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Abstract

Objective. To conduct a systematic literature review of peripheral nerve stimulation (PNS) for pain. Design. Grade the evidence for PNS.Methods. An international interdisciplinary work group conducted a literature search for PNS.
Abstracts were reviewed to select studies for grading. Inclusion/exclusion criteria included prospective randomized controlled trials (RCTs) with meaningful clinical outcomes that were not part of a larger or previously reported group. Excluded studies were retrospective, had less than two months of follow-up, or existed only as abstracts. Full studies were graded by two independent reviewers using the modified Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment, the Cochrane Collaborations Risk of Bias assessment, and the US Preventative Services Task Force level-of-evidence criteria. Results. Peripheral nerve stimulation was studied in 14 RCTs for a variety of painful conditions (headache, shoulder, pelvic, back, extremity, and trunk pain). Moderate to strong evidence supported the use of PNS to treat pain. Conclusion. Peripheral nerve stimulation has moderate/strong evidence. Additional prospective trials could further refine appropriate populations and pain diagnoses.

Key Words: Peripheral Nerve Stimulation; Peripheral Nerve Field Stimulation; Percutaneous Tibial Nerve Stimulation; Chronic Pain;
Systematic Review; Pain Management

Introduction
Neurostimulation is a well-established treatment option for people who suffer from chronic, refractory painful disorders. The longest history of clinical use belongs to spinal cord stimulation, followed by deep brain stimulation, though for Parkinson’s disease, not pain. Debate continues regarding the best neural targets and stimulation techniques as the clinical practice of neuromodulation evolves, with new insights into underlying brain and spinal cord physiology, and advances in technology and programming emerge. The peer-reviewed literature includes consensus statements and best practices for neurostimulation [1–7] but no comprehensive systematic literature review of evidence specifically for peripheral nerve stimulation (PNS) or peripheral nerve field stimulation (PNfS). This invited systematic review synthesizes the current evidence for PNS. The goal is to improve care for patients with chronic pain by analyzing the quality of the evidence for PNS, presenting key points, and discussing findings from specific studies. When integrated into clinical practice, the findings may lead to enhanced patient safety, outcomes, and access.

Methods
Development Process
A systematic literature review of PNS was initiated at the invitation of the journal editors. An international interdisciplinary work group was assembled based on experience with PNS, participation in research and publications, practice specialty, diversity, and practice setting. Participants were nominated by the West Virginia Society of Interventional Pain Physicians/ American Society for Pain and Neuroscience.

The reporting of this systematic review follows the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Due to the heterogeneity of populations, diagnoses, interventions and comparators, outcomes assessed, and overall study designs, quantitative analysis (meta-analysis) was not planned or performed.

Literature Search
A comprehensive literature search was conducted in order to generate a list of study/trial abstracts for screening. The search included the electronic databases MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, and Scopus, using various combinations of controlled vocabulary supplemented with key words and key authors to search for “implantable neurostimulators,” “electric stimulation therapy,” “spinal cord stimulation,” “neuromodulation,” “peripheral,” “occipital,” “genitofemoral,” “subcutaneous,” “ilioinguinal,” “median,” “ulnar,” “radial,” “sciatic,” “tibial,” “peroneal,” “axial,” “pain management,” “neuralgia,” “back pain,” “headache disorders,” “migraine,” “postoperative,” and “high-frequency spinal cord stimulation.” Search dates were from January 1967 (Wall and Sweet first described PNS in 1967) to September 2018. The search included all languages. Data sources, including cited articles and relevant systematic reviews, were searched manually for possible additional studies, and duplicates were excluded. The PRISMA diagram in Figure 1 summarizes the literature evaluation process.

Study Eligibility
The inclusion criteria were limited to randomized controlled trials (RCTs) that enrolled patients with intractable pain. We used the definition of intractable or refractory pain proposed by Deer et al.: “Pain is defined as refractory when 1) multiple evidence based biomedical therapies used in clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects, and when 2) psychiatric disorders and psychosocial factors that could influence pain outcomes have been assessed and appropriately addressed” [8]. The studies had a minimum patient follow-up period of two months, and experimental phases were often followed by open-label use for a year or longer.

Reviewers worked independently to screen the search results and identify studies eligible for further review. If a
study was determined to be relevant based on its abstract, the full-text article was obtained and reviewed.

Data Extraction and Study Scoring
A minimum of two reviewers worked independently to identify original studies eligible for further review by screening abstracts and titles. An author was not allowed to review and score a study for which he/she was a co-investigator. Data extracted from each study included patient demographics, baseline characteristics, study design variables, sample size, description of interventions, and outcome measures. Pain improvement was the primary outcome measure of interest for all trials. Trials that reported only technical results or other outcomes not associated with pain improvement were not included in the analysis. If there were discrepancies in scoring >5 points or discrepancies that would result in different overall scores of quality (e.g., different quality ratings for the same study by different reviewers), two additional reviewers without known bias were recruited. This process was followed until reproducible scoring for accuracy was achieved.

For all RCTs, the risk of bias was assessed using the Cochrane Collaboration’s Risk of Bias tool [9]. It assesses the risk of bias attributed to the method of randomization, allocation concealment, blinding of patients and all research personnel, baseline imbalance, and inclusion of all study subjects in primary and secondary data analyses, consistent with intent-to-treat principles (Supplementary Data). We also used the Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) scoring tool developed by the American Society of Interventional Pain Physicians (ASIPP) to assess RCTs [10]. We used the US Preventive Service Task Force hierarchy of studies to assign a final evidence level [11]. Table 1 outlines the nomenclature used throughout this review to assign levels and describe evidence. PNS study scoring is summarized in the Supplementary Data, and the selected PNS studies are summarized in Table 2.

Results

Study Quality Analysis
Fifteen manuscripts meeting inclusion criteria were selected and sent to reviewers [12–26]. Two manuscripts described different aspects of the same trial [18,19], resulting in 14 total studies. Levels of evidence were determined as follows:

- **USPSTF**: Level I evidence is based upon 14 RCTs for PNS in the treatment of migraine headache, cluster headache, shoulder pain, low back pain, pelvic pain, and neuropathic pain of other origin.
- **mIMP-QRB**: Level I for PNS for the treatment of chronic low back pain (targeting the cluneal nerve and its branches) based on three high-quality RCTs.
- **Cochrane criteria**: Support the findings of IMP-QRB criteria as low to moderate risk of bias.

USPSTF criteria suggest that all 14 studies evaluated meet Level I status as RCTs. Of these studies, using the mIPM-QRB method, 12 of the 14 were deemed high quality based on study design and clinically meaningful outcomes. Two were deemed moderate quality using the mIPM-QRB [14,26]. Of the 14 RCTs selected, two were deemed moderate risk of bias [14,26] and 12 were scored...
as low risk of bias using the Cochrane scoring method. With regard to the quality of the evidence in avoidance of bias using the Cochrane methodology, there is the acknowledgment that many of these studies suffer from lack of blinding. The scores on these categories had less to do with study design error and were more accurately attributed to the inherent conventional PNS treatment bias that is unavoidable. Given the limitations in the state of the art with paresthesia-based stimulation, the scores of moderate quality on bias risk are acceptable and speak to the highest-quality study design possible.

**Discussion**

For the purposes of this review, PNS and PNiS were included, as the techniques share many common features that would classify them in the same “modality application” family. There are other pain indications for which PNS application may prove beneficial, such as trigeminal neuropathic pain or pudendal neuralgia. At present, there is insufficient literature to comment on these uses, and they are excluded here. The current review supports the concept that PNS is safe and relatively effective for the treatment of migraine headache, cluster headache, shoulder pain, low back pain, pelvic pain, and neuropathic pain of other origin. Taken together, these 14 RCTs constitute the studies that were evaluated to determine the level of evidence and quality ratings.

**Occipital Nerve Stimulation for Treatment of Intractable Headache**

Saper et al. [15] conducted a multicenter, randomized, controlled, blinded, industry-funded feasibility study to determine the safety and efficacy of occipital nerve stimulation (ONS) in treating chronic migraine headaches. Seventy-five subjects were randomly assigned to one of three treatment groups: adjustable stimulation (AS), preset stimulation (PS), or medical management (MM). A fourth group (ancillary) consisted of subjects who had failed to respond to an occipital nerve block and were implanted, allowed to adjust stimulation, and treated identically to the AS group. At three months, responder rates (subjects who achieved a ≥50% reduction in number of headache days per month or a three-or-more-point reduction in average overall pain intensity) were 39% for the AS group, 6% for the PS group, and 0% for the MM group. There were also significant differences in disability and quality-of-life (QoL) outcomes between the AS and control groups. Unfortunately, there was a large number of device-related adverse effects. The strengths of this study include multiple investigational sites [9], appropriate randomization, blinded patients and investigators, and a placebo control group. Weaknesses include industry funding and underpowering for efficacy evaluation.

Serra et al. [14] evaluated 30 patients in a prospective, randomized crossover study for the management of chronic migraine and medication overuse headache with ONS. Participants were randomized to “stimulation-on” and “stimulation-off” arms. After four weeks, subjects were allowed to cross over. After another four weeks, all subjects were then able to turn their stimulation on. Subsequent follow-up visits occurred at three, six, and 12 months. There was a significant difference ($P < 0.05$) in headache intensity and frequency in the stimulation-on arm compared with the stimulation-off arm, as measured
## Table 2. Characteristics of PNS studies

<table>
<thead>
<tr>
<th>Study Characteristics Methodology Scoring</th>
<th>No. of Subjects Selection Criteria</th>
<th>Control</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Time of Measurement</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Headache Pain</td>
<td></td>
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<td>ONS device was permanently implanted following a successful 3–5-d trial to treat occipital neuralgia</td>
<td>1. Headache d</td>
<td>At 0, 4, 12, 24, and 52 wk</td>
<td>Headache d significantly reduced to 8.51 (±9.81) d per month 60% had &gt;30% relief 100% had reduction in MIDAS and Zung scores 75% had ≥1 AE (total of 20)</td>
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<td>3. MIDAS</td>
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<td>4. Zung PAD</td>
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<td>5. Quality of life, satisfaction</td>
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<td>6. AEs</td>
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<tr>
<td>Dodick et al. 2015 [13]</td>
<td>N = 105</td>
<td>N = 52</td>
<td></td>
<td>1. Number of headache d</td>
<td>4 wk before the start of the study, and again between 48 and 52 wk</td>
<td>Headache d significantly reduced by 6.7 (±8.4) d (ITT group) and 7.7 (±8.7) d (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% AE rate (183 total), of whom 8.6% were hospitalized and 40.7% required surgical revision</td>
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<td></td>
<td>157 were included in ITT analyses, and only 125 who met criteria for ICM were analyzed</td>
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<td>2. Pre- and post-VAS</td>
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<td>3. MIDAS</td>
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<td>5. QoL, satisfaction</td>
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<td>6. AEs</td>
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<tr>
<td>Serra et al. 2012 [14]</td>
<td>34 patients with a CM or MOH diagnosis (Headache Diary)</td>
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<td>INS “off” group Absence of true control group, where all patients were implanted</td>
<td>MIDAS, SF-36, NRS-11</td>
<td>1-mo crossover 1-y follow-up</td>
<td>On arm significantly better than off arm (P &lt; 0.05) Quality of life significantly improved (P &lt; 0.05) during study Decreased medication use</td>
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<tr>
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<td>Single-center, prospective, randomized crossover study at 1 mo</td>
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<td>INS “on” group</td>
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<tr>
<th>Study Characteristics Methodology Scoring</th>
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<tbody>
<tr>
<td>Saper et al. 2011 [15]</td>
<td>110 patients with intratable chronic migraine headaches</td>
<td>AS group control subjects implanted PS</td>
<td>75/100 patients were assigned to the treatment group</td>
<td>Functional disability scale, MIDAS, SF-36</td>
<td>Baseline, 1- and 3-mo follow-up</td>
<td>3-mo responder rates were 39% for AS, 6% for PS, and 0% for MM. No unexpected AEs occurred. Lead migration occurred in 12 of 51 (24%) subjects.</td>
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<td></td>
<td>3-arm, multicenter, randomized, blinded, and placebo-controlled trial</td>
<td>2) MM during the blinded phase of the study</td>
<td>After implantation, the AS group was “on” with adjustments to minimize pain evaluated at 1 and 3 mo</td>
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<td>CMIH (2004 IHS criteria) and &gt;12 mo</td>
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<td>Randomization ratio of 2:1:1, respectively to:</td>
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<td></td>
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<td>3. MM</td>
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<td>Schoenen 2013 [16]</td>
<td>28 patients with chronic cluster headaches, experienced 4+ cluster headaches per d</td>
<td>Patients were their own control with sham arm</td>
<td>All patients used SPG for CH attack, 3 different treatment possibilities: 1. Full stim, 2. Sub-perception stim, 3. Sham stim</td>
<td>CH attack frequency, HIT-6, SF-36.v2</td>
<td>Experimental 8 wk</td>
<td>Pain relief in 67.1% of full-stim group; 74% in sub-perception, and 73% in sham. 64% had improvement in HIT-6 scores. QoL improved in 75% of patients based on SF-36.v2.</td>
</tr>
<tr>
<td>Plazier et al. 2015 [17]</td>
<td>N = 40</td>
<td>Patients could cross over to be their own controls</td>
<td>Subcutaneous C2 stimulation for the treatment of headache syndrome among fibromyalgia patients</td>
<td>Fibromyalgia Impact Questionnaire scores, Pain Vigilance and Awareness Questionnaire, Pain Catastrophizing Scale, Tender point examination NRS, Beck Depression Inventory, Modified Fatigue Impact Scale, Pittsburgh Sleep Quality Index</td>
<td>Baseline, at the end of phase I and during baseline, 4, 12, 18, and 24 wk during phase I</td>
<td>36% reduction on FIQ, 33% decrease of fibromyalgia pain, and 42% functional and QoL improvement at 6 mo. 76% satisfied or very satisfied. Increased amplitude trended toward better outcomes. 41.2% AE rate.</td>
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<td>25 patients completed both study phases (6 wk of trial followed by implant)</td>
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<tr>
<td><strong>Shoulder Pain</strong></td>
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<tr>
<td>Wilson et al. 2017 [18]</td>
<td>25 subjects: 13 to PNS and 12 to PT</td>
<td>PT</td>
<td>PNS—single percutaneous electrode placed between deltoïds; 6 h stimulation per d for 3 wk</td>
<td>Isometric shoulder abduction strength, EMG delay times during shoulder abduction, pain-free shoulder ROM, Fugl-Meyer motor assessment</td>
<td>Outcomes measured before and at the end of the 4-wk treatment period and at 6 and 12 wk after treatment ended</td>
<td>Variable improvement in both groups; Significant strength improvement in both groups; Delay—no difference in shoulder abduction EMG; ROM—both groups with significant improvement; FMA—pain reductions: PNS with 65.3% and PT with 34.3%; the difference was clinically and statistically significant</td>
</tr>
<tr>
<td>Wilson et al. 2014 [19]</td>
<td>N = 25, 13 in PNS and 12 in UC; complete data obtained for 21 patients</td>
<td>Usual care</td>
<td>PNS—single percutaneous electrode placed between deltoïds; 6 h of stimulation per d for 3 wk; lead then removed</td>
<td>Primary: BPI-SF3; Secondary: BPI-SF9, VGRS, SF-36v2</td>
<td>5 end points: baseline, start of treatment, end of treatment, 6 wk post-treatment, 12 wk post-treatment</td>
<td>Primary: mean severity rating was statistically significant at 16 wk, favoring treatment arm; BPI-SF3, SF-36v2; VGRS: significant improvement in both groups, though not significantly different between groups; SF-36v2: significant improvement in both groups seen for each end point</td>
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<tr>
<td><strong>Leg and/or Back Pain</strong></td>
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<tr>
<td>Eldabe et al. 2018 [20]</td>
<td>N = 56</td>
<td>N = 60</td>
<td>SQS in the painful area plus OMM to treat low back pain</td>
<td>1. Compare SQS + OMM with OMM alone 2. Reduction in back pain intensity 3. VAS, ODI, EQ-5D-5L, SF-36, PGIC, health care utilization, and medication use 4. AEs</td>
<td>Baseline, 1, 3, 6, and 9 mo</td>
<td>33.9% SQS+OMM achieved &gt;50% reduction in back pain at 9 mo compared with 1.7% in OMM group; The SQS+OMM group had significantly lower pain scores</td>
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<tr>
<td>Study Characteristics</td>
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<td>Van Gorp et al. 2016</td>
<td>SCs for leg and back pain, with neuropathic pain in the L4-S1 distribution for at least 6 mo after lumbar spine surgery</td>
<td>97 patients treated with SCS for leg and back pain, with neuropathic pain in the L4-S1 distribution for at least 6 mo after lumbar spine surgery</td>
<td>32 patients in the first treatment arm received no SQS (control)</td>
<td>33 patients received optimal (SubQ ADD-ON) for a period of 3 mo (controlled phase); all patients were optimally treated with SCS for leg pain</td>
<td>Primary outcome measure: &gt;50% relief of back pain VAS at 3 mo</td>
<td>Baseline and 3 mo postimplant</td>
</tr>
<tr>
<td>McRoberts et al. 2013</td>
<td>Minimal stimulation</td>
<td>44 subjects enrolled, 32 trialed, 30 implanted</td>
<td>Chronic intractable pain, previous interventions, and conservative medical modalities</td>
<td>Three groups: -Standard stimulation -Low-frequency stimulation -Subthreshold stimulation</td>
<td>Primary outcomes: VAS and PPI assessed by SF-MPQ</td>
<td>Baseline, 4, 12, 24, and 52 wk</td>
</tr>
<tr>
<td>Deer et al. 2016</td>
<td>49 patients in control group with no therapeutic stim for 90 d were then allowed to cross over to treatment group</td>
<td>94 subjects: 45 in treatment, 49 in control</td>
<td>All subjects meeting inclusion criteria were implanted with PNS and then randomized to either control or treatment (active stimulation)</td>
<td>45 patients in 3 groups (upper extremities, lower extremities, trunk) received therapeutic stimulation for 90 d</td>
<td>Primary outcomes: pain relief (NRS) and safety (AEs)</td>
<td>Baseline, 30, 60, and 90 d for primary outcomes and 6 and 12 mo for safety and secondary outcomes</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>Usual care</td>
<td>24 subjects: 12 in PTNS and 12 in control</td>
<td>Diagnosis of chronic pelvic pain, VAS &gt;5, cessation of analgesics ≥2 wk before PTNS treatment, cessation of PT, or electrotherapy at least 3 mo before PTNS treatment</td>
<td>PTNS applied using a needle and stimulator</td>
<td>Data were collected through a questionnaire and included VAS, SF-36, MPQ for pelvic pain and Female Sexual Function Index</td>
<td>Beginning of treatment and end of treatment, 12 wk</td>
</tr>
<tr>
<td>Study Characteristics</td>
<td>Methodology Scoring</td>
<td>No. of Subjects</td>
<td>Selection Criteria</td>
<td>Control</td>
<td>Intervention</td>
<td>Outcome Measures</td>
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<tr>
<td>Istek et al. 2014 [25]</td>
<td></td>
<td>33 patients</td>
<td>with chronic</td>
<td>Only oral analgesics and no PTNS</td>
<td>PTNS performed once a wk for 30 min; total treatment period of 12 wk</td>
<td>PPI-VAS, SF-MPQ, and SF-36</td>
</tr>
<tr>
<td>Kabay et al. 2009 [26]</td>
<td></td>
<td>89 patients</td>
<td>with chronic pelvic pain (&gt;6 mo) randomized to active PTNS stimulation or sham needles placed but no electrical stimulation applied</td>
<td>Needles placed similar to active group but no electrical stim applied</td>
<td>Patients underwent 12 wk of outpatient treatment sessions with PTNS, with each session lasting 30 min</td>
<td>VAS, NIH-CPSI</td>
</tr>
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</table>

AE = adverse event; AS = adjustable stimulation; BPI = Brief Pain Inventory; CH = cluster headache; CM = chronic migraine; CMH = chronic migraine headache; EMG = electromyogram; EQ-5D-5L = European Quality of Life Five Dimensions; FBSS = failed back surgery syndrome; FIQ = Fibromyalgia Impact Questionnaire; FMA = Fugl-Meyer Motor Assessment; FSFI = Female Sexual Function Index; HA = headache; HADS = Hospital Anxiety and Depression Scale; HIT = Headache Impact Test; HSP = hemiplegic shoulder pain; ICM = intractable chronic migraine; IHS = International Headache Society; INS = internal occipital neurostimulator; ITT = intent-to-treat; LE = lower extremity; MIDAS = Migraine Disability Assessment; MM = medical management; MPQ-DLV = McGill Pain Questionnaire–Dutch Language Version; MOH = medication overuse headache; MOS = Medical Outcomes Sleep study; NIH-CPSI = National Institutes of Health–Chronic Prostatitis Symptom Index; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; ODI = Oswestry Disability Index; OMM = optimized medical management; ONS = occipital nerve stimulation; OT = occupational therapy; PAD = pain and distress; PGIC = Patient Global Impression of Pain; PNS = peripheral nerve stimulation; PPI = Present Pain Index; PS = preset stimulation; PT = physical therapy; PTNS = peripheral tibial nerve stimulation; QoL = quality of life; QOLLSF = Quality of Life SF-12v2 Health Survey (QoL SF-12v2); RCT = randomized controlled trial; Short Form 36 (health survey); SQS = subcutaneous nerve stimulation; ROM = range of motion; SPG = sphenopalatine ganglion; UC = usual care; VAS = visual analog scale; VGRS = visual graphic rating scales.
by Migraine Disability Assessment (MIDAS) scores. QoL measures were improved as well. Of note, triptan and nonsteroidal anti-inflammatory drug use dropped significantly as well, from baseline (20 and 25 doses/mo, respectively) to each follow-up visit (three and two doses per month, respectively, at one year, \( P < 0.001 \)). The weaknesses of the study include single-center setting, lack of blinding, small number of subjects, and a lack of control group beyond the first eight weeks of the study.

Dodick et al. [13] evaluated the efficacy and safety of PNS of occipital nerves for chronic migraine management in a randomized, multicenter, double-blind study where patients were implanted with a neurostimulation system, randomized to an active or control group for 12 weeks, and received open-label treatment for an additional 40 weeks. Measured outcomes included number of headache days, pain intensity, MIDAS, Zung Pain and Distress (PAD), direct patient reports of headache pain relief, QoL, satisfaction, and adverse events (AEs). At 52 weeks, a 30% or 50% reduction in headache days and/or pain intensity of 59.5% and 47.8%, respectively, was observed. It should be noted, however, that >70% of patients experienced an AE, with >8.6% of the patients requiring hospitalization and 40.7% requiring surgical intervention. This was the first large-scale, prospective controlled study evaluating PNS in the occipital region for chronic migraine to report one-year efficacy and safety results. Previously, Silberstein et al. [27] carried out a larger multicenter prospective RCT, but that was limited to 12-week follow-up. Other strengths include duration of follow-up, double-blinding, and multiple centers with no outside funding.

Mekhail et al. [12] evaluated the safety and efficacy of ONS for the treatment of chronic migraines. Twenty patients were implanted with a neurostimulation system and were randomized to an active or control group for 12 weeks and then received open-label treatment for an additional 40 weeks. Patients were assessed at baseline and at four, 12, 24, and 52 weeks after permanent implantation, when they completed the MIDAS questionnaire and provided pain relief ratings, QoL ratings, and a satisfaction report. Electronic diaries were used to capture headache frequency, duration, and intensity. The primary outcome for the controlled phase was mean daily VAS, and the primary end point was a comparison of the proportion of responders in the active group with those in the control group at 12 weeks. Secondary end points included reduction in number of headache days, MIDAS questionnaire, reports of headache relief, QoL, satisfaction, and AEs. Approximately 30% of the active group reported \( \geq 50\% \) reduction in VAS, compared with 0% in the control group, which was statistically significant. Additionally, at 12 weeks, the active group had statistically significant reductions in headache days per month, headache intensity, and headache interference. The active group also had statistically significantly improved QoL. There was a high rate of AEs, most hardware related. The results of this study were compared with the outcomes of a multicenter study of ONS, in hopes of elucidating differences in outcomes and AEs. This study demonstrated approximately similar results to the multicenter study. Its strengths include double-blinding, experienced implanters, and involvement of a multidisciplinary headache management team.

Thimineur and DeRidder [28] serendipitously found that patients with fibromyalgia who also had headaches and were treated with ONS reported improvement not only in their headaches but also in their widespread body pain, fatigue, and QoL. These findings were supported by a follow-up placebo-controlled pilot study by Plazier et al. [29]. Subsequently, Plazier et al. [17] followed up the pilot study with the prospective, double-blind, randomized, controlled, crossover study evaluating the effectiveness of ONS in the treatment of fibromyalgia resistant to conventional medical management. A total of 40 subjects were enrolled, and 25 subjects completed the study. Subjects reported significant improvements in both primary (improvement in Fibromyalgia Questionnaire scores) and secondary outcome measures (Pain Vigilance and Awareness Questionnaire, Pain Catastrophizing Scale, Tender Point Examination, numerical rating scale [NRS], Beck Depression Inventory [BDI], Modified Fatigue Impact Scale, and Pittsburgh Sleep Quality Index). Weaknesses of the study include industry funding and relatively small sample size.

**Sphenopalantine Ganglion Stimulation for Treatment of Cluster Headache**

Schoenen et al. [16] conducted a prospective, randomized, multicenter study with 28 cluster headache patients completing the experimental period. To treat acute cluster headache attacks, patients were implanted with an SPG stimulator, which was programmed with full, subperception, or sham stimulation. These parameters would occur randomly for each patient and were monitored by the authors. Pain relief was achieved in 67.1% of full stimulation–treated attacks compared with 7.4% of sham and 7.3% of subperception attacks. Furthermore, SPG stimulation resulted in both statistically and clinically significant reductions in headache attack frequency as well as disability. The authors concluded that on-demand SPG stimulation is an effective therapy for chronic cluster headache sufferers. The strengths of the study include prospective design, sham control, and multiple sites. Weaknesses include a relatively small sample size and industry funding.
PNS for the Treatment of Poststroke Shoulder Pain

Wilson et al. [19] conducted a single-site, randomized controlled pilot trial for 25 adults with chronic shoulder pain following stroke who underwent either single-lead PNS to obtain contraction of the middle and posterior deltoid muscles or "usual care," including physical therapy (PT) for range of motion and strengthening and upper extremity slings. Subjects were followed for 16 weeks. Results showed that short-term PNS (for three weeks) provided a greater reduction in shoulder pain (BPI-SF3) than usual care at six and 12 weeks post-treatment. Weaknesses of the study include small sample size and missing data due to several patients forgoing at least one follow-up assessment. Furthermore, the data for concomitant analgesic medication usage were not adequate for analysis due to missing data, and therefore a confounding effect of analgesic use cannot be ruled out.

Wilson et al. [18] three years later presented analyses of secondary outcomes from the previously described single-site RCT for 25 adults with chronic shoulder pain following stroke. This analysis compared the biomechanical outcomes (shoulder strength, range of motion, and motor control) of subjects who underwent either single-lead PNS between the anterior and middle deltoid muscles or PT and evaluated whether there is a correlation between pain reduction and these biomechanical outcomes. The results showed that both PNS and PT produced improved shoulder biomechanics, but these improvements alone could not account for the improved pain relief with PNS vs PT.

Posterior Tibial Nerve Stimulation for Treatment of Pelvic Pain

Tibial nerve stimulation involves stimulation of the posterior tibial nerve just proximal to the medial malleolus and delivers electrical stimulation via the sacral nerve plexus S2–4. The mechanism of action is thought to involve inhibition or modulation of the C-fiber and δ-afferent responses from the bladder. Many studies have examined functional outcomes of posterior tibial nerve stimulation (PTNS), but few have focused on pain outcomes. Van Balken et al. [30] first published a prospective multicenter observational trial of PTNS for the treatment of chronic pelvic pain with modest positive results over 12 weeks. In 21% of patients, the mean VAS decreased by >50%, and in 18% of patients the improvement was >25%. In all subjects, the QoL (SF-36) was significantly improved. The limitations of this study are the lack of placebo control and relatively short follow-up.

Gokylidiz et al. [24] conducted a prospective RCT evaluating the efficacy of PTNS in treating chronic pelvic pain. A total of 24 patients were enrolled, 12 in the control group and 12 who received PTNS once a week for 12 weeks. The pain frequency and intensity (VAS) decreased significantly in women who underwent PTNS. Women treated with PTNS also had less pain during intercourse (Female Sexual Function Index) and demonstrated functional improvements in their daily activities and improvement in QoL (SF-36). The limitations of the study include the short duration of follow-up and relatively small sample size.

Kabay et al. [26] conducted a prospective, randomized, sham-controlled study evaluating the efficacy of PTNS in treating category IIB chronic nonbacterial prostatitis/chronic pelvic pain syndrome. A total of 89 subjects were randomized to receive either stimulation or sham treatment. VAS scores and the National Institutes of Health Chronic Prostatitis Symptom Index were used to assess treatment success after 12 weeks of intervention. Mean symptom and VAS scores were significantly improved with PTNS compared with sham treatment.

Istek et al. [25] conducted an RCT evaluating the efficacy of PTNS in the treatment of chronic intractable pelvic pain in women. A total of 33 subjects were enrolled and randomized into a PTNS group or the control group (no stimulation). Present pain intensity VAS, short-form MPQ, and SF-36 were used at baseline, 12-week, and six-month follow-up. There were statistically significant improvements in pain (PPI-VAS scores) and QoL (SF-MPQ and SF-36) at six months. The study demonstrated modest improvements in pain scores and QoL assessments at six-month follow-up in the PTNS group. The authors concluded that there was a need for longer-term placebo-controlled studies to further evaluate efficacy.

PNS for the Treatment of Chronic Low Back Pain

Several prospective observational studies examined the efficacy of PNS for the treatment of chronic low back pain. However, McRoberts et al. [22] were the first to conduct a prospective, multicenter, randomized, controlled, double-blinded clinical trial investigating the use of peripheral nerve field stimulation (PNfS) in treatment of chronic low back pain. A total of 69.5% of patients reported improvement in pain at one year postimplantation. The strengths of the study included a well-described trial design and heterogeneity with respect to type of stimulation offered among different groups; a weakness was a relatively low number of enrolled and completed patients, which limits the authors' argument with respect to efficacy. Furthermore, although the authors report this to be a controlled study, there is no placebo or sham treatment group included, but rather varying degrees of stimulation intensity were employed.

Van Gorp et al. [21] conducted a multicenter RCT that reported ≥50% improvement in low back pain assessed by the VAS in patients treated with PNfS following spinal cord stimulation implantation for chronic low back and leg pain after spine surgery, compared with sham implantation control. The strengths of this study include a large number of patients, randomization, and the provision of a control group, but, as pointed out by
the authors, the inability to blind patients, surgeons, and assessors is a key weakness.

Eldabe et al. [20] conducted a multicenter RCT to compare the effectiveness of PNS utilizing a subcutaneous lead implant technique in addition to optimized medical management (OMM) vs optimized medical management alone in patients with back pain due to failed back surgery syndrome (FBSS). The primary end point was proportion of subjects with \( \geq 50\% \) reduction in back pain intensity from baseline to nine months. Secondary outcomes included ODI, EQ-5D-5L, SF-36, Patient Global Impression of Change (PGIC), and medication usage. The study was terminated early due to slow recruitment. Despite this, 116 subjects were randomized but only 74 were able to complete the nine-month primary end point visit. For the primary outcome, the responder rate in the PNS arm was 33.9% compared with 1.7% in the OMM arm. The difference between the arms in the intention-to-treat analysis was statistically significant. When omitting the missing data due to early study termination, the difference in responder rates was also statistically different. A statistically significant treatment effect favoring PNS was found for secondary outcomes including disability (ODI), QoL (EQ-5D-5L), and PGIC. Although the study was terminated early, the primary and secondary objectives of the study were met. There was a large number of AEs reported, although the majority were unrelated to the device or therapy. The strengths of the study include multicenter participation that supports generalizability of the results. Weaknesses of the study include lack of blinding, as it was not feasible in a comparative study of procedural intervention vs nonprocedural intervention. Furthermore, early termination of the study resulted in a smaller number of subjects contributing to the final analysis.

PNS for the Treatment of Neuropathic Pain of the Extremities and Trunk

Deer et al. [23] conducted a prospective, randomized, double-blind multicenter partial crossover study to assess the safety and efficacy of a new PNS device with Food and Drug Administration oversight. Ninety-four patients suffering from neuropathic pain of the extremities or trunk were implanted and then randomized to the treatment (N = 45) or control (N = 49) group. The treatment group showed a statistically significant improvement in pain relief at three months compared with the control group, in addition to significant improvements in QoL and satisfaction.

Conclusions

This systematic review of the use of PNS to treat chronic pain adds substantial credibility to the therapy and provides an extensive evidence-based analysis supporting it as a viable option for many patients. The use of PNS for chronic pain related to the peripheral nerves is supported by moderate- to high-level evidence. We recommend additional prospective trials to further determine patient populations and pain diagnoses that are most likely to benefit.

Supplementary Data

Supplementary data are available at Pain Medicine online.

Key Points

Taken together, these 14 RCTs suggest several key points:

1. multiple studies showing ONS can be beneficial for chronic migraine (CM), medication overuse headache (MOH), and intractable chronic migraine (ICM);
2. moderate evidence (Level II) that implanted SPG stimulation is effective for cluster headaches;
3. strong evidence (Level I) that PNS is beneficial for patients with continued low back pain following surgery, medications, and/or interventional pain procedures;
4. moderate evidence (Level II) that implanted PNS can be expected to provide at least modest improvements in mononeuropathic pain and hemiplegic shoulder pain;
5. PTNS may be helpful for overall pain, dyspareunia, and QoL in chronic pelvic pain (Level III).

Several RCTs did not meet criteria for evaluation in the systematic review process because of short duration (less than two months) or small sample size. There are also several prospective observational studies that examine the efficacy of PNS to treat chronic pain. Although these studies could not be deemed as having sufficient quality to be included due to the aforementioned factors, they can be viewed as indicating directions for further study.

Authors’ Contributions

Under the primary leadership of TRD with assistance from MFE and WPM, all authors in the work group participated in the acquisition, grading, and interpretation of the articles identified in the systematic literature search initiated by DAG and TJL, worked to achieve consensus when drafting the text, and revised and approved the final manuscript.

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