Neurostimulation for Neuropathic Pain: Outcomes and New Paradigms

Neuropathic pain afflicts millions of people globally and presents a major health and economic burden. Epidemiological studies carried out with validated screening tools estimate that as many as 7–8% of adults in the general population have pain with neuropathic characteristics. Neuropathic pain can result from various etiologies, such as traumatic or surgical injuries to peripheral nerves, infectious diseases (e.g., herpes zoster, HIV, or leprosy), metabolic disorders, cancer and its treatment, and injuries or diseases that affect the central nervous system (e.g., stroke or spinal cord injury). Nearly a fourth of people with chronic diabetes have neuropathic pain—a worldwide estimate of nearly 50 million individuals. Moreover, neuropathic pain is reported to be more severe than non-neuropathic pain and can dramatically affect health-related quality of life.

Several evidence-based recommendations for pharmacological treatments have been published, including a recently updated NeuPSIG recommendation based on a systematic review and meta-analysis of published and unpublished clinical trials. Data from these studies suggest that the management of patients with chronic neuropathic pain is challenging, with more than 50% of patients experiencing only partial or no relief of their pain. In addition, the adverse effects associated with the drugs used to manage the pain may limit their clinical utility, particularly in the elderly population. Hence, experts are increasingly considering interventional therapies such as nerve blocks and neuromodulatory strategies for patients with refractory neuropathic pain and those who are intolerant to systemic drugs. On the basis of the available evidence from clinical trials, NeuPSIG published recommendations in 2013 regarding the use of interventional therapies for neuropathic pain. Several more recent studies have provided additional evidence for the role of neurostimulation therapies in the management of neuropathic pain. This issue of Pain: Clinical Updates reviews the latest evidence for emerging neurostimulation therapies that may provide alternative therapeutic strategies for patients with neuropathic pain.

Spinal Cord Stimulation

Spinal cord stimulation (SCS) as a therapy for chronic pain was introduced nearly half a century ago by Norman Shealy and colleagues. Recent advances in percutaneous implantation techniques and devices, technological advances in stimulation electrodes, innovations in implantable pulse generators, and the introduction of novel stimulation parameters have resulted in a surge in the use of implantable therapies. The relative safety and reversibility of this treatment modality, as well as its cost-effectiveness over the long term, have made it an attractive strategy for managing patients with refractory, chronic neuropathic pain. Although SCS has been used to treat a variety of neuropathic pain states, controlled trials have shown the best evidence for long-term efficacy in patients with failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I, and more recently in diabetic neuropathic pain. Based on the GRADE criteria, a NeuPSIG consensus group rated the quality of evidence from clinical trials as moderate, and gave it a "weak" recommendation for use in FBSS with radiculopathy and CRPS. Although the same report considered the evidence for the efficacy of SCS in diabetic neuropathic pain to be low and labeled its...
recommendation as “inconclusive,” more recent controlled trials provide additional evidence for its efficacy.

**Stimulation Paradigms**

Conventional SCS that is associated with a paresthesia uses a monophasic, square-wave pulse at a frequency in the 40–80-Hz range. In an attempt to improve success and avoid some of the undesirable side effects of SCS, some physicians are using new stimulation parameters, such as burst and high-frequency SCS (Fig. 1). Recent studies examining the long-term effectiveness of these strategies provide encouraging observations that should be confirmed by additional controlled trials.

**Traditional SCS**

Whereas burst and high-frequency stimulation use fixed wave parameters, traditional SCS adjusts the different parameters to achieve fiber depolarization and paresthesias that overlap the painful area. Parameters that can be adjusted include electrode polarity, amplitude, pulse width, and frequency. Electrode polarity controls the shape and density of the electrical field, as determined by the distance between the electrodes and the number of positive versus negative electrodes used. The amplitude is the strength of the stimulation pulse. Measured in volts or milliamps, it is the primary control over the intensity of the sensation. Higher amplitudes will ultimately result in painful stimulations. The highest amplitude that can be achieved with current devices is 15 V. The pulse width is the amount of time the stimulation pulse lasts and is measured in microseconds. Higher (wider) settings will cause the stimulation field to “stay on” longer and depolarize both large- and small-diameter fibers. Lower pulse width will narrow the stimulation, resulting in mostly large-fiber depolarization. Typical clinically used pulse widths range from 175 to 600 µs but can go as high as 1000 µs. Frequency is the number of stimulation pulses delivered per second. The frequency of traditional SCS can be as high as 1200 Hz. Increasing the frequency boosts the number of action potentials generated by the nerve. Changes in frequency produce a change in sensation from pulsing (low) to fluttering (high). Higher frequencies dramatically affect battery consumption.

**Burst SCS**

Burst stimulation consists of closely spaced, high-frequency stimuli delivered to the spinal cord (Fig. 1). The stimulus paradigm consists of a 40-Hz burst mode of constant-current stimuli with 5 spikes at 500 Hz per burst and pulse width and interspike intervals of 1 ms. A possible advantage of this stimulus paradigm is that it does not cause paresthesia in the painful region. In a randomized controlled trial (RCT), burst stimulation was able to improve back, limb, and general pain by 51%, 53%, and 55%, respectively, compared to 30%, 52%, and 31% with tonic stimulation. Similar significant improvements in pain now, least pain, and worst pain were observed with burst stimulation. The differences between tonic and burst stimulation could be due to more selective modulation of the medial pain pathways by burst stimulation, as evidenced by activation of the dorsal anterior cingulate cortex. More recent retrospective analysis of patients who were switched from tonic to burst stimulation suggests that the latter can rescue a proportion of those who

---

Fig. 1. Spinal cord stimulation waveforms.
do not respond to tonic stimulation and improve pain reduction in those who do. Additional RCTs are needed to confirm these observations.

**High-Frequency Stimulation**

High-frequency stimulation uses frequencies up to 10 kHz. Although the currently available device is capable of amplitudes up to 15V and a pulse width up to 1000 ms, newer devices reach 10 KHz with amplitudes of 1 to 5 mA and very low pulse width, resulting in paresthesia-free stimulation. The exact mechanism of pain relief is unclear, but preclinical studies have shown that a high-frequency, alternating-current sinusoidal waveform applied to a nerve results in a reversible block of activity. This block occurs in three phases: an onset response, a period of asynchronous firing, and a steady state of complete or partial block. This technology is currently available in Europe and Australia and recently received approval in the United States. Because of the high frequencies used, the device requires a rechargeable battery to support the high power consumption. It is used primarily to treat back pain but has some effect on lower-extremity pain. Leads are placed anatomically over T9 in the midline; intraoperative paresthesia mapping is not necessary, thus shortening procedure time. A U.S. pilot study in 24 patients demonstrated a significant reduction in back and leg pain. A European study was conducted in 83 patients with primarily low-back pain. Seventy-two subjects had a successful trial. Long-term follow-up to 12 months showed a significant reduction in both back and leg pain. The study also reported significant improvements in the average Oswestry Disability Index score and in sleep disturbance, as well as high patient satisfaction. An ongoing clinical trial in the United States of subjects who have low back pain with or without lower-extremity pain is testing an SCS device that provides both traditional and high-frequency SCS (the ACCELERATE Trial).

**Complex Regional Pain Syndrome**

CRPS is a well-established indication for SCS, for which it is approved by the U.S. Food and Drug Administration (FDA). The primary evidence for effectiveness of SCS in CRPS patients is based on a prospective, randomized trial of 54 patients followed for up to 5 years. Kemler and coworkers randomized CRPS type I patients in a 2:1 ratio to two groups: SCS with physical therapy or physical therapy alone. Two-thirds of the 24 patients in the SCS group were implanted with devices after a successful trial stimulation. Pain was reduced by 2.4 cm on a 10-cm visual analogue scale (VAS) in the SCS group, whereas...
it increased by 0.2 cm in the physical therapy group. Moreover, 39% of SCS patients, compared to 6% of control patients, rated themselves as “much improved.” The observed beneficial effects in the SCS group persisted at 2 years, but subsequent evaluations at 3–5-year follow-ups failed to demonstrate differences in outcome between the groups.23 Despite a 42% reoperation rate in the SCS patients during the 5-year study, 95% of the patients who received SCS indicated that they would repeat the procedure.21 Other retrospective and prospective case series also have reported reduced pain, improved function, and reduced medication use after SCS in CRPS patients. An independent systematic review of the studies concluded that SCS showed evidence for efficacy relative to conventional medical management in patients with CRPS type I.28 Both NeuPSIG and the European Federation of Neurological Societies (EFNS) gave a weak recommendation for use of SCS in CRPS type I, on the basis of the moderate evidence.5,14

Failed Back Surgery Syndrome

Two published RCTs, along with several long-term outcome case series, support the use of SCS for FBSS. Most studies evaluated the effects of SCS in patients who had treatment-refractory FBSS with prominent radicular symptoms. In the first RCT, North et al.23 studied 50 patients who had undergone previous spinal surgeries and were candidates for reoperation to alleviate chronic pain that was more bothersome in their legs than their back. Patients were randomized to either treatment with SCS or reoperation, but they were allowed to cross over to the other treatment if dissatisfied with the results of their first treatment. The criterion for “success” was patient satisfaction with treatment and a 50% or greater reduction in pain. Among 45 patients available for evaluation approximately 3 years postoperatively, the authors reported a successful outcome in 47% of SCS patients versus 11.5% of the reoperation patients. The rate of crossover to alternative treatment was also significantly lower in the SCS patients (~20%) than in the reoperation patients (~50%).

In the second, larger RCT, 100 FBSS patients with more severe leg pain than back pain were randomized to conventional medical management (CMM) alone or CMM with SCS.27 The primary outcome measure was the responder rate (the proportion of patients obtaining at least 50% relief of leg pain) at 6 months, after which patients were allowed to cross over. In the 88 patients available for analysis, SCS was successful in 48% and 34% at 6 and 12 months, respectively, in contrast to 9% and 7% in the CMM group. More than 50% of subjects originally assigned to CMM crossed over to receive SCS, whereas only 18% of SCS patients crossed over to CMM. Although the total health care cost in the SCS group was significantly higher, subjects in the SCS group experienced significantly improved quality of life and functional capacity, as well as greater treatment satisfaction than those in the CMM group.21 Device-related reoperation is a concern, as 31% of the SCS patients available for follow-up at 2 years had required surgical revision. Considering the strengths and limitations of these trials, the authors of a systematic review concluded that SCS appears to be more effective than CMM and reoperation.28 Both NeuPSIG and the EFNS gave SCS a weak recommendation for FBSS.5,14 Because of the invasiveness of the procedure, the risk of complications, and the relatively low response rate to SCS, the NeuPSIG recommendation was to reserve SCS for patients who do not respond to less invasive treatment options, including consideration of a trial of epidural steroid injections.

In a recent observational study of 48 patients, burst stimulation led to a significant additional pain reduction of approximately 28% in patients with FBSS, compared to that in patients who received conventional tonic stimulation.20

Painful Diabetic Neuropathy

Earlier small, prospective observational trials evaluating the effects of SCS on pain in patients with refractory painful diabetic neuropathy (PDN) reported substantial benefits, although the complication rate was 33% in one of the trials.7,12 Two RCTs of SCS in patients with PDN reported in 2014 provide additional evidence for the effectiveness of SCS in the management of PDN. In a multicenter randomized trial, 36 PDN patients with severe lower-limb pain refractory to conventional therapy were randomized to receive either SCS in combination with the best medical treatment (SCS group, n = 22) or medical treatment alone (BMT group, n = 14).29 Treatment success, determined at 6 months, was defined as ≥50% pain relief or “(very) much improved” for pain and sleep on the Patient Global Impression of Change scale.

Treatment success was observed in 59% of patients in the SCS group compared to 7% in the BMT group. SCS was not without risk in this population, as one SCS patient died of a subdural hematoma. In a second, larger, multicenter controlled trial, 60 PDN patients were similarly randomized in a 2:1 ratio to receive best conventional medical practice with (SCS group) or without (control group) additional SCS therapy.11 After 6 months of treatment, average pain scores decreased significantly from 73 to 31 (0–100 VAS) in the SCS
group, but remained unchanged at 67 in the control group (Fig. 2). Improvements in quality of life measures were also observed. In a recent observational study that compared conventional tonic stimulation with burst stimulation, the latter led to a significant additional 44% pain reduction on average in patients with PDN. 10

Other Neuropathic Pain States

SCS is used to treat several other neuropathic pain states, such as post-amputation stump and phantom pains, postherpetic neuralgia, spinal cord injury, and other traumatic peripheral neuralgias. The evidence for effectiveness of SCS in these pain states has not been carefully evaluated in controlled trials and is based primarily on observational studies in small groups of subjects.

Predictors of Success

The success of SCS for neuropathic pain may depend on appropriate patient selection. Psychological traits may play an important role in modeling individual differences in the pain experience. Hence, psychological screening might be useful in helping to predict which patients are likely to benefit from SCS. 4 In addition, preliminary studies suggest that quantitative sensory testing may help physicians determine the sensory phenotype and the mechanism of pain in patients with neuropathic pain as well as their responses to SCS. 3 Studies are needed to further explore whether strict patient selection based on psychological and sensory profiles can reduce the failure rate of SCS.

Peripheral Nerve/Field Stimulation

Peripheral nerve stimulation (PNS), first described nearly 50 years ago, has recently become more attractive after the development of a percutaneous technique. 26,41 PNS has been used for a variety of chronic neuropathic pain states, such as postsurgical neuralgias, post-traumatic neuralgia, occipital neuralgia, and postherpetic neuralgia (for review see Petersen and Slavin 36). PNS has also been used to alleviate a variety of headaches, including chronic daily headaches, cluster headaches, and migraine, and to treat CRPS. Most studies reporting benefits of PNS have been uncontrolled case series. A randomized, double-blind, controlled trial of occipital nerve PNS for migraine failed to meet its primary endpoint (difference in responders, defined as patients who achieved a ≥50% reduction in mean dailyVAS scores). 27 However, the authors did find significant reductions in pain, headache days, and migraine-related disability. Peripheral nerve field stimulation in the region of maximal pain has also been used alone or in combination with SCS, particularly for chronic axial low back pain. 2,24 Although the devices used for PNS are “off-label” in the United States, they are approved in Europe for the treatment of intractable migraine and chronic low back pain.

Dorsal Root Ganglion Stimulation

Although traditional SCS has shown effectiveness in certain pain states, reports suggest that 30–40% of patients fail to achieve adequate pain relief or experience a reduction in effectiveness with time. Recently, the dorsal root ganglion (DRG) has emerged as a potential target for treating chronic neuropathic pain. 26 Experts hypothesize that, relative to traditional SCS, stimulation of sensory neurons in the DRG may result in more precise and selective stimulation, thereby reducing unwanted side effects observed with traditional SCS. 26 Some authors postulate that DRG stimulation may be

Timely topics in pain research and treatment have been selected for publication, but the information provided and opinions expressed have not involved any verification of the findings, conclusions, and opinions by IASP. Thus, opinions expressed in Pain: Clinical Updates do not necessarily reflect those of IASP or of the Officers or Councilors. No responsibility is assumed by IASP for any injury and/or damage to persons or property as a matter of product liability, negligence, or from any use of any methods, products, instruction, or ideas contained in the material herein.

Because of the rapid advances in the medical sciences, the publisher recommends independent verification of diagnoses and drug dosages.
or CRPS. The study’s results, which will include safety and efficacy endpoints and responder rate analysis, may help to determine the efficacy of DRG stimulation in this population.

Motor Cortex and Noninvasive Brain Stimulation

Motor cortex stimulation is based on an observation nearly 25 years ago by Tsubokawa et al.\textsuperscript{44} that stimulation of the precentral gyrus below motor threshold relieves pain in patients with thalamic pain. A number of subsequent clinical observations have shown efficacy in trigeminal neuropathic pain and deafferentation syndromes such as poststroke pain and pain resulting from spinal cord injury or brachial plexus injuries (for reviews see Sukul and Slavin\textsuperscript{45} and Moore et al.\textsuperscript{25}). Although more than 50% of patients appear to respond to motor cortex stimulation during the first few months, the pain relief may wane over longer periods of time.\textsuperscript{17,40}

Noninvasive brain stimulation techniques include repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), cranial electrotherapy stimulation (CES), and reduced impedance noninvasive cortical stimulation (RINCE; for recent reviews, see O’Connell et al.\textsuperscript{35} and Young et al.\textsuperscript{50}). In contrast to conventional electrical stimulation that is likely to reach only the most superficial layers of the cortex, the magnetic field created by rTMS passes through the scalp and cranium to excite or inhibit various cortical and subcortical neural networks. Similar beneficial results were observed in a group of subjects with lower-extremity CRPS (8 of 11 trialed subjects received device implants) who were followed for a year.\textsuperscript{46} Several recent abstracts presented at the North American Neuromodulation Society also suggest promising benefits of DRG stimulation in mixed neuropathic pain states that are worthy of further investigation. Huygen et al.\textsuperscript{18} reported pooled data from prospective studies in Europe of 19 patients with upper-limb neuropathic pain of various etiologies and showed mean reductions in pain of 54.6% and 58.6% at 3 and 6 months, respectively, with concurrent improvements in quality of life.

Recently, 152 patients were enrolled in a prospective, randomized, multicenter, controlled trial (ACCURATE Trial) designed to evaluate the safety and efficacy of a DRG stimulation device for treatment of chronic lower-limb pain caused by nerve injuries (causalgia) or CRPS. The study’s results, which will include safety and efficacy endpoints and responder rate analysis, may help to determine the efficacy of DRG stimulation in this population.

![Fig. 3. Lead placement for dorsal root ganglion stimulation.](image-url)
stimulation parameters, and the duration of stimulation. Reviewers postulate that high-frequency (>5 Hz) stimulation leads to increased cortical excitability and a reduction in cortical inhibition, whereas low-frequency stimulation (≤1 Hz) causes a transient reduction in cortical excitability without affecting cortical inhibition. Although several reports of uncontrolled trials suggest that rTMS of the motor cortex (M1) has beneficial effects in various central and peripheral neuropathic pain states, results of controlled trials have been mixed. A recently updated Cochrane review included 56 trials (1710 randomized subjects): 30 studies of rTMS, 11 of tDCS, 14 of tDCS, and one study of RINCE. Several studies included a mixture of central, peripheral, and facial neuropathic pain states of various etiologies. The authors concluded that single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain (12%; 95% CI, 8–15%). In addition, multiple-dose studies failed to consistently demonstrate effectiveness, and low-frequency rTMS, rTMS applied to the prefrontal cortex, CES, and tDCS were ineffective in the treatment of chronic pain. The primary advantage of these techniques is their excellent safety profile, but the evidence for efficacy is inconclusive and the magnitude of beneficial effects failed to meet the threshold of minimal clinical significance (≤15%) in the systematic review. Some have suggested that rTMS can be used as a complementary therapy in patients with chronic refractory neuropathic pain syndromes. A recent evidence-based guideline concluded that “there is a sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain.” Relative contraindications of TMS include a history of epilepsy and the presence of aneurysm clips, deep brain electrodes, and cochlear implants.

Deep Brain Stimulation

Deep brain stimulation (DBS) is an accepted treatment for disorders like Parkinson’s disease that are associated with motor signs such as rigidity, bradykinesia, and tremor. The use of chronic intracranial stimulation for pain, however, remains controversial. Various DBS sites, including the internal capsule, various nuclei in the sensory thalamus, the periaqueductal and periventricular gray, the motor cortex, septum, nucleus accumbens, posterior hypothalamus, and anterior cingulate cortex, have been examined as potential brain targets for pain control. The effectiveness of DBS has been the subject of case series in diverse etiologies of chronic pain, but results have been inconsistent. Two multicenter trials of DBS for chronic pain conducted in the 1990s failed to demonstrate long-term beneficial effects. Thus, current evidence is inconclusive for determining the role of DBS in the treatment of neuropathic pain. Ongoing, better-controlled trials may shed more light on its role as a therapeutic alternative (see review by Keifer et al. for details).

Conclusions

The clinical literature now spans more than three decades on the clinical use of spinal cord stimulation to treat chronic neuropathic pain. Although the evidence is “weak” on the efficacy of this important therapy, this does not imply that it is not an effective therapy. The “weak” evidence is not the result of failed trials but rather a consequence of difficulties in successfully conducting controlled clinical trials with interventional therapies. This problem stresses the need for alternative methods such as large registries to study the indications and clinical benefits of this important therapy. Nonetheless, more recent, well-conducted studies support both the efficacy and cost-effectiveness of this therapy in several neuropathic pain syndromes.

Although SCS has dominated the field of stimulation over the past three decades, improvements in SCS technology as well as new stimulation therapies are emerging that should prove to be an important addition to our stimulation armamentarium. These new therapies are not likely to replace SCS, but rather will supplement it or treat patients not responsive to traditional SCS. By expanding the horizon of stimulation techniques, we will continue to successfully treat an increasing proportion of neuropathic pain patients who currently have limited options.

References