, pp 19-33.
27. Abd-Elsayed A, D'Souza RS. Peripheral nerve stimulation: The evolution in pain medicine. *Biomedicines* 2021; 10:18.
28. Fontaine D. Spinal cord stimulation for neuropathic pain. *Rev Neurol (Paris)* 2021; 177:838-842.
29. Barad M, Ailani J, Hakim SM, Kissoon NR, Schuster NM. Percutaneous interventional strategies for migraine prevention: A systematic review and practice guideline. *Pain Med* 2022; 23:164-188.
30. Deer TR, Esposito MF, McRoberts WP, et al. A systematic literature review of peripheral nerve stimulation therapies for the treatment of pain. *Pain Med* 2020; 21:1590-1603.
31. Char S, Jin MY, Francio VT, et al. Implantable peripheral nerve stimulation for peripheral neuropathic pain: A systematic review of prospective studies. *Biomedicines* 2022; 10:2606.
32. Helm S, Shirsat N, Calodney A, et al. Peripheral nerve stimulation for chronic pain: A systematic review of effectiveness and safety. *Pain Ther* 2021; 10:985-1002.
33. Xu J, Sun Z, Wu J, et al. Peripheral nerve stimulation in pain management: A systematic review. *Pain Physician* 2021; 24:E131-E152.
34. Amirianfar E, Rosales R, Logan A, Doshi TL, Reynolds J, Price C. Peripheral nerve stimulation for chronic knee pain following total knee arthroplasty: A systematic review. *Pain Manag* 2023; 13:667-676.
35. D'Souza RS, Jin MY, Abd-Elsayed A. Peripheral nerve stimulation for low back pain: A systematic review. *Curr Pain Headache Rep* 2023; 27:117-128.
36. Parikh S, Echevarria AC, Cemenski BR, Small T. The relevance of implanted percutaneous electrical nerve stimulation in orthopedics surgery: A systematic review. *J Clin Med* 2024; 13:3699.
37. Manchikanti L, Abd-Elsayed A, Kaye AD, Sanapati MR, Pampati V, Hirsch JA. A systematic review of regenerative medicine therapies for axial spinal pain of facet joint origin. *Curr Pain Headache Rep* 2025; 29:61.
38. Manchikanti L, Knezevic E, Knezevic NN, et al. Effectiveness of intradiscal regenerative medicine therapies

for long-term relief of chronic low back pain: A systematic review and meta-analysis. *Pain Physician* 2024; 27:E995-E1032.

39. Manchikanti L, Kaye AD, Abd-Elsayed A, et al. A systematic review of sacroiliac joint injections of platelet-rich plasma (PRP) and stem cells. *Curr Pain Headache Rep* 2025; 29:63.
40. Janapala RN, Knezevic E, Knezevic NN, et al. Systematic review and meta-analysis of the effectiveness of radiofrequency ablation of the sacroiliac joint. *Curr Pain Headache Rep* 2024; 28:335-372.
41. Kaye AD, Brouillette AE, Howe CA, et al. Efficacy of steroid facet joint injections for axial spinal pain and post radiofrequency ablation neuritis: A systematic review. *Curr Pain Headache Rep* 2025; 29:53.
42. Manchikanti L, Knezevic E, Knezevic NN, et al. Effectiveness of facet joint nerve blocks in managing chronic axial spinal pain of facet joint origin: A systematic review and meta-analysis. *Pain Physician* 2024; 27:E169-E206.
43. Manchikanti L, Knezevic E, Knezevic NN, et al. The effectiveness of medial branch blocks and radiofrequency neurotomy in managing chronic thoracic pain: A systematic review and meta-analysis. *Pain Physician* 2023; 26:413-435.
44. Manchikanti L, Knezevic E, Latchaw RE, et al. Comparative systematic review and meta-analysis of Cochrane review of epidural injections for lumbar radiculopathy or sciatica. *Pain Physician* 2022; 25:E889-E916.
45. Manchikanti L, Knezevic NN, Sanapati J, Kaye AD, Sanapati MR, Hirsch JA. Is epidural injection of sodium chloride solution a true placebo or an active control agent? A systematic review and meta-analysis. *Pain Physician* 2021; 24:41-59.
46. Knezevic N, Manchikanti L, Urits I, et al. Lack of superiority of epidural injections with lidocaine with steroids compared to without steroids in spinal pain: A systematic review and meta-analysis. *Pain Physician* 2020; 23:S239-S270.
47. Manchikanti L, Knezevic NN, Parr A, Kaye AD, Sanapati MR, Hirsch JA. Does epidural bupivacaine with or without steroids provide long-term relief? A systematic review and meta-analysis. *Curr Pain Headache Rep* 2020; 24:26.
48. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71.
49. Manchikanti L, Atluri S, Boswell MV, et al. Methodology for evidence synthesis and development of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. *Pain Physician* 2021; 24:S1-S26.
50. Furlan AD, Malmivaara A, Chou R, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for reviews in the Cochrane back and neck group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673.
51. Manchikanti L, Hirsch JA, Cohen SP, 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.
52. Cuello-Garcia CA, Santesso N, Morgan RL, et al. GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. *J Clin Epidemiol* 2022; 142:200-208.
53. 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/
54. Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325.
55. Jue JJ, Cunningham S, Lohr K, et al. Developing and Testing the Agency for Healthcare Research and Quality's National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) Instrument. *Ann Intern Med* 2019; 170:480-487.
56. Gilligan C, Volschenk W, Russo M, et al. An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: A randomized sham-controlled clinical trial. *Pain* 2021; 162:2486-2498.
57. Liu Y, Yan H, Wan C, et al. Short-term supraorbital nerve stimulation and pain relief for acute and subacute ophthalmic herpetic neuralgia: A randomized controlled crossover trial. *Pain Physician* 2024; 27:203-212.
58. Schwab F, Mekhail N, Patel KV, et al; RESTORE investigators. Restorative Neurostimulation Therapy Compared to Optimal Medical Management: A randomized evaluation (RESTORE) for the treatment of chronic mechanical low back pain due to multifidus dysfunction. *Pain Ther* 2025; 14:401-423.
59. Gilmore C, Ilfeld B, Rosenow J, et al. Percutaneous peripheral nerve stimulation for the treatment of chronic neuropathic post-amputation pain: A multicenter, randomized, placebo-controlled trial. *Reg Anesth Pain Med* 2019; 44:637-645.
60. Deer T, Pope J, Benyamin R, et al. Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin. *Neuromodulation* 2016; 19:91-100.
61. Goree JH, Grant SA, Dickerson DM, et al. Randomized placebo-controlled trial of 60-day percutaneous peripheral nerve stimulation treatment indicates relief of persistent postoperative pain, and improved function after knee replacement. *Neuromodulation* 2024; 27:847-861.
62. Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2015; 35:344-358.
63. Gilmore CA, Ilfeld BM, Rosenow JM, et al. Percutaneous 60-day peripheral nerve stimulation implant provides sustained relief of chronic pain following amputation: 12-month follow-up of a randomized, double-blind, placebo-controlled trial. *Reg Anesth Pain Med* 2020; 45:44-51.
64. Hayek S, Haider N, Viswanathan A, Desai M, Rosenberg J. CFPNS multi-center, prospective, randomized, controlled clinical trial of HF-EMC powered Freedom® permanent peripheral nerve stimulator (PNS) for the treatment of chronic craniofacial pain. *Pain Physician* 2025; in submission.
65. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: A randomized trial. *Pain Physician* 2012; 15:245-253.
66. Hatheway J, Hersel A, Song J, et al. Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain: 3-month and 6-month results from the COMFORT-randomised controlled trial. *Reg Anesth Pain Med* 2025; 50:561-567.
67. Kapural L, Melton J, Kim B, et al. 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. *J Pain Res* 2024; 17:2001-2014.

68. Gilligan C, Volschenk W, Russo M, et al; ReActiv8-B Investigators. Long-term outcomes of restorative neurostimulation in patients with refractory chronic low back pain secondary to multifidus dysfunction: Two-year results of the ReActiv8-B pivotal trial. *Neuromodulation* 2023; 26:87-97.
69. Gilligan C, Volschenk W, Russo M, et al. Three-year durability of restorative neurostimulation effectiveness in patients with chronic low back pain and multifidus muscle dysfunction. *Neuromodulation* 2023; 26:98-108.
70. Gilligan C, Volschenk W, Russo M, et al. Five-year longitudinal follow-up of restorative neurostimulation shows durability of effectiveness in patients with refractory chronic low back pain associated with multifidus muscle dysfunction. *Neuromodulation* 2024; 27:930-943.
71. Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. *BJU Int* 2007; 100:835-839.
72. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2012; 32:1165-1179.
73. Slotty PJ, Bara G, Kowatz L, et al. Occipital nerve stimulation for chronic migraine: A randomized trial on subthreshold stimulation. *Cephalalgia* 2015; 35:73-78.
74. Wilson RD, Knutson JS, Bennett ME, Chae J. The effect of peripheral nerve stimulation on shoulder biomechanics: A randomized controlled trial in comparison to physical therapy. *Am J Phys Med Rehabil* 2017; 96:191-198.
75. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. *Cephalalgia* 2013; 33:816-830.
76. Eldabe SS, Taylor RS, Goossens S, et al. A randomized controlled trial of subcutaneous nerve stimulation for back pain due to failed back surgery syndrome: The SubQStim study. *Neuromodulation* 2019; 22:519-528.
77. van Gorp EJ, Teernstra OP, Gültuna I, et al. 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. *Neuromodulation* 2016; 19:171-178.
78. McRoberts WP, Wolkowitz R, Meyer DJ, et al. Peripheral nerve field stimulation for the management of localized chronic intractable back pain: Results from a randomized controlled study. *Neuromodulation* 2013; 16:565-574; discussion 574-575.
79. Istek A, Gungor Ugurlucan F, Yasa C, Gokyildiz S, Yalcin O. Randomized trial of long-term effects of percutaneous tibial nerve stimulation on chronic pelvic pain. *Arch Gynecol Obstet* 2014; 290:291-298.
80. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. C2 nerve field stimulation for the treatment of fibromyalgia: A prospective, double-blind, randomized, controlled cross-over study. *Brain Stimul* 2015; 8:751-757.
81. Mekhail NA, Estemalik E, Azer G, Davis K, Tepper SJ. Safety and efficacy of occipital nerves stimulation for the treatment of chronic migraines: Randomized, double-blind controlled single-center experience. *Pain Pract* 2017; 17:669-677.
82. Wilson RD, Gunzler DD, Bennett ME, Chae J. Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: A randomized controlled trial. *Am J Phys Med Rehabil* 2014; 93:17-28. Erratum in: *Am J Phys Med Rehabil* 2016; 95:e29.
83. Shanthanna H, Bhatia A, Radhakrishna M, et al. Interventional pain management for chronic pain: A survey of physicians in Canada. *Can J Anaesth* 2020; 67:343-352.
84. Ong Sio LC, Hom B, Garg S, AbdElsayed A. Mechanism of action of peripheral nerve stimulation for chronic pain: A narrative review. *Int J Mol Sci* 2023; 24:4540.
85. Noridian Healthcare Solutions, LLC. LCD for Peripheral Nerve Stimulation (L34328). Revision Effective Date: 12/01/2019.

Appendix Table 1. *Sources of risk of bias and Cochrane Review rating system.*

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
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

Appendix Table 1 cont. *Sources of risk of bias and Cochrane Review rating system.*

Bias Domain	**Source of Bias**		**Possible Answers**
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

Adapted and modified from: 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 (50).

Appendix Table 2. *Item checklist for assessment of randomized controlled trials of IPM techniques 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	
7a.	For epidural procedures:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	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

Appendix Table 2 cont. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM-QRB.*

		Scoring
	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	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

Appendix Table 2 cont. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM-QRB.*

		Scoring
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
	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

Modified from: 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 (51).