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The Appropriate Use of Neurostimulation of the Spinal Cord and Peripheral Nervous System for the Treatment of Chronic Pain and Ischemic Diseases: The Neuromodulation Appropriateness Consensus Committee

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Introduction: The Neuromodulation Appropriateness Consensus Committee (NACC) of the International Neuromodulation Society (INS) evaluated evidence regarding the safety and efficacy of neurostimulation to treat chronic pain, chronic critical limb ischemia, and refractory angina and recommended appropriate clinical applications.

Methods: The NACC used literature reviews, expert opinion, clinical experience, and individual research. Authors consulted the Practice Parameters for the Use of Spinal Cord Stimulation in the Treatment of Neuropathic Pain (2006), systematic reviews (1984 to 2013), and prospective and randomized controlled trials (2005 to 2013) identified through PubMed, EMBASE, and Google Scholar.

Results: Neurostimulation is relatively safe because of its minimally invasive and reversible characteristics. Comparison with medical management is difficult, as patients considered for neurostimulation have failed conservative management. Unlike alternative therapies, neurostimulation is not associated with medication-related side effects and has enduring effect. Device-related complications are not uncommon; however, the incidence is becoming less frequent as technology progresses and surgical skills improve. Randomized controlled studies support the efficacy of spinal cord stimulation in treating failed back surgery syndrome and complex regional pain syndrome. Similar studies of neurostimulation for peripheral neuropathic pain, postamputation pain, postherpetic neuralgia, and other causes of nerve injury are needed. International guidelines recommend spinal cord stimulation to treat refractory angina; other indications, such as congestive heart failure, are being investigated.

Conclusions: Appropriate neurostimulation is safe and effective in some chronic pain conditions. Technological refinements and clinical evidence will continue to expand its use. The NACC seeks to facilitate the efficacy and safety of neurostimulation.

Keywords: Angina pectoris, chronic pain, complex regional pain syndrome, failed back surgery syndrome, high-frequency electrical stimulation, ischemic pain, neuropathic pain, nociceptive pain, phantom limb pain, postherpetic neuralgia, Reynaud's syndrome, spinal cord stimulation

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INTRODUCTION

Spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS) have become important tools in the management of otherwise intractable pain, including pain caused by pathology in the central or peripheral nervous systems. The recognition of the appropriateness of using these devices for the control of chronic pain and other chronic diseases is evolving and is often obscured by poor understanding of the physiological mechanisms of the diseases or the mechanisms of the therapies themselves, uncontrolled research data, poor patient selection, and lack of appropriate outcome measures. Uninformed insurance carriers, lack of properly trained implanters, and lack of standardized credentialing are barriers to the appropriate use of neurostimulation.

The need to better define the appropriateness of the use of these advanced therapeutic tools was identified by the International Neuromodulation Society (INS), leading to the formation of the Neuromodulation Appropriateness Consensus Committee (NACC). The NACC was formed to evaluate current literature and best practice, to collect expert opinions, and to give guidance to physicians, other health-care providers, and payors on the appropriateness of PNS and SCS for chronic disease and pain. The goal of this endeavor is to improve patient care for those afflicted with these chronic conditions.

This article is the first of four companion articles analyzing the world literature and the practice of neuromodulation for chronic pain. The International Association for the Study of Pain (IASP) defined chronic pain as "ongoing or recurrent pain lasting beyond the usual course of acute illness or injury or more than three to six months, and which adversely affects the individual's well-being. Chronic pain can exist as a condition in its own right, or as a component of other long-term conditions" (1). The INS has also convened working groups on the appropriate use of neuromodulation for the treatment of pain in the head and face (2), the reduction of complications and improved care in patients with untoward outcomes (3), and the future development and use of new technologies, devices, and neural circuitry (4).

Why Analysis Is Important

In 1972, the eminent British epidemiologist Archie Cochrane (1909–1988) published *Effectiveness and Efficiency; Random Reflections on the Health Services*, an influential book in which Cochrane argued that the scarce existing resources for health care can be managed efficiently only if we know which treatments are effective and which are not (5). As a result of Cochrane's argument, the concept of evidence-based medicine (EBM) was developed by Gordon Guyatt at the McMaster School of Medicine (Canada) in 1980 (6). EBM is defined as "the conscious, explicit and judicious use of the best current evidence in making decisions about the care of individual patients." "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice" (7,8). Table 1 presents one of several evidence classification scales that have been developed from which recommendations have been made regarding the adoption of certain medical procedures or surgical interventions (9).

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force) (9).

Evidence level	Study type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experience
III	Clinical experience-based opinions, descriptive studies, clinical observations, or reports of expert committees

In today's clinical practice, it is vital that our use of treatments for pain and disease, including the use of devices, be based on the best medical evidence available. In cases where there is little or no available evidence, experts in the field should render their collective opinion regarding best practice to improve overall patient care. The arguments against EBM are that the ability to study treatments often lags well behind the clinical practice of medicine and that the ability to control confounding factors in pain and disease management can be very difficult. This quandary has led to the need for

Table 2. Level of Certainty Regarding Net Benefit Based on Evidence Strength (9).

Level of certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. Inconsistency of findings across individual studies. Limited generalizability of findings to routine practice. Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of • the limited number or size of studies;. • important flaws in study design or methods; • inconsistency of findings across individual studies; • gaps in the chain of evidence; • findings not generalizable to routine practice; • lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Table 3. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force) (9).

Degree of recommendation	Meaning
A	Extremely recommendable (high-level evidence that the measure is effective and benefits outweigh the harms)
B	Recommendable (at least moderate evidence that the measure is effective and benefits exceed harms)
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low-quality, or contradictory evidence; the balance between benefit and harms cannot be determined

Table 4. Evidence Rankings From the Centers for Disease Control and Prevention (12).

IA	Strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiological studies
IB	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and strong theoretical rationale
II	Suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale
No recommendation/ unresolved issue	Practices for which insufficient evidence or no consensus regarding efficacy exists

consensus of expert opinion. In this paper, we will review pertinent literature and render our expert opinion/recommendations on the use of neuromodulation therapies for chronic pain.

How Consensus Was Developed

The INS reviewed the initial published development of evidence-based and consensus-based guides when forming the NACC. The first scientific evidence guide was developed in 1979 and published in 1980 by the Canadian Task Force on the Periodic Health Examination to evaluate preventive measures (10) and was adapted in 1984 by the U.S. Preventive Services Task Force (USPSTF). In the third USPSTF edition, published in 2001, evidence quality was assessed by taking into account not only the design of studies but also the net benefit obtained from the application of a procedure or treatment to patients (9). Currently, the Centre for Evidence-Based Medicine at Oxford University (Oxford, UK) considers as evidence not only therapeutic and preventive procedures, but also other variables connected to diagnostics, prognostics, risk factors, and economic evaluation (11).

Evidence Synthesis

Differing EBM grading systems (9,12) are used in our analysis and grading of levels of evidence for neuromodulation therapies. The criteria listed in Table 1, developed by the USPSTF, base the highest evidence level on randomized controlled trials (RCTs) and the lowest on clinical experience-based opinions or expert committees. Table 2 establishes criteria for levels of certainty regarding net benefits. Table 3 defines the meanings of various degrees of recommendation. Table 4 lists evidence rankings established by the Centers for Disease Control and Prevention (CDC) and applied in our analysis to perioperative practices.

When literature support is lacking, expert opinion and clinical experience should be called upon to fill the void. As an example, there have been no randomized placebo-controlled trials comparing surgical morbidity for patients with and without preexisting systemic infections. Common sense and clinical experience overwhelmingly suggest intervention is safer in those without a preexisting infection, although formal literature support is lacking. Similar scenarios commonly occur in medicine; expert consensus and common sense are important to fill the void.

The highest level of evidence often is not applicable to individual patients in clinical practice. RCTs are excellent methods for collecting data, removing bias, and answering questions in selected subsets of patient populations, but often the results cannot be generalized. RCTs can thus inform clinical decisions only for a limited number of standardized therapies for treating subsets of patients with common chronic pain conditions. Patients' treatment must be

individualized, and lack of the highest level of evidence should not override good clinical judgment. Restricting treatments to those with the highest level of evidence compromises not only patient care but also technological progress and innovation.

TERMINOLOGY

The INS defines therapeutic neuromodulation as "the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body" (13). Neurostimulation devices stimulate nerves, modulating abnormal neural activity caused by disease or injury. Depending on the target for neurostimulation, the resulting effects might include but are not limited to relief of pain; restoration of function; control of seizures, tremor, or spasticity; and improvement in quality of life (QOL) (14).

Taxonomy of Pain

SCS, PNS, and peripheral nerve field stimulation (PNfS, electrical stimulation of the end "fields" of peripheral nerves) have been utilized traditionally for pain described as neuropathic or mixed neuropathic/nociceptive in nature. It is the opinion of the NACC that before utilizing neuromodulation devices, the physician should understand the terms used to describe the experience of pain.

Neuropathic Pain

Neuropathic pain is defined as pain originating from nerve damage or altered nerve function. It is mediated by numerous neurotransmitters/receptors and typically described as burning, tingling, shooting, and/or electric. Neuropathic pain is aberrant and not normal. Neuropathic pain is often opioid-resistant or requires higher doses of analgesics to achieve relief but may respond to antiepileptic and antidepressant medications acting on shared mechanisms (15,16).

Neuropathic pain predominates in certain disease states and syndromes. Straightforward examples of neuropathic pain in cancer patients include neuritis caused by radiation therapy, chemotherapy-induced neuropathy, brachial plexus invasion due to lung cancer, and tumor compression of nerves or the spinal cord. Non-cancer-related neuropathic pain conditions include, among others, spinal nerve root injury, peripheral nerve injury, complex regional pain syndrome types I and II (CRPS-I and CRPS-II), postherpetic neuralgia (PHN), peripheral neuropathy (idiopathic or diabetic), central neuropathic pain from stroke or multiple sclerosis (MS), spinal cord injury, and ischemia leading to nerve degeneration.

Nociceptive Pain

Nociceptive pain is expected as the result of normal pain-processing mechanisms; it serves a biologic purpose by alerting the body to noxious input and elicits appropriate behavioral responses. Nociceptive pain is mediated by Aδ and C nociceptive fibers activated by mechanical, chemical, or thermal irritation. It is typically described as aching, dull, throbbing, or sharp pain. Nociceptive pain is often divided into categories of somatic and visceral pain. Nociceptive pain can be seen in certain disease states and conditions such as soft tissue trauma, arthritis, pancreatitis, inflammation, and metastatic cancer. Although animals observed in nociceptive pain models can respond to SCS and PNS, it has been difficult to establish this response in humans (17).

Mixed Pain

Many clinical pain states are neither exclusively neuropathic nor exclusively nociceptive. Patients with heterogeneous pain patterns with both neuropathic and nociceptive pain may be considered to have "mixed" pain. Examples of mixed pain include chronic pelvic pain, tumor invasion of the bony spine with simultaneous neural compression, and perhaps many cases of failed back surgery syndrome (FBSS).

Dysfunctional Pain

In some pain conditions the diagnosis and etiology are unclear in that there is no identifiable noxious stimulus (e.g., fibromyalgia), inflammation (e.g., interstitial cystitis), or damage to the nervous system (e.g., irritable bowel syndrome). Our understanding of "dysfunctional pain" syndromes is growing. For example, fibromyalgia has been attributed to a deficit of endogenous pain inhibitory systems, and it has been speculated that it might be treated by stimulation (18,19), but evidence for this remains to be presented. The best evidence for neuromodulation has been in conditions with well-understood diagnostic criteria and mechanisms.

NEUROMODULATION TARGETS AND STIMULATION MODES

Spinal Cord Stimulation

The treatment of pain by applying electrical currents to the spinal cord, initially called dorsal column stimulation (DCS) and now, by wide consensus, spinal cord stimulation (SCS), is delivered by electrodes over the dorsal columns of the spinal cord so as to modulate pain generation or processing. The goal of conventional SCS (<1 kHz) is to replace the experience of pain with pleasant paresthesias in the same location. High-frequency SCS at 10 kHz (HF10-SCS, Nevro Corp., Menlo Park, CA, USA), hereafter called 10-kHz-frequency SCS, is said to provide pain relief without generating paresthesias (20,21). SCS at 500 Hz delivered in "bursts" of five pulses 40 times per second is an intermediate or hybrid strategy that reportedly affords relief while minimizing paresthesia (22).

SCS has evolved from simple monopolar or bipolar configurations to complicated electrode arrays delivered either by percutaneously placed cylindrical platforms or surgically placed paddle platforms. Table 5 lists neurostimulators and stimulation leads currently available globally.

The established evidence that most strongly supports neuromodulation for pain is based largely on conventional SCS, although recent studies on the use of high-frequency and burst SCS and on SCS of the dorsal root ganglion (DRG), hereafter called DRG stimulation, have led to the generation of new evidence and may shift the treatment paradigm in the future (20–25).

Stimulation Modes

Since its inception as a therapy for chronic pain, SCS has been performed using biphasic, charge-balanced stimulation at frequencies that typically range from 30 to 100 Hz and that are generally below 300 Hz, which was previously considered to be the highest physiological response rate of neural tissue (22).

Burst Stimulation

There are preclinical data suggesting that Aδ, Aβ, and C fibers are preferentially activated at specific current frequencies when a sinusoidal (as opposed to square-wave) electrical stimulation is applied (22,26). This knowledge has been translated into a clinical application by De Ridder et al., who published initial results of SCS in a burst pattern (22). Using modified commercially available SCS systems to deliver 40-Hz bursts with five spikes at 500 Hz per burst at a rate of

Table 5. Commercially Available Neurostimulators and Leads.

Company	Device	Device type	Target	Approvals
BioControl Medical	CardioFit	Responsive stimulation of right vagus nerve	Right vagus nerve	EU
Bioness	H200 Wireless	Noninvasive prosthesis for functional electrical stimulation	Arm flexor, extensor muscles	EU, US
Bioness	L300	Noninvasive prosthesis for functional electrical stimulation	Peroneal nerve, anterior tibialis	EU, US
Bioness	L300 Plus	Noninvasive prosthesis for functional electrical stimulation	Quadriceps or hamstring	US
Bioness	StimRouter	External pulse transmitter, implanted lead	Median nerve	Pending US
Boston Scientific	Artisan 2 × 8 Surgical Lead	Paddle lead with 16 electrodes	Spinal cord	AU, CA, EU, US
Boston Scientific	Infinion 16 Lead	Cylindrical lead with 16 electrodes	Spinal cord	AU, CA, EU, US
Boston Scientific	Linear 8 Contact Lead	Cylindrical lead with 8 electrodes; 6-, 4-, or 1-mm spacing	Spinal cord	AU, CA, EU, US
Boston Scientific	Precision Plus	Rechargeable, constant-current IPG	Spinal cord	AU, CA, EU, US
Boston Scientific	Precision Spectra	IPG	Spinal cord	EU
Boston Scientific	Vercise	IPG	Brain	AU, EU
Cerbomed	NEMOS	Transcutaneous vagus nerve stimulator	Vagus nerve	EU
CerebralRx	FitNeS	IPG	Left vagus nerve	EU
CVRx	Barostim Neo	IPG	Right carotid artery	EU
CVRx	Rheos	IPG	Carotid arteries	EU
Cyberonics	VNS Therapy Generators	IPG	Left vagus nerve	CA, EU, US
Cyberonics	VNS Therapy Leads	Leads	Left vagus nerve	CA, EU, US
EndoStim	EndoStim	IPG	Lower esophageal sphincter	EU
EnteroMedics	Maestro RC	Rechargeable high-frequency IPG	Vagus nerve	AU, EU
EnteroMedics	Maestro RC leads	Anterior and posterior leads	Vagus nerve	AU, EU
ImThera	aura6000	Rechargeable IPG	Hypoglossal nerve	EU
IntraPace	abiliti	IPG	Stomach	EU
Medtronic	1 × 4 Percutaneous Leads	Cylindrical lead with four electrodes; 12-, 6- or 4-mm spacing	Spinal cord	AU, CA, EU, US
Medtronic	1 × 8 Percutaneous Leads	Cylindrical lead with eight electrodes; 6-, 4- or 1.5-mm spacing	Spinal cord	AU, CA, EU, US
Medtronic	4-Electrode Surgical Leads	Paddle lead with four electrodes	Spinal cord	AU, CA, EU, US
Medtronic	8-Electrode Surgical Leads	Paddle lead with eight electrodes	Spinal cord	AU, CA, EU, US
Medtronic	16-Electrode Surgical Leads	Paddle lead with 16 electrodes	Spinal cord	AU, CA, EU, US
Medtronic	Activa PC	Dual-channel, nonrechargeable, constant-current/voltage IPG	Brain	AU, CA, EU, US
Medtronic	Activa RC	Dual-channel, rechargeable, constant-current/voltage IPG	Brain	AU, CA, EU, US
Medtronic	Activa SC	Single-channel, nonrechargeable, constant-current/voltage IPG	Brain	AU, CA, EU, US
Medtronic	DBS Lead 3387	Cylindrical lead with four electrodes, 1.5-mm spacing	Brain	AU, CA, EU, US
Medtronic	DBS Lead 3389	Cylindrical lead with four electrodes, 0.5 mm spacing	Brain	AU, CA, EU, US
Medtronic	Enterra	Nonrechargeable IPG	Stomach muscle	CA, EU, US
Medtronic	InterStim & InterStim II	Nonrechargeable IPG	Sacral nerve	AU, CA, EU, US
Medtronic	Itrel 4	Nonrechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	PrimeAdvanced	Nonrechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	RestoreAdvanced	Rechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	RestorePrime	Nonrechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	RestoreSensor	Rechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	RestoreUltra	Rechargeable constant-voltage IPG	Spinal cord	AU, CA, EU, US
Medtronic	Tined Leads 3889 & 3093	Cylindrical lead with four electrodes; 1.5- or 3.0-mm spacing	Sacral nerve	AU, CA, EU, US
Medtronic	Unipolar Intramuscular Lead	10-mm electrode	Stomach muscle	CA, EU, US
NeuroPace	RNS System	Responsive neurostimulator	Cortex	US
Neurostream	Neurostep	IPG	Leg peripheral nerves	EU
Nevro	8-Contact Percutaneous Leads	Cylindrical lead with eight electrodes	Spinal cord	EU
Nevro	Senza HF-SCS	Rechargeable high-frequency IPG	Spinal cord	EU
Second Sight	Argus II	Epiretinal prosthesis	Retina	EU
Spinal Modulation	Axium	Constant-voltage IPG	Spinal cord, dorsal root ganglion	AU, EU
Spinal Modulation	Axium Leads	Cylindrical leads	Spinal cord, dorsal root ganglion	AU, EU
St. Jude Medical	1-Column Paddle Lead	Paddle lead	Spinal cord	AU, EU, US
St. Jude Medical	2-Column Paddle Lead	Paddle lead	Spinal cord	AU, EU, US
St. Jude Medical	3-Column Paddle Lead	Paddle lead	Spinal cord	AU, EU, US
St. Jude Medical	5-Column Paddle Lead	Paddle lead	Spinal cord	AU, EU, US
St. Jude Medical	Brio	Rechargeable, dual-channel, constant-current IPG	Brain	AU, EU
St. Jude Medical	DBS Leads	Cylindrical lead with four electrodes; 1.5- or 0.5-mm spacing	Brain	AU, EU
St. Jude Medical	Eon	Rechargeable constant-current IPG	Spinal cord	AU, EU, US
St. Jude Medical	Eon	Rechargeable constant-current IPG	Peripheral nerves	AU, EU
St. Jude Medical	EonC	Nonrechargeable constant-current IPG	Spinal cord	AU, EU, US
St. Jude Medical	EonC	Nonrechargeable constant-current IPG	Peripheral nerves	AU, EU
St. Jude Medical	Eon Mini	Rechargeable constant-current IPG	Spinal cord	AU, EU, US
St. Jude Medical	Eon Mini	Rechargeable constant-current IPG	Peripheral nerves	AU, EU
St. Jude Medical	Genesis	Nonrechargeable IPG	Spinal cord	AU, EU, US
St. Jude Medical	Genesis	Nonrechargeable IPG	Peripheral nerves	AU, EU
St. Jude Medical	Libra	Single-channel, constant-current, nonrechargeable IPG	Brain	AU, EU
St. Jude Medical	Libra XP	Dual-channel, constant-current, nonrechargeable IPG	Brain	AU, EU
St. Jude Medical	Percutaneous Leads	Cylindrical lead	Spinal cord	AU, EU, US
St. Jude Medical	Percutaneous Leads	Cylindrical lead	Peripheral nerves	AU, EU

AU, Australia, CA, Canada; DBS, deep brain stimulation; EU, European Union; IPG, implantable pulse generator; US, United States.

40 bursts per second, they reported persistent (at 20.5 months) equivalent or better pain relief in patients with chronic neuropathic pain compared with conventional tonic stimulation, without the production of paresthesia in more than 80% of cases (27). These results were confirmed by a randomized placebo-controlled trial in 15 patients with low back and leg pain. These early studies using burst frequencies for the control of pain are promising and suggest that the algorithm for SCS may evolve to include this novel waveform (28).

Kilohertz-Frequency SCS

High-frequency SCS using 10-kHz frequencies of stimulation, called 10-kHz-frequency SCS, might expand the utility of SCS, particularly for nociceptive or mixed axial pain components (21). Pain control reportedly is achieved, as with burst stimulation, without the production of paresthesia, and coverage of the patient's painful areas reportedly is not required. Van Buyten et al. were the first group to publish their results in 83 patients using the SENZA SCS device (Nevro Corp.), commercially available in Europe and Australia, which delivers stimulation over the spinal cord at a frequency of 10 kHz with a short pulse width and sinusoidal waveform (20). Their two-center uncontrolled case series of patients with "difficult-to-treat" low back and leg pain suggests that 10-kHz SCS can provide significant analgesia in >70% of patients without generating paresthesia. Initial reports suggest electrode targeting may be less specific than targeting for conventional SCS and thus less likely to be impacted by electrode migration (20). The same group recently reported their results after two years of follow-up (29). High-frequency stimulation resulted in significant and sustained back and leg pain relief, functional and sleep improvements, opioid use reduction, and high patient satisfaction. Another recent case series reported by Tiede et al. found that there was significant improvement from baseline in overall and back pain scores ($p < 0.001$) and that 88% (21/24) of patients preferred the 10-kHz-frequency SCS system to currently available and conventional SCS technology (21).

The efficacy of high-frequency SCS has been challenged. A trial performed with commercially available systems that were modified to deliver monotonic stimulation at 5 kHz failed to show benefit of 5-kHz-frequency SCS over placebo. Using an RCT design, Perruchoud et al. studied 40 patients with implanted SCS systems for low back and leg pain (30). This study used 5-kHz-frequency SCS, a pulse width of 60 μsec, and monophasic pulses delivered with intensities set below perception. Patient global impressions of change (main outcome), pain intensity (measured by visual analogue scale or VAS), and QOL (measured by EQ-5D) were not observed to be different from 5-kHz-frequency SCS compared with sham stimulation (no stimulation, placebo) in the study population as a whole.

Multiple factors could explain these different clinical results regarding kilohertz-frequency spinal cord current delivery. Most importantly, in the Perruchoud study (30), all patients had prior successful experience with conventional SCS at frequencies producing paresthesia, which neither the sham group nor the 5-kHz-frequency group experienced. It is generally accepted that paresthesias are required for efficacy when conventional frequencies of stimulation are used for SCS, and all patients in the Perruchoud study were most probably conditioned to this coupling of paresthesia with success of therapy. Other factors that might explain these differing clinical results include 1) the possibility that 10-kHz-frequency SCS is efficacious but 5 kHz is not; 2) that study design flaws (study bias) existed in one or both of the investigations; 3) that there are differing amounts of electrical energy delivered to the spinal cord by each system; and 4) that the leads in each study were placed in different areas of the spinal cord.

Shechter et al. compared the inhibitory effect on mechanical hypersensitivity from bipolar SCS of different intensities (20%, 40%, and 80% of the motor threshold) and frequencies (50 Hz, 1 kHz, and 10 kHz) in a rat model of neuropathic pain (31). This study showed that SCS analgesia in rats depends on both intensity and frequency of stimulation, and high-intensity, kilohertz-level SCS provided earlier inhibition of mechanical hypersensitivity than conventional 50-Hz SCS. Importantly, pain inhibition resulting from kilohertz and 50-Hz SCS may involve different peripheral (afferent conduction property change) and spinal segmental (dorsal horn neuronal inhibition) mechanisms, though elucidating the exact mechanisms will require additional research.

Given that two clinical studies at 10-kHz-frequency SCS show significant efficacy (20,21) and that one preclinical study shows that kHz-frequency stimulation is better than conventional stimulation in increasing reduced paw thresholds to mechanical stimulation in sciatic-nerve-injured rats (31), further study is recommended by the NACC, specifically a prospective RCT comparing 10-kHz-frequency SCS to conventional-frequency SCS in SCS-naïve patients. Given the reported results of burst SCS, the NACC recommends that it be studied in the same fashion. Although paresthesias are assumed essential for pain relief when using conventional SCS (32,33), paresthesia can be uncomfortable for some patients, and side effects limit the acceptable amplitude of stimulation (34). Pain relief without paresthesia in patients who do not respond to or tolerate conventional SCS would expand the role of SCS. Ideally, a single implant should be capable of delivering all modes of SCS.

Paresthesias with conventional SCS have posed an additional problem for clinical trials by compromising masked study designs. Masking is among the criteria for the highest-quality clinical trials (35), and this has limited the evidence base for SCS. Burst and kilohertz-frequency stimulation are potential solutions to the paresthesia problem.

The NACC feels that prospective, randomized, and well-controlled studies with novel SCS therapies will expand the field and change the practice of neuromodulation. Currently, multicenter randomized studies are under way in the USA.

STIMULATION OF THE SPINAL CORD BY REGION

Neuromodulation, and specifically SCS, has been applied effectively to treat chronic pain in many areas of the body. The lessons learned from clinical practice have influenced neurostimulator lead design, placement, and programming. The NACC considered these issues in our evaluation.

Anatomic Considerations

Although the spinal cord is generally considered a single entity, it possesses distinct regional anatomical differences, which affect the placement of leads for optimal coverage/pain control as well as the potential complications associated with neurostimulation. The size and shape of the spinal canal and spinal cord, the position of the cord within the canal, and the amount of cerebrospinal fluid (CSF) in a particular region vary at each level of the vertebral spinal column. In addition, neural and nonneural tissues within the spine respond differently to stimulation. Thus, epidurally applied electric current must travel through low-impedance tissues (such as CSF) before reaching higher-impedance tissues (such as the spinal cord). In addition, the diameter of CSF within the thecal sac at different areas

of the spinal column, which is typically smallest at C6 and greatest at T6 (36), affects the delivery of current to targeted tissues. Patients may experience this clinically as changes in posture alter their perception of stimulation, paresthesia, and pain relief.

The Cervical Spine

The spinal cord becomes wider and thicker in the mid-to-lower cervical spine, where the brachial plexus emerges to support sensory and motor functions of the arms and hands. This area of the cervical spine is also more mobile than the upper cervical spine and thus more vulnerable to varying paresthesias from conventional SCS as the neck moves. This increase in mobility of the cervical spine is also a risk factor for cervical lead migrations, which are thought to be more frequent than in the lower part of the spinal column. Newer anchoring techniques and anchors may challenge this long-held perception for the better.

Although cervical lead placement can be performed using percutaneous cylindrical leads, it can also be performed with open laminotomy at the desired location using paddle leads. Percutaneous leads are most often introduced through a needle between T1 and T4 and advanced to desired cervical levels. Some clinicians prefer to enter the epidural space at the upper lumbar spine levels, advancing the catheter with a long lead to the desired target level in the cervical spine. This technique is not always successful; as the lead is advanced and its intraspinal length increases level by level, the cumulative drag and thus resistance to insertion increase progressively, to the point that the lead can buckle.

The Thoracic Spine

The relative immobility of the thoracic spine because of spinal fixation to the ribs makes lead migration less likely. Most typically, lead placement in the midthoracic region at T8–T9 targets pain in the lower back and legs. Effective stimulation for visceral pain, PHN, intercostal neuralgia, angina, and pancreatitis can be achieved with lead placement in the mid-to-high thoracic region. The thoracic spine is convex dorsally, with the apex usually in the midthoracic area. The dorsal CSF diameter is largest at T5, making thresholds higher; stimulation there can be especially subject to postural changes (37).

The Lumbar Spine

Pain in the lower back and lower extremities is commonly treated by lead placement between T7 and T12. Placement of the lead at L1 can direct current over the conus medullaris and/or cauda equina rather than the spinal cord. This may be helpful for pelvic pain, foot pain, and pain of the sacrum (14,38). Spinal nerves at the end of the spinal cord float freely within the CSF and are, therefore, particularly affected by postural changes and movement, which can compromise stability of stimulation (39).

Practical Considerations

Preoperative and intraoperative imaging can reveal the regional and individual differences in spinal anatomy that affect choice of entry level and lead and implantable pulse generator (IPG) placement. Preoperative images should be examined carefully for changes that could complicate or impede lead placement, especially as skin entry is often as much as two levels below spinal entry. As examples, a previous laminectomy in the cervical or lumbar regions or tight interlaminal spacing (as in the elderly with advanced degenerative disk disease) can make passing a lead posteriorly difficult or impossible. Anterior discectomy, which does not involve the dorsal epidural space, is less likely to cause this problem. A large herniated disk alone or in combination with ligamentum flavum hypertrophy, as in spinal stenosis, can obliterate the epidural space, and spinal stenosis or scoliosis may change the spinal dimensions and the distances stimulation must traverse. Significant stenosis may increase the risk for cord compression from the implanted lead and should be considered in electrode selection and procedure planning.

It is also important to note that the radiologic midline of the spine often differs from the physiologic midline. Consequently, leads placed strictly by anatomic (fluoroscopic) guidance may not optimally stimulate the desired physiologic targets. Wide paresthesia coverage and postimplantation programming adjustments may partially compensate for suboptimal lead placement, but careful preoperative planning and careful initial intraoperative lead placement are ideal and sometimes essential to long-term success of the therapy. Preoperative planning should also include decision-making regarding IPG placement as it relates to cosmesis, bony landmarks, body shape, where the patient wears his or her clothing, and joint mobility.

Cervical vs. Thoracic Spinal Cord Stimulation

Background

Cervical SCS has been performed successfully in thousands of patients, although it has been studied less frequently than thoracolumbar SCS. A number of studies have examined the effects and complications of cervical SCS, mostly for the treatment of upper-extremity neuropathic pain. Cervical SCS has been questioned by payors, who might have misinterpreted the labeling of SCS for "pain of the trunk and limbs" by the Food and Drug Administration (FDA) as applying only to the lower limbs and low back. There is limited but substantial evidence of cervical SCS causing an increase in cerebral blood flow (40), and some data suggest that it may be useful in treating some facial pain entities and upper-extremity vascular ischemic pain (41).

Evidence

In a recent analysis of a prospective registry, Deer and colleagues assessed the efficacy and safety of cervical stimulation in a "real-time," noncontrolled fashion (42). In this registry, 38 patients received leads in the cervical spine at 19 international study sites. Patient-reported percentage of pain relief was 54.2%, 60.2%, and 66.8% at three, six, and 12 months post-implant, respectively. QOL indices all improved, and most patients were satisfied by their cervical SCS system at last follow-up. Other studies of cervical SCS are described in Table 6.

Discussion

Based on current literature and experience, cervical SCS is not less effective or safe than thoracic SCS. A recent and extensive literature search identified 321 articles, of which 12 studies of 211 patients met rigorous inclusion/exclusion criteria (52). This review documented comparable efficacy for cervical SCS and thoracic SCS, reaching the same conclusion as the registry analysis mentioned previously (42).

Recommendations

SCS in the cervical epidural space appears to be effective in relieving upper extremity pain of neuropathic or vascular etiology and is as safe as thoracolumbar SCS. The NACC recommends the use of cervical SCS for neuropathic pain syndromes affecting the upper extremities.

Table 6. Summary of Studies Using Cervical Spinal Cord Stimulation.

Authors	Study description	Outcomes
Robaina et al. 1989 (43)	Observational; refractory sympathetic dystrophy (CRPS, *N* = 8) or Raynaud's syndrome (*N* = 3); TENS trial, cervical percutaneous leads; follow-up of 27 months	>90% good or excellent pain relief Improvements in blood flow and temperature Infection in one patient, lead migration in two patients
Francaviglia et al. 1994 (44)	*N* = 15; progressive systemic sclerosis (scleroderma) and Raynaud's phenomenon in upper extremities; quadripolar, single percutaneous leads placed C4–C7	Significant improvements in Raynaud's episodes in 14/15 patients, edema and mobility in 13/15 patients, and arthralgic pain reduction in 10/12 patients
Calvillo et al. 1998 (45)	Observational; CRPS of one upper extremity using SCS (*N* = 24), PNS (*N* = 5) or both (*N* = 7); 35 months' follow-up	VAS decreased by 45.3% (SCS), 51.3% (PNS) and 63.5% (both) Opioid consumption decreased by >50% in 44.4% of the patients 41% of patients returned to work Infection at the generator site (*N* = 2) and lead migration/revision (*N* = 2)
Simpson et al. 2003 (46)	41 patients with upper extremity or facial pain of neuropathic or ischemic origin; leads placed without trial; median follow-up of four years (five months to 11 years)	Paresthesia overlapped painful area appropriately in 76% of patients, partially in 17%, and inappropriately in 7% Two-thirds of patients had sustained pain relief 75% of patients with cervical postlaminectomy syndrome experienced significant pain relief Infection (*N* = 2), reoperations (*N* = 37), lead fracture in 15%
Whitworth and Feler 2003 (47)	20 patients with upper extremity neuropathic pain; dual paddle leads at C1–C2; percutaneous trials (*N* = 16), surgical lead trials (*N* = 4); median follow-up 26 months	Mean VAS decreased (8.2 to 3) 70% of patients had good or excellent pain relief One revision for a malpositioned lead and one explant for infection
Forouzanfar et al. 2004 (48)	Prospective study; 36 consecutive patients with CRPS; percutaneous quadripolar leads; cervical device (*N* = 19), lumbar device (*N* = 17); followed for at least two years	Five patients explanted at one year At six, 12, and 24 months pain intensity decreased Statistically significant linear increase in the VAS score No significant differences in outcome between cervical and lumbar SCS Quality of life (EQ-5D) improved 42% of the cervical patients and 47% of the lumbar patients reported at least "much improvement" on the global perceived effect scale 23 patients had complications, related mainly to technical defects
Hayek et al. 2009 (49)	Percutaneous octapolar leads placed in the lower cervical spine (C4–C7)	Successful four-limb stimulation in 11/12 patients
Kumar et al. 2011 (50)	CRPS; *N* = 25, 10 for upper extremity, 15 for lower extremity; mean follow-up 88 months	No differences between SCS for upper limb or lower limb CRPS Improvements in VAS, Oswestry Disability Index, Beck Depression Inventory, EQ-5D, and SF-36 Analgesic medication consumption declined SCS did not prevent disease spread Best results noted in patients younger than 40 years and in cases when SCS was implemented within one year of disease onset
Wolter and Kieselbach 2012 (51)	Retrospective review over 10-year period; neuropathic and ischemic etiologies; 14/23 available for interview; 21 of original 23 had percutaneous leads; 7/14 available patients used continuous stimulation and 7/14 intermittent stimulation (mean 4.9 hours/day)	No statistically significant difference between intermittent or continuous stimulation 14 revisions in nine patients 13/14 patients said they would have the implant again for the same outcome
Deer et al. 2013 (42)	Prospective registry	61.6% excellent/good results at three months with similar results at six and 12 months Mean Pain and Disability Index scores were 49.6 (+14.4) at baseline, 34.5 (+15.7) at three months ($p = 0.0013$), 33.4 (+15.5) at six months ($p = 0.0014$), and 28.4 (+13.4) at 12 months ($p = 0.0001$) At three months, 92.4% of patients were very satisfied or satisfied; none was dissatisfied. Similar results at six and 12 months Overall quality of life improved or greatly improved in 73.1% of patients at three months, with similar results at six and 12 months

CRPS, complex regional pain syndrome; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale.

Dorsal Root Ganglion Electrical Stimulation

The cells of the DRG are integral to the development of both nociceptive and neuropathic pain (53). In the not-too-distant past, the pseudo-unipolar cells of the DRG were thought only to play a supportive role in peripheral nociception and were not known to participate in the generation of neuropathic pain. In their study utilizing fine filament dissection, Wall and Devor (54) showed that electrical impulses can originate within the DRG and concluded that "the DRG, with its ongoing activity and mechanical sensitivity, could be a source of pain producing impulses and could particularly contribute to pain in those conditions of peripheral nerve damage where pain persists after peripheral anaesthesia or where vertebral manipulation is painful."

The development of neuropathic pain is complex and involves many different cell types that include DRG cell bodies, satellite glial cells that wrap and surround the pseudo-unipolar DRG somata, glial cells, astrocytes and Schwann cells, the immune system, and neuronal pathways (55). A massive spontaneous discharge within large axotomized A-neurons within the DRG occurs after cutting spinal nerves distal to the DRG (56). This and observations by Sukhotinsky et al. (56) support the hypothesis that "ectopic firing in DRG A-neurons induces central sensitization" (57) and clinical allodynia.

Because of its ease of accessibility within the vertebral column (58–60), the activity of the pain pathways within the pseudo-unipolar cell bodies of the DRG, and the action of the DRG as a "grand central station" for all communication from the periphery to the spinal cord and subsequently to the brain, the DRG is a very attractive target for neuromodulation. Interest in treating the DRG has existed in the pain medicine community for many years, and treatment has included steroid injections (61), pulsed radiofrequency ablation (62), and ganglionectomy (63–66). Unfortunately, these strategies largely failed to provide sustained long-term relief.

In recent years, these developments have led to an interest in treating the DRG with neurostimulation (67). Work in the USA by Deer and colleagues (68) on acute treatment of pain by placing a novel lead configuration at the DRG has led to additional work in the chronic pain setting in both Europe and Australia (25). The placement of the novel lead is performed via needle entry into the epidural space and using a modified Seldinger technique and specially designed equipment to place the lead overlying the DRG. Compared with traditional SCS technology, this may improve the ability to sustainably provide therapeutic paresthesia overlying historically challenging pain targets such as the foot or chest wall (68). Furthermore, therapeutic coverage of the axial low back has been demonstrated because, studies suggest, of the multisegmental innervation and cross-dermatomal coverage (25).

Peripheral Nerve Stimulation

PNS is the direct electrical stimulation of involved nerves outside of the neuroaxis. PNS represented the first clinical application of the gate control theory proposed by Melzack and Wall (69) when Wall and Sweet applied stimulation to their own trigeminal nerve branches to study the effects of stimulation on evoked pain (70). Thereafter, conventional SCS came to dominate neurostimulation, but PNS was practiced in a few centers where expertise was developed.

Initially, PNS therapy was performed by surgical dissection, direct identification of the target nerve, fascial graft harvest (in some cases), and electrode placement (71). Nerves targeted in these early cases were generally in either the upper or lower extremity (common peroneal, median, ulnar nerves, etc.), and the most common pathology for stimulation was trauma, surgical scarring, or CRPS-II. Because of its invasiveness, this method of PNS has been supplanted in selected cases by less invasive methods of placing electrodes (72).

As this form of treatment for chronic pain has evolved, descriptions of needle-delivered leads in the vicinity of the named nerve, including the greater occipital nerve (73), have been published. Ultrasound guidance of electrode placement has further influenced a shift in clinical practice (74,75).

Peripheral Nerve Field Stimulation

The placement of PNS leads within subcutaneous peripheral receptive "fields" of a single nerve or overlapping "fields" of multiple nerves where pain is believed to be primarily neuropathic is termed peripheral nerve field stimulation or PNfS. PNfS is successful in producing prolonged efficacious stimulation for truncal, axial back, and neck pain where conventional SCS is most often not. PNfS systems are sometimes combined and programmed with dorsal column leads to create hybrid systems (76,77). PNfS is currently being studied in many settings, and the evidence is building for PNfS as a primary treatment and as an adjuvant to conventional SCS (57,76,78–81).

PERIOPERATIVE RECOMMENDATIONS OF THE NACC

The recommendations of the NACC regarding perioperative management (Table 7), implanter training (Table 8), disease-specific indications (Table 9), cautious use (Table 10), and inappropriate use (Table 11) with regard to neuromodulation therapies have been summarized for convenient reference. Table 12 addresses legal points to be considered for patients being treated with neuromodulation.

SAFETY OF NEUROSTIMULATION

SCS is generally believed to be a safe procedure because it is considered minimally invasive and reversible. Despite this positive safety profile, risks do exist, and the implanter should be vigilant in trying to mitigate both the occurrence of complications and their sequelae. When considering the safety of implantation in these complex patients whose therapy has progressed along the treatment algorithm for pain, we must compare SCS with alternative therapies.

Compared With High-Dose Opioids

Numerous studies demonstrate that high-dose, long-term opioid use is associated with hormonal and immune system dysfunction, depression, weight gain, tolerance, opioid-induced hyperalgesia (OIH), and the potential for dependence, abuse, and addiction (141–145). The Institute of Medicine (IOM) and the CDC recently issued reports characterizing prescription medicine overdose deaths as a growing, deadly epidemic (146,147), with opioid pain analgesics present in 74% (14,800 of 20,044) of the prescription overdose deaths that occurred in 2008. In addition to the danger of high-dose

Table 7. Recommendations for Perioperative Management Made by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society Using U.S. Preventive Services Task Force (USPSTF) or Centers for Disease Control Criteria.

Perioperative management	USPSTF evidence strength (9); see Table 1	USPSTF and CDC recommendation strength (9,12); see Table 4
Preoperative risk assessment		
The use of a psychological assessment to address any concerning psychiatric comorbidities before proceeding with an implant (82–86); use of standardized questionnaires for psychological assessment (87)	II-2	B
Use of preoperative MRI to determine the appropriateness of neuromodulation before implant; MRI of the thoracic and cervical spine has the goal of reducing the risks by ruling out critical stenosis or other anatomical abnormality that would compromise trial or implant	III	C, consensus panel strong
Preoperative optimization of diabetes management (88)	II-1	B, CDC recommendation category 1B for glucose control
Preoperative optimization of health status, including immunosuppression, and other diseases that may impact wound healing and increase infection risks (12,89)	III	I, consensus panel strong
Address any recent systemic infection or local skin infection at the site of planned implant	III	I, consensus panel strong
Address any chronic dermatological diseases	III	I, consensus panel low
Address platelet counts of 100,000 or less, or abnormal clotting studies	II-3	B
Preoperative laboratory testing: complete blood count with differential; basic metabolic profile; urinalysis (with culture if indicated)	III	C, consensus panel strong
Chlorhexidine bathing in the 24 hours prior to surgery might be helpful, although current evidence does not show an impact on outcomes (12,90,91)	I	B, CDC category 1B
Preoperative screening/decolonization for nasal carriers of *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant) with mupirocin nasal ointment twice daily and chlorhexidine washings once daily for five days preoperatively (92–96)	I	B
Surgical risk reduction (12,89)		
Laminar-flow operating suite to minimize outside airborne pathogens (97–103)	II-2	B, CDC category 1B
Chlorhexidine–alcohol- or povidone–iodine-based preparations should be utilized when there are no contraindications to application (104,105)	I	A, CDC category 1B
Removal of hair by clipping immediately before the procedure only if required (106,107)	I	A, CDC category 1A
Minimizing room traffic in the operating suite (108)	III	B, CDC category 2
Minimizing surgical time when possible (109–111)	III	B
Careful hemostasis with cautery, sutures, gelfoam, and/or thrombin	III	I, consensus panel strong; CDC category 1B
Good surgical technique: minimizing tissue trauma by gentle dissection, minimizing tissue coagulation (cautery) near skin edges, and devoting careful attention to tissue handling	III	B, CDC category 1B
Nonpressurized irrigation of all wounds vigorously by saline solution (112–117)	II-1	A
Careful attention to a multilayer closure to reduce postoperative wound complications	III	B, consensus panel strong
Surgical incisions should be protected with an occlusive sterile dressing that keeps the area dry and secure for 24 to 48 hours postoperatively (118,119)	I	A, CDC category 1B
Postoperative surgical surveillance		
Postoperative inspection of the wound within the first seven to 10 days after surgery (120)	III	I, consensus panel moderate; CDC category 1B if incision is closed primarily
A successful trial should be defined as the patient having had at least 50% pain relief (121); evidence of improved function is a goal and should be measured in appropriate patients	III	B

oral opioids for chronic pain management, outcome data examining long-term (more than six months) efficacy are lacking (148,149). Results of opioid therapy have been questionable in patients suffering from neuropathic pain (150,151).

Opioid Limitations

Many studies contain insufficient evidence to prove the safety or effectiveness of any long-term opioid regimen for chronic pain. Indeed, many patients discontinue long-term opioid therapy due to insufficient pain relief or adverse events (149). Early opioid prescription and higher opioid dosing have been associated with subsequent disability and poor functional outcomes in workers with back injuries (152,153) and with higher prevalence of lifetime addictions in patients with back pain (154).

Hyperalgesia

Hyperalgesia can develop during chronic administration of opioids. OIH, a state of nociceptive sensitization, was demonstrated when a low dose of naloxone produced analgesia (155). Wu et al. have suggested that opioid peptides may play a dual role in modulating pain perception and inducing OIH (156). SCS may serve as an alternative to chronic opioid administration for chronic pain,

Table 8. Recommendations for Implanter Training Made by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society Using U.S. Preventive Services Task Force Criteria.

Implanter training	Evidence strength USPSTF (9)	Recommendation strength USPSTF (9)
Proper training for implantation in a fellowship of at least six months' duration, with at least 12 hours of continuing medical education per year directly related to improving outcomes with neuromodulation (122–124)	II-3	B
Physicians without fellowship training should only attempt implantation after appropriate hands-on training, with active mentorship and additional training in patient selection, complications and improving outcomes (122,123)	III	I, consensus panel strong
Clinicians with trial-to-permanent implant (using current technology) ratios of <50% in routine cases should cease to implant devices or consider remedial training	III	I, consensus panel strong
Clinicians with high rates of biologic or mechanical complications should cease to implant devices or consider remedial training	III	I, consensus panel strong
Clinicians who do not have an identified physician to perform the permanent implant should cease to do trialing	III	I, consensus panel strong

Table 9. Recommendations for Disease-Specific Indications and Considerations Made by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society Using U.S. Preventive Services Task Force Criteria.

Disease-specific indications	USPSTF evidence strength (9)	USPSTF recommendation strength (9)
The use of SCS early in the treatment algorithm for failed back surgery syndrome in the absence of neurological progression requiring surgical intervention with persistent axial and radicular complaints (121,125–127)	I	A
The use of SCS should be either conventional SCS or DRG stimulation when the pain is dominantly radicular in nature	II-2	B
The use of cervical SCS for the treatment of upper extremity pain of neuropathic pain syndromes affecting the upper extremities, including, but not limited to, radiculopathy	II-2	A
The use of SCS for the treatment of CRPS-I and CRPS-II	I	A
The use of SCS with pacemakers appears to be safe in most settings (128)	III	C
The use of neurostimulation has been shown to have a better outcome if used early in the course of the disease process; SCS and PNS would be considered earlier, when possible, and recommended to be trialed within the first two years of chronic pain (129,130)	II-3	B
High-frequency stimulation or burst stimulation may be helpful in treating axial back pain and those with tonic stimulation resistance	III	I, consensus panel strong
DRG stimulation should be trialed for discrete areas of neuropathic pain	II-1	B
The NACC recommends SCS as an early intervention in patients with Raynaud's syndrome and other painful ischemic vascular disorders; if ischemic symptoms persist despite initial surgical or reasonable medical treatment, SCS should be trialed (131)	II-3	C

CRPS, complex regional pain syndrome; DRG, dorsal root ganglion; NACC, Neuromodulation Appropriateness Consensus Committee; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

especially when OIH occurs. SCS has been shown to reduce opioid consumption in several prospective trials (45,121,157–160).

Compared with Conservative Medical Management

The criteria for placement of an implantable neurostimulation device require failure or inadequate response to conservative medical management (CMM); thus, the data on true comparative therapies are limited. The PROCESS study (161) and a study in patients with CRPS (162), comparing SCS with CMM in a randomized and controlled manner, suggest that SCS is superior to CMM. Literature reviews in 2011 and 2013 of the safety, appropriateness, fiscal neutrality, and effectiveness (SAFE) of SCS suggest that it be considered before submitting patients to long-term opioid therapy for chronic pain from FBSS and CRPS (163,164).

A prospective RCT of SCS in patients with FBSS, the multicenter PROCESS trial, compared SCS in combination with CMM against CMM alone, with follow-up at six, 12, and 24 months (121,161). The PROCESS study recruited 100 patients from 12 multinational centers. All patients had neuropathic pain of radicular origin (radiating in dermatomal segments L4, L5, and/or S1), predominantly in the lower extremities. The primary reason for exclusion was predominant back pain. Eligible patients (N = 100) were randomly assigned to receive SCS plus CMM (SCS group, 52 patients) or CMM alone (CMM group, 48 patients) for at least six months. Crossover after the six-month visit was permitted, and all patients were followed for up to one year. The primary outcome was the proportion of patients achieving ≥50% relief of leg pain. Secondary outcomes were improvement in back and leg pain, health-related QOL, functional capacity, use of pain medication and nondrug pain treatment, patient satisfaction, and incidence of complications and adverse effects. Using an intention-to-treat (ITT) analysis at six months, 24 patients in the SCS group (48%) and four patients in the CMM group (9%) achieved the primary outcome of ≥50% leg pain relief (p <

Table 10. Disease-Specific States and Areas That Deserve Caution as Identified by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society Using U.S. Preventive Services Task Force Criteria.

Areas of caution	USPSTF evidence strength (9)	USPSTF recommendation strength (9)
When considering SCS for the patient with multiple or poorly defined pain generators or diagnoses	II-3	C
In patients who have areas of spinal stenosis or cord compression from disk disease, bony overgrowth, or other structural abnormalities in areas where lead placement is required for therapeutic stimulation	III	I
For those undergoing SCS with an indwelling pacemaker or automatic implanted cardiac defibrillator, proper evaluation and monitoring should be available, and the patient should be cleared by cardiology prior to permanent implant; many patients have been implanted successfully with both systems, and this may become more common with work being done on congestive heart failure	III	C
When using SCS or PNS for patients with active malignancies who may require MRI scanning to monitor disease progress. The use of neurostimulation is warranted for patients with moderate to severe neuropathic or mixed pain who are in remission or have tumors expected to grow at a slow and often painful rate	III	C, consensus panel moderate
When considering SCS or PNS for nonradicular focal bone pain; this therapy should only be considered in extreme cases	III	C
The use of SCS for the treatment of axial back pain after identifying a specific pain generator(s)—for PnfS, both alone or in combination to treat axial back pain, should be performed with use of strict protocols; the use of combined SCS and PNfS should be considered when pain is equal or slightly greater in the axial back or neck; in dominant axial back pain, complex paddle leads or complex percutaneous leads should be considered; kilohertz-frequency SCS and burst SCS may change this recommendation in future	III	I, consensus panel strong
When using conventional SCS as a treatment for chest wall pain, PNS, PNfS, and DRG stimulation offer potential options in areas difficult to capture with dorsal column targeting	III	I, consensus panel strong
When using SCS to treat HIV neuropathy, decision-making should be performed on an individual basis, based on comorbidities and medications	III	I, consensus panel strong
Use of SCS to treat painful diabetic peripheral neuropathy is often helpful but should be approached with caution considering the increased risk of infection; SCS might improve blood flow in this group, which may promote wound healing and limb salvage	III	I, consensus panel strong
Use of SCS to treat postamputation pain, realizing that the pain may vary and results may be unpredictable	II-3	C
Spinal cord injury should be approached on a case-by-case basis and neuromodulation therapies used judiciously if the pain extends beyond a well-circumscribed, segmental distribution	III	I, consensus panel moderate
The use of PNS should be reserved for patients in whom the pain distribution is primarily in and in close proximity to a named nerve known to innervate the area of pain	II-2	B
With PNS or PNfS, the temporary relief of the patient's pain by an injection of local anesthetic in the nerve distribution should be seen as an encouraging sign, but not mandatory, as prognostic value is not established	III	I, consensus panel moderate

DRG, dorsal root ganglion; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

Table 11. Inappropriate Practices and Disease-Specific States Identified by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society Using U.S. Preventive Services Task Force Criteria.

Inappropriate practices	USPSTF evidence strength (9)	USPSTF recommendation strength (9)
Patients with inadequately controlled psychiatric/psychological problems should not be implanted (84).	II-3	B
Patients who cannot be taken off anticoagulants or bridged safely for the proper duration surrounding the trial or surgery should not undergo SCS or PNS. PNS and PNfS may be of less risk in the anticoagulated, but current data do not support the use of these techniques in this setting.	II-2	A
Patients in whom a systemic infection cannot be cured should not undergo implant.	III	A. consensus panel strong
Patients in whom the treating physician does not have a strong working differential diagnosis in regard to the pain generator should not be implanted.	III	I, consensus panel strong
In patients with platelet counts less than 50,000, SCS trials and implants should be avoided, unless managed in close collaboration with the treating hematologist (132).	II-3	I, consensus panel moderate
Patients with the inability to cognitively participate in their care should not be implanted. In partially impaired patients, implant may be acceptable if the primary caregiver is able to participate actively. Nonrechargeable batteries should be considered in this second group of patients.	III	I, consensus panel low

PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

Table 12. Legal Considerations Associated With Neuromodulation Therapy Presented by the Neuromodulation Appropriateness Consensus Committee of the International Neuromodulation Society.

Caution should be maintained in those who choose to drive with their SCS device in the active mode. The device companies do not recommend that patients drive with the device producing active paresthesias. Patients who operate potentially dangerous or heavy equipment or automobiles with SCS active do so against medical advice. Most patients report persistence of relief for some time after turning SCS off, and this can allow safe operation while pain remains controlled. In many settings, the use of SCS allows the patient to wean off cognitive-impairing drugs and their driving likely improves, despite the warnings that are currently in place. Additional studies on driving are needed.
Caution should be maintained in pregnancy. Successful stimulation during pregnancy has been reported, but devices are not currently approved for women who are pregnant (133–137).
Some have questioned the appropriateness of implanting patients with active litigation, worker's compensation claims, or obvious secondary gain (138,139). The NACC recommends this be addressed during the psychological assessment and, if any contraindications are documented, further discussions should occur (140).

NACC, Neuromodulation Appropriateness Consensus Committee; SCS, spinal cord stimulation.

0.001). Exploratory subgroup analyses of patients with either less than three back surgeries or a diagnosis of FBSS of <12 months' duration indicated that these patients were more likely to achieve the primary outcome with SCS than the patients with CMM alone. The SCS patients experienced lower levels of back pain ($p = 0.008$) and leg pain ($p < 0.0001$), enhanced health-related QOL on seven of the eight dimensions of the SF-36 ($p < 0.02$), superior function ($p < 0.001$), and greater treatment satisfaction ($p < 0.001$). The SCS group exhibited a trend toward a decrease in both analgesic drug intake and in nondrug therapy use, but these improvements were not statistically significant.

Between six and 12 months, five SCS patients crossed to CMM, and 32 CMM patients crossed to SCS. According to their "per-treatment analysis" at 12 months, the primary outcome was achieved in 48% of the 71 SCS patients and 18% of the 17 patients receiving CMM alone ($p = 0.03$). To quantify the impact of crossovers, the investigators performed a "modified ITT analysis" where patients who crossed over at six months were categorized as primary outcome failures. In this modified ITT analysis, 34% of the SCS group and 7% of the CMM group achieved the primary outcome ($p = 0.005$).

At 12 months, 27 SCS patients (32%) had experienced device-related complications, and 20 patients (24%) required surgery to resolve the event. Principal complications were electrode migration (10%), infection or wound breakdown (8%), and loss of paresthesia (7%). The authors concluded that in selected patients with FBSS, SCS provides better pain relief and improves health-related QOL and functional capacity compared with CMM alone.

The 24-month follow-up data from the PROCESS study were reported separately (165). Of the 52 patients who were randomized to SCS, 42 were receiving SCS at 24 months. Compared with baseline, these 42 experienced lower levels of leg pain ($p < 0.0001$) but no significant difference in back pain ($p = 0.21$). Patients also reported superior functional capacity on the ODI and enhanced health-related QOL on seven of eight dimensions of the SF-36. However, neither analgesic drug intake nor nondrug therapy showed a clear pattern of change. Forty-six of 52 patients randomized to SCS and 41 of 48 patients randomized to CMM were available for follow-up. In the "modified ITT" analysis, with outcomes assigned to randomized group and crossover considered a failure, 17 SCS patients (37%) vs. one CMM patient (2%) achieved the primary outcome ($p = 0.003$). In the most conservative scenario (i.e., assuming that patients who withdrew or were lost to follow-up in the SCS group were failures and their counterparts in the CMM group were successes), 17 of 52 patients (33%) randomized to SCS and eight of 48 patients (17%) randomized to CMM achieved the primary outcome ($p = 0.07$). In the "per-treatment analysis," of the 72 patients who received SCS as the final treatment, 34 (47%) achieved the primary outcome vs. one of 15 patients (7%) who received CMM as the final treatment ($p = 0.02$).

Compared With Spine Surgery

North and colleagues (127) randomized 60 FBSS patients to either SCS or repeated lumbosacral spine surgery with an average follow-up of three years. If the results of the randomized treatment were unsatisfactory, patients were allowed to cross over to the alternative treatment. All patients complained of persistent or recurrent radicular pain with or without low back pain after one or more lumbosacral spine surgeries. Investigators excluded patients with a chief complaint of axial low back pain exceeding radicular pain. Outcome variables included self-reported pain relief, patient satisfaction, whether patients crossed over to the alternative procedure, use of analgesics, activities of daily living (ADLs), and work status. Success was defined as both self-reported pain relief of ≥50% and patient satisfaction. Fifty patients proceeded to treatment, and 45 patients (90%) were available for follow-up. SCS was significantly more successful than reoperation (nine of 19 patients in the SCS group vs. three of 26 patients in the reoperation group, respectively; $p < 0.01$). Patients initially randomized to SCS were significantly less likely to cross over than were those randomized to reoperation (five of 24 patients in the SCS group vs. 14 of 26 patients in the reoperation group; $p < 0.02$). Patients randomized to reoperation required increased opioid analgesics significantly more often than those randomized to SCS ($p < 0.025$). Opioid use was stable or decreased in 87% of SCS patients vs. 58% of reoperation patients, whereas opioid use increased in 13% of SCS patients vs. 42% of reoperation patients. No significant treatment differences were detected in patients' ability to return to work and ADLs; of those employed, all but one remained employed. The authors concluded that SCS is more effective than reoperation as a treatment for persistent radicular pain after lumbosacral spine surgery and, in the majority of patients, obviates the need for reoperation.

COST-EFFECTIVENESS OF SCS COMPARED WITH OTHER TREATMENTS

Cost-Effectiveness in Failed Back Surgery Syndrome

In 2002, Kumar et al. studied 104 patients with FBSS by monitoring them for five years and collecting data about total cost of care,

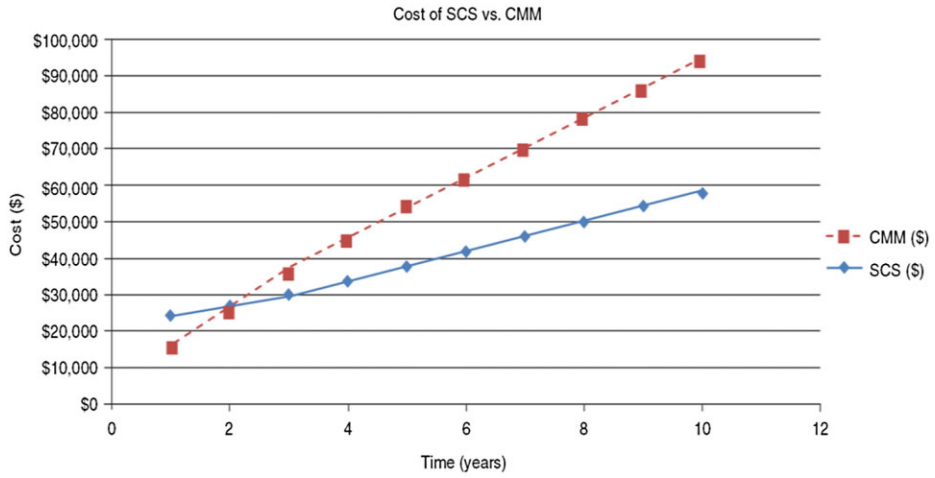

Figure 1. Cost of spinal cord stimulation vs. conservative medical management (Canadian dollars). Compared with CMM, SCS, although more expensive initially, becomes over time less expensive than CMM. CMM, conservative medical management; SCS, spinal cord stimulation.
Source: Kumar et al. (167). Reprinted with kind permission from Springer Science and Business Media.

QOL, and ability to return to employment (166). Sixty patients received SCS and 44 patients CMM. The total cost of care and drug intake were lower in the SCS-treated patients, and 15% of this group returned to work compared with none of the CMM patients. SCS became cost-neutral at 2.25 years and was less costly than CMM thereafter (Fig. 1). This return-to-work status is exceptional and may represent an important benefit to society.

In a 2004 systematic review of the literature specifically examining the cost-effectiveness of SCS for FBBS, Taylor et al. (168) found that the initial health-care acquisition costs of SCS, surgical implantation, and early maintenance were offset by a reduction in post-implant health-care resource utilization and cost. At five years, the mean costs were $29,123 in the intervention group compared with $38,029 in the control group.

In 2007, North et al. collaborated with Taylor and published a cost-effectiveness study based on their RCT, comparing SCS with reoperation for FBSS (169). Not only did this add a higher level of evidence, it showed that SCS was "dominant" (more effective and, at the same time, less costly than reoperation).

Bala et al. (170) subsequently performed a systematic review of the cost-effectiveness of SCS for patients with FBSS. Three studies met the inclusion criteria and confirmed that SCS is more effective and less costly than other options over the long term.

Kumar and Rizvi (171) recently compared the cost-effectiveness of SCS plus CMM for FBSS vs. CMM alone from a societal perspective over a 20-year period. The incremental cost-effectiveness of SCS was Can$9293 per quality-adjusted life year (QALY) gained, and there was a 75% likelihood that SCS would prove more cost-effective than CMM at a willingness-to-pay threshold of $50,000 per QALY. The cost-difference between the two strategies was only $12,297 over 20 years, while patients who received SCS gained an additional +1.39 QALYs over the same time. The authors concluded that SCS was highly cost-effective compared with CMM alone. Figure 2 illustrates the cost-effectiveness of SCS over CMM based on incremental net monetary benefit generated.

Krames et al., using their SAFE analysis, also reviewed cost-efficacy of SCS compared to other therapies for FBSS and concluded, based on their literature review, that SCS should come before CMM using opioid pain management (163).

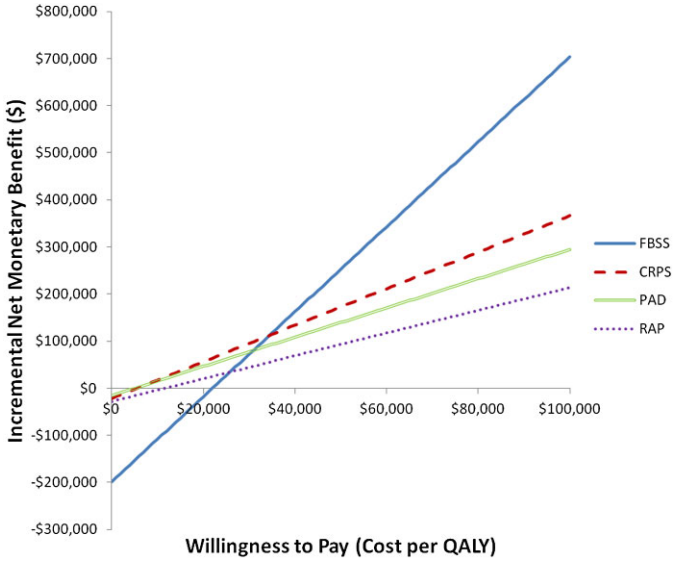

Figure 2. Incremental net monetary benefit for SCS over conservative medical management at varying willingness-to-pay thresholds (Canadian dollars). Instituting SCS over conservative medical management generates a positive incremental net monetary benefit at willingness-to-pay thresholds ≥$7000 (Canadian dollars) per QALY gained. FBSS, failed back surgery syndrome; CRPS, complex regional pain syndrome; PAD, peripheral arterial disease; RAP, refractory angina pectoris.
Source: Kumar and Rizvi (171). Used with permission of John Wiley and Sons.

Cost-Effectiveness in Complex Regional Pain Syndrome

Taylor et al. performed a systematic review of literature up to 2002 to determine the clinical and cost-effectiveness of SCS for treatment of CRPS (172). These authors concluded that there is level A evidence for SCS treatment of CRPS-I and level D evidence for CRPS-II. Furthermore, they predicted a lifetime cost savings of US$60,800 when SCS was used in conjunction with physical therapy compared with physical therapy alone. In 2010, Kemler and colleagues used a decision-analytic model to review and synthesize data from the UK National Health Services over a 15-year period to

report on the cost effectiveness of SCS (173). The authors, using data from two SCS RCTs, found an incremental cost-effectiveness of SCS vs. CMM per QALY of £3562 in 2008 costs.

Kumar and Rizvi recently demonstrated that SCS plus CMM was more cost-effective than CMM alone for management of CRPS over a 20-year span (171). They constructed a Markov model from a societal perspective in order to perform a cost-effectiveness analysis. The incremental cost-effectiveness of FBSS was Can$9319 per QALY gained, and there was a 93% likelihood that SCS would prove more cost-effective than CMM at a willingness-to-pay threshold of $50,000 per QALY. The favorable cost-effectiveness profile of SCS was maintained in spite of the high costs and mortality associated with peripheral arterial disease (PAD). The SCS-plus-CMM strategy demonstrated an additional gain of 1.67 QALYs over CMM alone.

Cost-Effectiveness in Peripheral Arterial Disease

Kumar and Rizvi recently demonstrated that SCS is worth implementing for the management of nonreconstructable PAD (171). In contrast to earlier studies that did not account for therapeutic effects on health-related QOL and thus subsequently failed to establish the cost-effectiveness of SCS (174,175), Kumar and Rizvi showed a superior gain in QALYs with SCS vs. CMM alone. The incremental cost-effectiveness of SCS was Can$11,216 per QALY gained, and there was an 87% likelihood that SCS would prove more cost-effective than CMM at a willingness-to-pay threshold of $50,000 per QALY. Over 20 years, costs for the SCS-plus-CMM strategy totaled $172,577 compared to $148,799 for CMM alone. However, the SCS-plus-CMM strategy accrued twice as many QALYs (4.24 QALYs for SCS plus CMM vs. 2.12 for CMM alone).

Ubbink et al. (174) calculated that eight patients required treatment with SCS in order to salvage one limb, leading to an additional cost of €64,000 to achieve this goal. Klomp et al. (175) found the costs of SCS to be 28% higher than standard group therapy at two years for treatment of nonreconstructable critical limb ischemia and suggested that SCS was not cost-effective for this indication.

Cost-Effectiveness in Refractory Angina Pectoris

Kumar and Rizvi, using the Markov model, also demonstrated that SCS plus CMM was more cost-effective than CMM alone for management of refractory angina pectoris that persists after coronary artery bypass grafting (CABG) over a 20-year span (171). The SCS-plus-CMM strategy generated an additional 2.21 QALYs (4.88 QALYs for SCS plus CMM vs. 2.67 for CMM alone). Similarly, an RCT analyzing SCS vs. bypass (the Electrical Stimulation vs. Coronary Artery Bypass Surgery in Severe Angina Pectoris or ESBY trial) (176) revealed that SCS and CABG were both cost-effective, with SCS having a lower initial cost and shorter duration of hospitalization but a higher overall complication rate that was secondary to complications related to the implanted hardware, whereas CABG had significantly higher perioperative mortality. Of course, it should be recognized that by definition, refractory angina has a relatively unfavorable risk–benefit ratio for revascularization procedures. The ESBY study was performed on a specific group of patients at high risk of dying as a consequence of the surgical bypass procedure, and so its results should not be extrapolated to bypass surgery in general. By the same token, a study comparing percutaneous coronary intervention (PCI) with SCS would be difficult to conduct. To date, the cost-effectiveness studies have focused mainly on other comparators than revascularization procedures or have made subsidiary comparisons.

A cost-effectiveness analysis of SCS vs. percutaneous myocardial laser revascularization (PMR) in patients with refractory angina pectoris (the SPiRiT RCT) failed to establish a favorable cost-effectiveness profile for SCS at 24 months' follow-up (177). However, significant changes in the incremental cost-effectiveness ratio (ICER) (178) were observed over time, which the authors attributed to a learning-curve effect. For patients recruited during 2000/2001, the ICER of SCS over PMR was estimated to be £230,000 per QALY, whereas for 2002/2003 the ICER dropped to £18,000 per QALY.

Simpson et al. estimated costs and utility scores for SCS and PCI (179). At six years, patients appropriate for PCI incurred a cost of £12,183 with a utility score of 0.65 and gain of 2.93 QALYs vs. a cost of £16,857 for the SCS-plus-CMM group with no utility score or QALY provided. Unfortunately, despite demonstrated clinical efficacy, SCS remains underutilized for refractory angina pectoris (180). A new study, RASCAL, is a multicenter randomized trial ongoing in three centers in the UK that is comparing the effectiveness and cost-effectiveness of SCS combined with usual care vs. usual care alone for refractory angina (181).

Continuing education of interventional cardiologists should clarify that SCS and PCI are complementary techniques to be used in different scenarios of cardiac ischemia. The medical history, the clinical state of the patient, and the outcome of cardiac angiography should determine which technique to use. In current practice, it is reasonable that one or two occlusions in large vessels be considered suitable for PCI, while multiple occlusions in peripheral branches in an elderly and sick patient are best treated with SCS.

Cost-Effectiveness of Rechargeable vs. Nonrechargeable Implantable Generators

Kumar and Rizvi (171) demonstrated that if the longevity of a nonrechargeable IPG is less than 4.25 years, a rechargeable (initially more expensive) IPG is more cost-effective (Fig. 3). Similarly, Hornberger et al. concluded that a rechargeable battery, which is initially more expensive, is more cost-effective than a nonrechargeable battery, which must be replaced more frequently (173). Utilizing a rechargeable pulse generator saves an estimated $100,000 over a patient's lifetime, and fewer replacement operations may reduce the potential for complications (173).

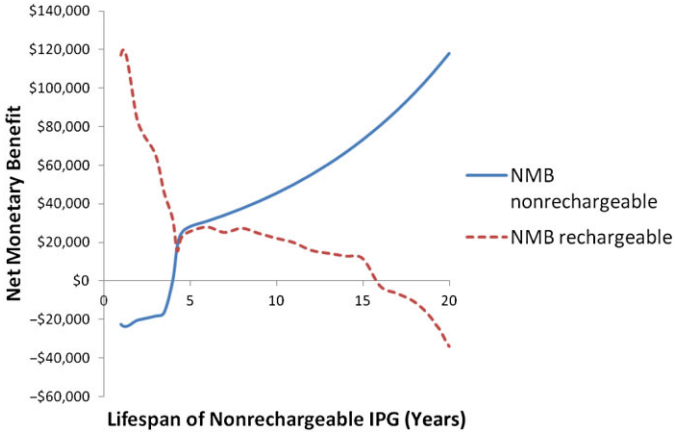

Figure 3. Net monetary benefits of a nonrechargeable or rechargeable implantable generator (IPG) for SCS (Canadian dollars). When the longevity of a nonrechargeable IPG is less than 4.25 years, a rechargeable (initially more expensive) IPG is more cost-effective than a nonrechargeable IPG. NMB, net monetary benefit.
Source: Kumar and Rizvi (171). Used with permission of John Wiley & Sons Inc.

COMPLICATIONS ASSOCIATED WITH SCS

SCS has a low risk of major complications, as befits a neuromodulation procedure. Minor complications, on the other hand, are more common. The majority of complications associated with SCS implants involve electrode fracture or lead migration, which are correctable by replacing or repositioning the lead (50). The technologies for SCS leads, IPGs, and programmers are rapidly evolving, resulting in fewer device-related events. Continued refinements in technology, increased knowledge regarding patient selection, and greater implanter experience are likely to further enhance safety and outcomes (3). The NACC group has collaborated to create a risk-reduction and outcome improvement plan for complications (3).

Surgical Paddle vs. Percutaneous Approach

Compared with spine surgery, SCS is intuitively safer. The risks associated with SCS might be presumed to be higher with the more invasive surgical implantation of paddle leads than with percutaneous cylindrical leads, in part because paddle leads are used in more difficult cases. Indeed, in a large retrospective survey comparing the outcomes of percutaneous leads vs. surgical paddle leads, Rosenow et al. reported that the chances of complications, fractures, and infections were higher with surgically implanted paddle leads (182). No prospective study, to our knowledge, has compared the risks of these techniques adequately; the only RCT involved too small a sample to address these infrequent events (183,184). Permanent neurological deficits and serious spinal cord injury due to either lead placement or epidural hematoma have occurred during trial and implantation with both percutaneous and plate electrodes (185–189), although this problem can occur with any epidural intervention. The incidences of epidural hematoma, epidural abscess, and spine injury are much higher with spine surgery than with any SCS procedure (190).

APPROPRIATENESS OF EMPLOYING NEUROSTIMULATION TECHNIQUES

Appropriate Implanter Training and Mentorship

Implanters should be properly trained in interventional pain management or spinal surgical interventions (124) and should have undergone training in a credentialed high-volume center. The NACC recommends that during formal training, trainees should ideally perform ten cases at a minimum as the primary implanter, under supervision. Training should include proper patient selection, contraindications, complication identification and management, and collaboration with colleagues in other pertinent disciplines. The implanter should be comfortable with troubleshooting during the implantation procedure and with methods and techniques to achieve proper stimulation while maintaining safety. The implanter should be able to recognize and treat hardware-related and biological complications and should be able to recognize the benefits and pitfalls of various commercial leads and lead types and their specific indications.

Although implanters may choose to implant trial systems in the office setting, they should be able to obtain privileges to perform implantation in a Joint Commission-accredited hospital setting, properly certified surgical center, or similar facility. The NACC does not recommend performing permanent SCS implantation in the office setting.

Failure of Conservative Medical Management

The NACC recommends that neuromodulation for the treatment of pain should be used in patients who fail to have acceptable relief with reasonable efforts and/or who have unmanageable side effects with their current conservative treatment regimen. There is good evidence that SCS should be used before another back surgery for FBSS (127) and before starting the patient on long-term, systemic administration of long-acting opioids (163).

Surgical Candidates and Preoperative Considerations for Neuromodulation Therapies

Surgical candidacy reflects interplay between a surgically treatable condition, risk mitigation, and a benefit advantage. Individuals with neuropathic pain might have the potential to respond to SCS but be deemed inappropriate surgical candidates because of anesthesia risk or significant comorbidities. Decisions regarding SCS should include, as appropriate, the patient's other treating clinicians, such as those in primary care, cardiology, or neurology. Agents that affect clotting pathways should be managed with the prescribing physician. Before surgery the patient should review with the anesthesiologist any and all perioperative concerns.

The patient's diagnosis and the patient's wishes and well-being should be the main determinants for the appropriateness of surgery. Informed consent is of course required; preoperative discussions should include description of the procedure and device and treatment alternatives, as well as possible positive and negative outcomes and the surgical expectations and cosmetic desires of the patient. The clinician should be alert for risk factors, such as poorly controlled diabetes, active infections, noncompliance, and psychological issues.

Psychological Clearance for Neuromodulation Procedures

Pain is, by definition, a sensory and emotional experience associated with or described in terms of actual or perceived tissue damage (1). The clinician may not recognize the impact of mood, depression, anxiety, or other negative affective states on the experience of pain. The experience of pain always involves emotional factors. The challenge for the pain practitioner is to differentiate between the component that is biologically driven and the component that is emotionally driven or magnified. Patients should be evaluated by a mental health professional prior to implant. The NACC recommends a psychological evaluation within less than one year before implementing any neuromodulation therapies (84,85).

Contraindications

Exclusion criteria for SCS include evidence of active, uncontrolled psychiatric disorder or inability to comply with therapy, persistent local or systemic infection, immunosuppression, and anticoagulant or antiplatelet therapy that cannot be suspended temporarily for implantation (191). Previously, a technically adequate but failed trial was thought to be a contraindication to another implantation, but work in kilohertz-frequency SCS, burst SCS, and DRG stimulation suggests that there is not necessarily a correlation between a failed trial with conventional SCS and potential future success (20–22,27,192). The NACC recommends that both patients and physicians consider using new technologies to give hope to those patients who have failed trials of conventional SCS.

Anticoagulation Management

No specific consensus documents have been published on neuromodulation and anticoagulation. This deficiency leads the

NACC to give guidance regarding neuromodulation and anticoagulation in this document and to encourage an international effort to define the best practices in this arena. Additional information is available in a companion article that addresses the prevention and treatment of complications associated with neuromodulation (3).

Accessing the epidural space either surgically or by needle placement is a common procedure with a very low incidence of bleeding, but any intervention demands vigilance for complications that might occur. Currently, standard recommendations regarding spine surgery and anticoagulation as well as neuraxial anesthesia and anticoagulation are acknowledged by the NACC in the absence of any further specific evidence-based literature. Clearance to discontinue anticoagulants for the purpose of neuromodulation trials and implantation should first be obtained from the anticoagulant-prescribing provider (193–195).

The length of preoperative discontinuance of anticoagulants depends on the medication's half-life, whether the drug is being prescribed for primary or secondary prevention, and the invasiveness of the planned surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs), for example, can be discontinued for at least five half-lives before performing the intended procedure, so that only a small percentage of the drug remains at the time of surgery. Patients who cannot be taken off anticoagulants for the proper duration should not undergo SCS or PNS trials or implantation, unless permission is obtained from the prescribing physician. A bridging method of anticoagulation from long-acting anticoagulants to short-acting anticoagulants may be implemented, as determined by the implanter and the prescribing physician.

Relatively few case reports have been published regarding epidural hematoma occurring immediately after SCS placement leading to subsequent neurological impairment as the presenting feature (increasing pain, numbness, and weakness below the placement level). In existing case reports, detailed information is missing regarding the particular issues or difficulties encountered in the placement of the lead (e.g., number of attempts, duration of procedure, bloody epidural tap prior to lead placement). Without these details, it is difficult to draw any firm conclusions regarding steps that need to be taken intraoperatively to prevent the occurrence of epidural hematoma. The NACC recommends using the most atraumatic method possible for needle placement, judicious use of force when placing percutaneous leads, and commitment to excellent hemostasis when placing paddles.

The NACC recommends that urgent neurological evaluation, including immediate CT scanning with and/or without contrast, be undertaken for any patient presenting with deterioration of neurologic status after SCS implantation, especially within the first 24 hours after lead insertion. The evaluation should rule out intramedullary electrode placement, subdural hematoma, epidural hematoma, or spinal cord compression, along with any associated spinal canal stenosis. Treatment should be in accord with standard neurosurgical or surgical guidelines (3).

TRIALING

Trialing Method of Choice

Trial SCS, PNS, and PNfS stimulation is recommended by the NACC for the treatment of pain. Trialing affords the opportunity to assess the therapy before committing to permanent implantation of an expensive and potentially more invasive SCS, PNS, or PNfS device. The trial method to use may vary, depending on the indication, implanter, or patient.

Assessment of the trial outcome by the clinician includes evaluations of pain relief, improvement in patient function, associated treatment (in particular medication) utilization, and any complications of therapy. From the patient's perspective, assessment includes acceptance and satisfaction with the outcomes of the treatment.

Preoperative Preparation

Preoperative preparation for neuromodulation trials is patient-specific and disease-driven. A preoperative checklist can be helpful (Table 13). For SCS, plain film x-rays, MRI, or CT scanning may be helpful to define spinal anatomy. PNS and PNfS require defining the areas where electrodes will be placed in order to yield paresthesia in the painful distribution of the affected nerve or nerve field. A peripheral nerve may be visualized with ultrasound guidance. Of course, anatomic landmarks may also be used for lead placement. Preoperative patient marking is helpful when planning implant location.

Specific recommendations for reducing biologic, patient-related, and device-related complications of SCS appear in a companion article (3).

Definition of a Successful Trial

The definition of a successful SCS trial may vary among clinicians; however, some criteria are consistently reported as elements of a positive trial. The NACC recommends that a successful trial be defined as the patient experiencing and recording ≥50% pain relief during the trial (121). This should, of course, occur with stable or, even better, reduced pain medications, in particular opioids, and with at least stable levels of daily activity. In the opinion of some clinicians, a substantial improvement in ADL or QOL may be considered as an alternative definition of success. However, when this is used as the major determinant of trial success, it should be coupled with objective improvement in measures such as walking tolerance, sleep, and ability to perform ADLs. Ideally, objective data should be obtained by an independent observer like a physical therapist or rehabilitation specialist.

Timing of SCS Intervention

SCS performed early in the course of patients' chronic pain processes is associated with better outcomes than SCS performed late in the disease. Kumar et al., in their 22-year experience of 410 patients treated with SCS, showed that success was inversely proportional to time between initial pain diagnosis and implantation (129). If time to SCS treatment was less than two years, the long-term success rate was 85%, but it declined precipitously—to only 9%—if implantation was delayed beyond 15 years from pain onset (Fig. 4) (129,196). Similarly, Kumar et al. retrospectively analyzed the long-term outcomes of 25 patients with CRPS-I treated for a mean of 7.3 years. They observed the greatest improvement in health status (measured by EQ-5D) and pain relief (based on patient-reported VAS) in patients with stage I pathology in whom the intervention was conducted within one year of the onset of symptoms (50).

Globally, wait times for SCS average from five to six years. In the multicenter PROCESS trial, 4.7 ± 5.1 years had elapsed between last surgery and randomization to SCS (165). Recently, Kumar et al. presented a retrospective analysis of 437 patients treated with SCS and reported a mean wait time of 5.45 years (130). In this study, the authors determined the points of delay from onset of symptoms to

Table 13. Procedure Checklist.

Preoperative medical issues

___ Check for evidence of active dermal, dental, urologic, or other infections and treat as necessary.
___ Order urinalysis before procedure.
___ Address prior history of infection and make a plan for prophylaxis.
___ Review MRI imaging of the spine in past 12 months depending on diagnosis and planned placement of stimulator tip.
___ Discontinue anticoagulation with approval of treating physician for a length of time prior to procedure that is appropriate for the specific anticoagulant and surgical bleeding risk.
___ If patient was on warfarin, order prothrombin time testing on or before the morning of the procedure.
___ Review psychological evaluation.
___ Obtain cardiac clearance in patients at risk.
___ Review trial films and operative notes in preparation for permanent implant.
___ Examine the potential sites of implantation and battery pocket for infection or inflammatory process.
___ If there are any potential technical or patient-specific concerns, communicate with the treating physician and/or the anesthesiologist prior to implant.
___ Educate the patient/caregiver(s).
___ Obtain insurance coverage and document medical necessity.

Surgical considerations

___ Assess health status the day of surgery.
___ Have patient empty bladder preoperatively.
___ Review postoperative instruction sheet with patient/caregiver preoperatively.
___ Check that adult driver has been arranged to take patient home, if necessary.
___ Order preoperative antibiotics and administer 30 to 60 minutes before incision.
___ Plan wound closure.
___ Arrange for family to stay in postoperative area to observe programming and learn about recharging.
___ Confirm follow-up appointment before discharge.
___ Write prescriptions for postoperative antibiotics and analgesics if needed.

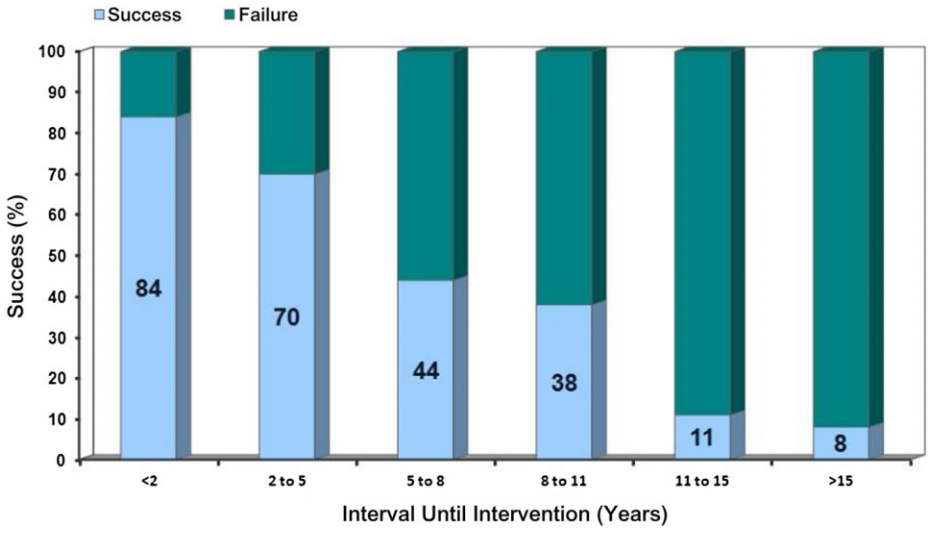

Figure 4. Interval to intervention and neurostimulation success rates (%). The rate of success of spinal cord stimulation is inversely related to time interval between onset of chronic pain syndrome and time of implantation.
Used with permission of the authors (129).

implantation in Canada and found that initial physician contact with the patient in chronic pain occurred at a mean of 3.4 ± 0.12 months after development of the pain syndrome. Family physicians managed these cases for 11.9 ± 0.45 months and various specialists for an additional 39.8 ± 1.22 months. Neurosurgeons were the quickest to refer to an implant physician (average delay of 2.69 ± 0.22 years), while orthopedic surgeons and nonimplanting pain physicians took the longest, contributing to delays of 4.30 ± 0.42 and 4.84 ± 0.48 years, respectively. Once the decision for implantation was made, the implanting surgeon required 3.31 ± 0.09 months to complete the procedure. A gradual decline in wait times was observed from 1980 to the present. Veizi and Hayek reviewed the data of 275 patients who underwent an SCS trial over a five-year period (2006–2011) and calculated a mean wait time of 6.50 years (197).

The multiple regression models used by Kumar and Rizvi (130) indicated that age, sex, workers' compensation coverage, and referring specialty were significant predictors of implantation delay ($p < 0.0001$). An increase of one year in age correlated with a 0.09 ± 0.01

year increase in implantation delay. Women had a significantly lower implantation delay of 11.92 months. The cohort of patients without workers' compensation coverage had a significantly longer implantation delay of 8.97 months over the group of patients with coverage.

It should be remembered that these results of Kumar and Rizvi reflect the health-care system in Canada and might not apply to other national health-care systems. Greater awareness by health-care providers, education, funding, and interdisciplinary collaboration are required to address the shortfalls in processing patients to the suitable treating physician. The NACC recommends that SCS and PNS be considered earlier and trialed in the first two years of chronic pain if certain conservative measures, such as over-the-counter (OTC) analgesics, exercise, physical therapeutic modalities, cognitive behavioral therapies, injection therapies, and the like have failed to provide acceptable pain relief and before another back operation or initiation of long-term long-acting opioid maintenance.

NACC EVALUATION OF NEUROMODULATION FOR COMMON CHRONIC PAIN CONDITIONS

Background

Cervical SCS for chronic radiculopathy was evaluated in an institutional review board-approved prospective multicenter international registry in which patients were enrolled after implantation (198). Twenty-eight patients (73.7%) were implanted with percutaneous leads, and ten patients (26.3%) received paddle leads. The majority of leads were implanted with the lead tip at C2 or C3. Direct patient report of percentage of pain relief was 54.2% (±21.4%), 60.2% (±24.8%), and 66.8% (±22.5%) at three, six, and 12 months post-implant, respectively. Pain relief was categorized as excellent/good (61.6%) at three months, with similar results observed at six and 12 months. Mean pain disability index (PDI) scores were 49.6 (±14.4) at baseline and were significantly reduced to 34.5 (±15.7) at three months ($p = 0.0013$), to 33.4 (±15.5) at six months ($p = 0.0014$), and to 28.4 (±13.4) at 12 months ($p = 0.0001$). At three months post-implant, 92.4% of patients indicated they were very satisfied or satisfied with the SCS device; none indicated dissatisfaction. Similar results were noted at six and 12 months. Overall QOL was reported as improved or greatly improved by 73.1% of patients at three months, with similar results at six and 12 months.

The outcomes of SCS to treat lumbar radiculopathy, whether associated with FBSS or not, have been evaluated in several RCTs (121,127), as well as in a large prospective international registry (42). In the PROCESS study (121) discussed previously, patients with FBSS who were treated with SCS reported sustained pain relief, improvements in functional capacity and health-related QOL, and satisfaction with the treatment after implantation. In another RCT, patients with persistent or recurrent radicular pain after FBSS who were treated with SCS reported significantly greater pain relief and satisfaction with treatment than patients who underwent reoperation (127). In this crossover study design, patients initially randomized to SCS were also significantly less likely to cross over to reoperation than those randomly assigned to reoperation. In the aforesaid prospective international registry, 70% of the patients (406/580) had pain in the lumbar spine and 20% (114/572) had radiculopathies. In their interim analysis, Deer and colleagues found sustained pain relief at three, six, and 12 months post-enrollment, as well as significantly reduced PDI scores (42). The majority of patients categorized their pain relief as excellent or good and said their overall QOL improved or greatly improved.

Axial Back Pain

Background

Data regarding SCS to treat isolated axial back pain are limited (199), in part because of the mixed nociceptive and neuropathic nature of this condition (121,165). Since the 1990s, intrathecal drug delivery (IDD) has been used successfully to manage axial back pain (200,201) but, along with SCS, PNS, and PNfS, has been relegated to last-resort therapy (202). Increased awareness of the iatrogenic morbidity and mortality associated with IDD (203–205), as well as new insights into the mechanisms of SCS and evolving SCS technology, have revived interest in treating axial back pain with SCS (206) before IDD (207). Earlier implementation of SCS has been suggested for FBSS (163), and novel lead designs that combine percutaneous and epidural neurostimulation are under development (76,77,208–212).

The success of SCS in treating axial back pain rests on many factors, including the underlying pain pathology and its potential responsiveness to neurostimulation, patient selection with regard to indications and comorbidities, and awareness of contemporary lead configurations and their optimal applications and proper placement and programming. A current FDA-approved noninferiority study comparing conventional SCS with 10-kHz-frequency SCS using the SENZA 10-kHz-frequency SCS device will be helpful in assessing whether 10-kHz-frequency SCS is the same as conventional SCS. Likewise, ongoing work on DRG stimulation (24,67,68) and burst stimulation (22,27) might define new approaches to axial back pain.

Evidence

In the mid-1990s, Turner and Loeser reported that evidence for the use of SCS for chronic low back pain was inconclusive due to the lack of randomized trials (213). However, since then, North et al. have published RCTs that examined SCS vs. reoperation, and SCS technology has evolved to include new lead configurations and simultaneous use of SCS and PNfS. Using traditional SCS leads and programming technologies, North and colleagues (32) published the strongest evidence from a prospective controlled clinical trial comparing single and dual percutaneous electrodes in the treatment of predominantly axial low back pain from FBSS. Another prospective study reported the efficacy of paddle electrodes after a single 1×4 percutaneous trial in the treatment of 44 patients with predominant or comparable lower back pain with leg pain (214). Although SCS effectively relieves low back pain, leg pain relief exceeds back pain relief at six and 12 months, with the gap widening at 12 months (215). Van Buyten and colleagues retrospectively studied 17 FBSS patients with axial low back and leg pain and found that treatment with 2×4 electrodes significantly reduced back and leg pain as well as analgesic use (215). Ohnmeiss and Rashbaum reported satisfaction with SCS for predominant chronic low back pain in 41 patients. They found that 60% considered themselves improved and 75% would undergo the procedure again for the same result (199).

A systematic review concluded that there was level II-1 or level II-2 evidence for SCS in relieving chronic intractable pain of FBSS on a long-term basis (216). Bala et al. conducted a systematic review to assess the cost-effectiveness of SCS in relieving chronic pain in patients with FBSS (170). They concluded that SCS effectively treated FBSS in terms of pain reduction, QOL, and functional status. In terms of cost-effectiveness, SCS is both more effective and less costly in the long term, but an initial high cost is associated with device implantation and adjustment.

Although there are no RCTs yet, recent results from uncontrolled or randomized trials with PNfS alone or in combination with SCS in treating axial low back pain have been encouraging (76,77,209,217–220). The advantages of PNfS include simplicity and low risk.

Conversely, intracranial neurostimulation, specifically deep brain stimulation, has demonstrated some success in treating pain related to FBSS (221,222). The NACC has published a companion article on the appropriate use of intracranial neurostimulation to treat chronic pain, including axial low back pain (2).

Discussion

The resurgence of interest in using SCS to treat axial back pain is due, variously, to 1) increasingly sophisticated percutaneous and paddle lead configurations; 2) PNfS alone or PNfS combined with SCS; and 3) stimulation protocols. Recent encouraging new work suggests that DRG-SCS (24,25), burst frequency (22), and kilohertz-frequency (20,21) SCS may significantly improve the chances of success. In at least one study, transverse tripolar leads produced larger decreases in VAS than conventional stimulation (32% vs. 16%, respectively), in patients with chronic, intractable neuropathic pain of the trunk and/or limbs of more than three months' duration (223). Tripole paddle designs recently introduced in the USA, including the Specify 5-6-5 (Medtronic, Minneapolis, MN, USA), and the Penta, Tripole, and Exclaim leads (St. Jude, Minneapolis, MN, USA), may allow more effective paresthesia coverage of the axial lower back (224).

There have been more than 2000 implants using a new method of delivering percutaneous paddle leads within the epidural space via a sheath (Epiducer, St. Jude Neuromodulation, Plano, TX, USA) placed using the Seldinger technique (225). The initial results of this new method of placing paddle leads percutaneously were first presented in 2011 (226); of note was the reported ease of placement, excellent safety profile without significant adverse events, and a positive effect on pain reduction at one year. Mironer and colleagues recently presented their multicenter initial experience in the USA using this technique and system, implanting paddle leads, complex coaxial lead constructs, and hybrids of both systems (227). The placement of the percutaneous sheath was successful in 42 of 43 cases, and no significant adverse events occurred. However, before concluding that this technique of lead placement is equal to, better than, or worse than conventional placements of SCS leads via an epidural needle, an RCT should be performed comparing the two techniques. PfNS is the subject of a European trial, comparing it with usual care in FBSS with axial back pain (228). The study has started recruiting in Europe; a similar study is to start in the USA.

Recommendations

The NACC recommends that SCS be used for axial back pain after identifying a specific pain generator. Options to be considered include hybrid epidural and PNfS (76,77,193), complex paddles and multilead configurations, kilohertz-frequency SCS (20,21), and DRG stimulation (24,67,68). PNfS carries the potential for overuse or abuse by overzealous, poorly trained practitioners who lack an investment in the therapy's long-term success. Therefore, the recommendation of NACC is to use strict protocols to ensure proper application and to monitor outcomes of PNfS.

Cluneal Neuralgia

Superior cluneal neuralgia is thought to arise from structural or functional entrapment of the nerve within the muscular layers of the back or to arise after posterior bone graft harvesting of the ilium (229,230). As the terminal branches of the superior cluneal nerves lie consistently over the upper posterior aspect of the ilium, they should be amenable to PNS in this area, whether placed via a fluoroscopic or ultrasound-guided technique. Current evidence is limited for this type of stimulation, and no evidence exists on outcomes or long-term follow-up. The NACC recommends additional study or consideration of the cluneal nerve as a target in planned PNS studies.

NEUROPATHIC PAIN ASSOCIATED WITH VARIOUS DISEASES

Diabetes-Associated Neuropathy

Background

Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus (DM) and is associated with high pain scores and significant reduction in QOL. This pervasive and costly complication is present in up to 50% of all DM patients with long duration of disease (231). Although poor glucose control and cardiovascular risk factors have been reported to be associated with PDPN, exact etiology and pathophysiological mechanisms remain largely unknown (232). Nerve conduction studies and quantitative sensory testing may support the clinical diagnosis.

Evidence

Pluijms and colleagues recently presented a systematic review on treatment efficacy and safety of SCS in PDPN (233). The authors identified three prospective case studies (234–236) and one retrospective cohort study (237) for a total of 25 patients who met the inclusion criteria of the review. At one-year follow-up, SCS resulted in ≥50% pain relief in 63% of the patients. Analgesic use was reduced in most conventional SCS-treated patients with complete withdrawal in 60%. No major adverse events were reported. Another recent article by Pluijms et al. (238) published the results of 15 patients with PDPN who were treated with SCS. Clinically relevant pain relief was present in 11 patients after trial stimulation and in ten patients at 12 months' follow-up. QOL and sleep hygiene, as well as several neuropathic pain measures, were reported to have maintained improvement at 12-month follow-up. The authors concluded that SCS appears to be an effective and feasible treatment for intractable PDPN.

Recently, the Maastricht group completed a study in which patients with PDPN were randomized 2 : 1 to SCS or best medical treatment, respectively (personal communication from M. van Kleef). Significantly more patients in the SCS group (13/22, 56%) achieved success compared with patients in the best medical care group (1/14, 7%) over a six-month period ($p < 0.01$). Quality of life (EQ-5D) increased 0.25 points compared to baseline in patients treated with SCS; however, there was no statistical difference in utility scores between patients in the SCS and best medical care groups.

Discussion

In summary, one systematic review (233), one exploratory overview (232), three prospective case series (234–236), and one retrospective cohort study (237) that include a total of 40 patients treated with SCS for PDPN have been identified. The NACC believes that the available literature indicates that SCS seems to be an efficacious and feasible treatment for intractable PDPN. Given that the pain of diabetic neuropathy is neuropathic, SCS should be considered early if conventional pharmacological treatment for PDPN has provided insufficient pain relief or intolerable side effects. Caution should be taken, as DM patients have increased risk of infection with surgery and implantable devices.

Recommendations

The Toronto Expert Panel on Diabetic Neuropathy has recently presented a treatment algorithm for PDPN (231). The authors state

that management of patients with PDPN must be tailored to individual requirements, taking into consideration morbidities and other factors. Optimization of glycemic control and aggressive management of cardiovascular risk factors are mandatory.

In the past, the generally accepted treatment algorithm for PDPN had not included interventional pain therapies as first-line therapy. The Toronto Expert Panel concluded from their deliberations on algorithms of care for PDPN that there were a number of unmet needs regarding the therapeutic management of PDPN, including appropriately designed studies to investigate nonpharmacologic approaches. The NACC opines that the algorithm should be revised to use SCS earlier in the process. This is particularly true when considering the poor response of PDPN patients to opioids. Recent studies also suggest that DRG-SCS may be particularly suited for this disorder (25).

Human Immunodeficiency Virus Neuropathy

Background

To date there have been no recommendations concerning neuromodulation as a treatment for refractory HIV-associated painful neuropathy (HIV-N) and resultant neuropathic pain, because the pathophysiological mechanisms of HIV-N are heterogeneous and poorly understood (239–242). Possible mechanisms of HIV-N include viral infection-induced nerve-fiber damage or HIV treatment-associated neuropathy. Morphological alterations were found in experimental animal models in the spinal dorsal column, the DRG, or the axonal nerve terminal, with certain inflammatory cytokines (TNF-α, interleukins, etc.) amplifying the tissue reaction (243). In addition, disease duration, comorbidity, malnutrition, demographic factors, ethnicity, and gene-induced mitochondrial dysfunction have been discussed as cofactors (244–248).

Recommendations

The NACC opines that SCS is appropriate therapy for the treatment of HIV-N, just as SCS is appropriate therapy for other causes of neuropathic pain. Conventional SCS and DRG-SCS appear to be reasonable options for this form of neuropathy.

Postherpetic Neuralgia

Background

PHN is an intractable, chronic, painful neuropathic condition that follows herpes zoster reactivation. The diagnosis of PHN is made when dermatomal lancinating and/or burning pain persists longer than expected after the skin lesions have crusted. The virus, which remains dormant in the DRG, is reactivated with decreases in cell-mediated immunity. Vaccination for herpes zoster may reduce the intensity and severity of PHN (249,250). A number of treatments are validated for the management of PHN, including anticonvulsants, antidepressants, topical agents, and opioids. However, these treatments are poorly tolerated by many patients or do not result in significant pain relief for many others (251). Because of this relative failure of medication management to successfully treat patients with PHN, neuromodulation therapies have been utilized when more conservative therapies have failed.

Evidence

While there are no RCTs, there is some support in the literature for the use of SCS or PNS in managing PHN (252). In an early retrospective study, Meglio and colleagues described successful SCS trials in six of ten patients with PHN, and pain relief was maintained over the long-term follow-up of 15 to 46 months (253). The largest study on neurostimulation in PHN involved prospective follow-up of 28 patients over a median duration of 29 months (254). In this study, patients were in pain for at least two years prior to SCS placement, and the median age was 70 years. Long-term pain relief was accomplished in 23/28 patients (82%) with a concomitant decrease in VAS pain scores from 9 to 1. There were also qualitative improvements in daily function, as evidenced by significant decreases in PDI scores. In addition, this study examined the effect of SCS in four patients with acute herpes zoster pain. SCS resulted in prompt pain relief, and the patients' pain subsided after two to three months of stimulation. Moriyama applied extended temporary SCS using percutaneously placed quadripolar leads for seven to 14 days in 14 patients during the subacute stage of zoster pain (20 to 82 days following rash appearance) who did not receive sufficient pain relief with continuous epidural blockade (255). The 14 patients reported pain relief during temporary stimulation. In another report, two patients with subacute PHN refractory to medications and injection received excellent pain control for seven to ten days after percutaneous SCS placement (256). SCS was also helpful in managing intractable PHN pain in four of 11 patients with PHN and concomitant chronic kidney disease who had inadequate pain relief with conventional therapies. Implanted patients were followed for more than two years, and VAS scores decreased from 8 to <3 on a scale of 0 to 10.

Although some centers have reported very positive experience with SCS treatment for PHN (253), the general consensus is that the degree of positive response may be inversely correlated with the level of deafferentation. In small case studies, PNS has proven effective for the treatment of PHN in the distribution of the trigeminal nerves (257–260).

Abdominal/Pelvic Pain

Background

Chronic abdominal pain affects QOL (261) and can result in increased health-care utilization, and in many instances the actual cause of the pain remains unknown (262,263). Abdominal pain leads to increased physician office visits and is the main reason for gastrointestinal (GI) consultation (264–266). SCS reportedly provides significant relief from chronic visceral pain and improves patients' QOL by decreasing opioid use (267–269).

Although the mechanisms of abdominal pain relief with SCS are not clearly identified, several plausible theories exist to explain how it might work (270,271). Activation of the supraspinal pain modulatory pathways by SCS, release of inhibitory neuromodulators such as γ-aminobutyric acid (GABA), blockade of nerve conduction by antidromic activation, direct stimulation of the postsynaptic visceral dorsal column pathway, or down-regulation of segmental or supraspinal sympathetic outflow are possible explanations of the analgesic effect of SCS for chronic abdominal pain (270–275).

SCS has been studied in visceral hyperalgesia using a well-established rat model of visceromotor reflex (VMR) elicited by colonic distension (276,277). This reflex was suppressed by SCS implants in both normal and sensitized rats. A hypothesis for this suppression is that SCS causes antidromic activation of peripheral sensory fibers, negating afferent input of nociception (276,278,279).

Evidence

Currently, there are limited outcomes data on SCS for various chronic visceral pain syndromes. What limited data exist in the literature are in the form of case reports and smaller case series that demonstrate significant clinical improvement in patients with chronic visceral syndromes: mesenteric ischemic pain (280), esophageal dysmotility (281), gastroparesis (282), irritable bowel syndrome (IBS) (283), chronic pancreatitis (261,262,284–286),

familial Mediterranean fever (287), posttraumatic splenectomy (263), generalized chronic abdominal pain (288), chronic mesenteric ischemia (280), and chronic visceral pelvic pain (288). A recent small prospective randomized crossover study on IBS patients receiving SCS demonstrated significant pain relief with SCS (289).

Recently, several case series (267,268,285,286) provide some evidence that various causes of chronic abdominal pain and pain from dysmotility syndromes—such as chronic pancreatitis, gastroparesis, mesenteric ischemia, postgastric bypass chronic epigastric pain, and chronic visceral pain after intra-abdominal surgeries with evidence of abdominal adhesions—could be helped with SCS. A small retrospective study of 35 consecutive patients who underwent SCS trial for chronic visceral pain with clearly defined cause provided some short-term evidence of the efficacy of SCS (267). The majority of the patients (30 of 35) reported >50% reduction in their pain and decreased opioid use. However, only 19 patients were followed for the whole year; the rest were either followed for less than a year, had their SCS system removed due to infection or lead migration, were lost to follow-up, or requested explant.

A national email survey regarding the technical aspects of SCS when used for chronic abdominal pain was sent out to implanters of SCS asking them if they used SCS for visceral pain syndromes. Seventy-six case reports from 23 responding interventional pain medicine physicians were collected. Six incompletely filled reports were excluded from the analysis, resulting in the reporting of 70 cases (269). The technical aspects of SCS (e.g., lead placement, type of stimulation) were similar to those published in previous studies (267). The most frequent placement of the lead was in the posterior epidural midline, and the most frequent vertebral level for the lead tip position was T5 (269).

Recommendations

Although there are a number of case reports and small case series to support the use of SCS for visceral pain, high-level evidence in the form of an RCT does not exist. The NACC recommends that SCS for visceral pain be used on a case-by-case basis with careful algorithmic thinking. SCS, whether conventional SCS, burst SCS, kilohertz-frequency SCS, or DRG stimulation, should be used when more conservative therapies, including OTC analgesics, exercise, physical therapeutic modalities, cognitive behavioral therapies, injection therapies, and the like, have failed to provide acceptable pain relief and before initiating long-term long-acting opioid maintenance.

Postamputation Pain

Background

PAP presents as a heterogeneous group of overlapping pain syndromes. It can be secondary to neuroma, CRPS, somatic pain, and phantom limb pain (PLP). Distinguishable from other limb pains, PLP is localized to the absent limb. Most PAP pain syndromes are neuropathic in origin. Frequently, the syndromes and symptoms overlap (290). There exists no consensus on the treatment for PAP. The prevalence of PAP is as follows: phantom limb sensations, 64%; PLP, 32%; and residual limb pain, 24% (291). Approximately 95% of amputees suffer associated chronic pain, although the pain severity varies (292).

Evidence

Case series data support the use of SCS for pain following limb amputation (293–295). Postamputation and stump pain are generally considered better indications for conventional SCS, if it is possible to generate paresthesia in the phantom limb. Two studies reported that PLP was more difficult to treat reliably with conventional SCS than other responsive pathologies (33,296). The experience with DRG stimulation suggests that the treatment of phantom pain may be amenable to this therapy (25).

Since the early 1930s, it has been known that increasing frequencies of stimulation of peripheral nerves to kilohertz levels has different effects on nerve blockade from driving action potentials at lower frequencies of 10–600 Hz (297–301). Kilgore and Bhadra have recently published on reversible nerve block with kilohertz-frequency electrical stimulation (302). These authors suggest that "kHz frequency electrical stimulation could be used to block sensory nerves for the treatment of peripheral nerve pain and may provide a more effective alternative when compared with peripheral nerve stimulation." Soin recently showed that the kilohertz-frequency nerve block was effective in producing long-lasting relief of PAP in a small group of patients (303).

Any diagnosis that antedates amputation may influence treatment success, especially if accompanied by preamputation pain (304,305).

Recommendations

The NACC recommends proceeding with neuromodulation therapies but underscores the necessity of using caution, realizing that the etiology of the pain may vary for the reasons noted and the results may be unpredictable. The work being done by Soin and his colleagues with kilohertz-frequency PNS, producing a block of nerves in amputees, may add to our ability to successfully treat PAP, and we are looking forward to planned RCTs using kilohertz-frequency block of nerves in amputees (303).

Compressive Lesions From Malignancies

There are many ways active malignancies may cause pain, including direct tumor invasion of bone, viscera, or neural structures and/or causing compressive neuropathies (306). For progressive, severe, refractory cancer pain, IDD is often effective for pain control (307).

For chronic cancer pain among long-term survivors, chronic pain treatment algorithms should be used, and these algorithms do include consideration of neurostimulation therapies (308,309). The use of neurostimulation should be reserved for those with expected extended periods of remission, slow disease progression, or resolution of the disease. The NACC recommends considering future MRI needs when choosing a device. In patients with thrombocytopenia, the use of PNS or PNfS should be considered, weighing the risks and benefits of the pain-relieving therapy.

Chest Wall Pain Syndromes

Background

Post-thoracotomy pain syndrome (PTPS) is persistent pain in the area of the thoracotomy incision that extends beyond the expected course of acute illness or injury, usually thought to be three to six months (1). The true incidence of PTPS is hard to define (310,311). In postmastectomy pain syndrome (PMPS), patients complain of pain and sensory changes in the region of the surgical scar, chest wall, upper arm, axilla, shoulder discomfort, phantom breast dysesthesias, and paresthesias. The most common identifiable cause of PMPS is damage to the intercostobrachial nerve—so-called intercostobrachial neuralgia (ICBN) (311).

In a review of 21 studies with follow-up periods from one to 96 months, Jung et al. found that the reported prevalence of phantom breast pain, ICBN, and neuroma pain varied widely (311), and most patients with ICBN or PTPS were previously treated with intercostal nerve blocks, neurolysis, and/or thoracic epidural steroid injections

(310,312,313). The highest incidence (53%) of pain occurred in the patients who had combined mastectomy and reconstruction with breast implants (313).

Evidence and Discussion

PHN and PTPS or PMPS have been treated successfully with SCS and PNS. Alexander Yakovlev et al. reported on 14 patients with lung cancer, status post-thoracotomy, lung resection, and postoperative external radiation who experienced constant burning, stabbing pain of the chest wall. They were implanted with octapolar leads and reported sustained relief at 12 months (314). Currently, one FDA-approved pivotal trial is under way (Stimrouter, Bioness, Valencia, CA, USA).

Because of the cross-dermatomal coverage and multisegmental innervation, along with avoidance of a higher volume of CSF that is common overlying the thoracic spine, DRG stimulation (Axium, Spinal Modulation, Menlo Park, CA, USA) may offer a unique strategy for sustained therapeutic coverage of the chest wall. Current data suggest that this strategy may offer another treatment option for historically challenging neuromodulation targets (25). At the time of this writing, a pivotal study is under way in the USA.

Recommendations

The NACC recommends caution when using conventional SCS as a treatment for chest wall pain. The use of DRG stimulation may be considered as an option in countries where it is presently approved but should only be used under a research protocol in countries where it is not. Another consideration would be the use of PNS with conventional SCS leads or a self-contained lead with external energy supply in cases of small geographic areas of pain. Currently, one FDA-approved pivotal trial is under way (Stimrouter, Bioness, Valencia, CA, USA).

Demyelinating Central Pain States

SCS has been shown to be helpful in treating neuropathic pain secondary to the demyelinating disease MS (315). The early work of Illis et al. on the use of SCS for MS appeared promising; however, this therapy has been limited by the need for repeated MRI imaging studies in this group of patients. Today, there is a new interest in SCS for MS because of the development and approval of new MRI-compatible SCS devices. The NACC recommends that patients with demyelinating diseases such as MS be considered for SCS if the managing physician feels the potential benefits outweigh the risks and after establishing that available leads and IPGs will meet the patient's imaging needs.

Spinal Cord Injury

Evidence

The medical literature for the treatment of pain secondary to spinal cord injury is limited, and strong opinions exist among experts regarding both the positive and negative aspects of SCS for these patients. "Complete" spinal cord injury (i.e., a proven total functional transection) removes the dorsal columns (which are branches of primary afferents) above the lesion; thus, patients with diffuse pain below the injury will not feel paresthesia with conventional SCS. Patients with well-circumscribed segmental pain at the level of injury, on the other hand, are more amenable to SCS; for example, in a large mixed case series with seven-year mean follow-up, North et al. reported on a subset of 11 spinal cord injury patients with favorable results (158).

Recommendations

Spinal cord injury patients commonly have posttraumatic or post-surgical scarring and other pathology, which can preclude percutaneous access, and so surgical paddle placement can be necessary just for an SCS trial. The NACC recommends that these patients be approached on a case-by-case basis and that neuromodulation be used judiciously.

MIXED NEUROPATHIC–VASCULAR CONDITIONS

Complex Regional Pain Syndrome

Background

CRPS is a debilitating neuropathic condition characterized by intractable pain, autonomic dysfunction, edema, vasomotor changes, movement disorder, and atrophy in late stages (316). Two forms of CRPS have been defined by the IASP: CRPS-I, which occurs without discernible nerve injury, and CRPS-II, which accompanies a definable nerve injury (1).

The etiology of CRPS remains elusive, although in the majority of patients, it develops after injury or surgery (317). The involvement of the inflammatory mediators in CRPS I indicates that inflammation might play an important role in the etiology of CRPS (318). Stringent diagnostic criteria first established by the IASP (319) have since been updated to improve the specificity of the diagnosis (320–322). In the absence of objective diagnostic tests, the diagnosis of CRPS, whether type I or type II, relies on a detailed clinical history coupled with evidence derived from the physical examination (323).

The most recent IASP clinical diagnostic criteria for a diagnosis of CRPS include 1) continuing pain disproportionate to any inciting incident; 2) at least one symptom in any of four categories—sensory (hyperalgesia and/or allodynia), vasomotor (temperature asymmetry and/or skin color changes), sudomotor/edema (edema and/or sweating changes or asymmetry), or motor/trophic (decreased range of motion and/or motor dysfunction and/or trophic changes); 3) at least one sign at time of evaluation in two or more of the sensory, vasomotor, sudomotor/edema, and motor/trophic categories; and 4) no other diagnosis that better explains the signs and symptoms (322). Criterion 4 defines a third CRPS subtype called CRPS not otherwise specified (CRPS-NOS), in which patients partially meet CRPS criteria and their presentation is not better explained by any other condition.

A variety of therapies have been offered for CRPS-I that include pharmacotherapy, transcutaneous electrical nerve stimulation (TENS), SCS, sympathetic blocks, and chemical or surgical sympathectomies (324,325). SCS is minimally invasive and reversible; it reduces pain and allodynia, improves limb function and QOL, and lessens depression in patients with CRPS-I (129,158,319,326,327). An interdisciplinary treatment protocol, developed under the aegis of IASP, recommends simultaneous psychological, rehabilitative, and interventional pain management with therapeutic options determined by the patient's clinical progress (322,328). Although SCS traditionally follows a prolonged systematic course of conservative care for CRPS-I, earlier aggressive treatment may produce better outcomes (50). Accordingly, the treatment algorithm should be sufficiently flexible to allow SCS earlier when rehabilitation fails to progress rapidly (164).

Evidence

In 2007, the Neuromodulation Therapy Access Coalition published their summary of grade A evidence supporting the use of SCS to treat CRPS, including three RCTs, six long-term follow-up studies, six short-term follow-up studies, ten retrospective case studies, and numerous studies of CRPS for mixed indications (191).

A UK Health Technology Assessment published in 2009 concluded that the clinical efficacy and cost-effectiveness of SCS in treating neuropathic pain (including CRPS-I and ischemic

conditions) were superior to CMM (179). This assessment was based on a systematic literature review of approximately 6000 citations from 13 electronic databases. Of 11 RCTs, three specifically addressed neuropathic pain.

In 2010, a CRPS-I Task Force of the Dutch Society of Rehabilitation Specialists and the Dutch Society of Anesthesiologists was set up to create evidence-based guidelines for the treatment of CRPS-I. This task force concluded that SCS achieves long-term pain reduction and improves QOL but does not improve function and recommended SCS use in carefully selected patients with CRPS-I who had undergone a successful trial of stimulation (329). Shortly thereafter, an international group of clinicians also used an evidence-based method to conclude that SCS is recommended for the treatment of CRPS-I if other treatments fail to improve pain and dysfunction (330). They rated the evidence level for this therapy as 2 and the recommendation as B+.

A 2013 PubMed literature search, using "SCS and complex regional pain syndrome" for studies published in the past five years, yielded 44 articles, four of which were clinical or RCT studies and only one of which was prospective. That multicenter, open-label prospective study recruited 55 patients, 34 of whom responded to SCS during a trial and were implanted (331). Only 14 of the 34 SCS-treated patients were diagnosed with CRPS. At six months, the mean VAS and QOL scores had improved. The other three RCT studies examined brush-evoked allodynia as a predictor of SCS outcome in CRPS (332), patients with FBSS enrolled in the PROCESS study (333), and motor cortex stimulation for CRPS (334). An additional prospective cohort study was available by Epub ahead of print (335). In that study by Guerts et al., 84 consecutive patients with SCS-treated CRPS-I were enrolled between 1997 and 2008. During 11 years of follow-up, 41% experienced at least 30% pain relief, and at 12 years, 63% were still using their SCS device. A total of 122 additional SCS interventions were required in 51 patients over the 12-year period: 13 for complications, 44 for battery changes, and 65 related to equipment.

Sears et al. (336) reported on the long-term follow-up of patients receiving SCS for CRPS-I and FBSS. Eighteen patients with CRPS received SCS with paddle leads between 1997 and 2008. These patients experienced a significant reduction in pain after implantation (–4.5 VAS score, $p < 0.0001$), and 55.6% (10/18) of them reported >50% pain relief at a mean of 4.4 years' follow-up. Patient satisfaction was high, with 77.8% (14/18) of patients saying that they would repeat the same procedure for the same outcome. There was a slight loss of efficacy over time; however, loss of efficacy was more pronounced in the FBSS group than in the CRPS group.

In the longest reported follow-up of SCS-treated patients with CRPS to date, Kumar et al. (171) documented pain reduction, decreased medication use, improved QOL, and improved functional status among 25 patients with a mean follow-up of 7.3 years. At last follow-up, even with slight regression, these patients maintained statistically significant benefits compared to baseline ($p < 0.001$). Patient satisfaction also remained high, with 22 of 25 (88%) patients satisfied with their pain relief and expressing willingness to repeat the procedure based on their experience. Best results were associated with early stage 1 CRPS-I patients younger than 40 years of age and with SCS treatment within a year of the onset of CRPS. In its most recent CRPS treatment algorithm, the IASP recommends that SCS be started within 12 to 16 weeks if conventional therapy fails (337).

Discussion

Treatment algorithms for CRPS invariably include SCS, and no other modality for this disease has been as thoroughly documented or has achieved similar long-term success. In adolescents, SCS may be considered as a possibly curative therapy (324).

Recommendations

The NACC recommends SCS for the treatment of CRPS-I and CRPS-II with pain of at least three months' duration or severe, rapidly progressing disease that is not responding to more conservative measures such as rehabilitation, but only after informed consent has been obtained and a psychological evaluation and successful trial have been performed (338).

Ischemic Pain Syndromes

Background

Insufficient blood supply results in ischemia of the extremities and peripheral tissues, and this, in turn, causes pain and functional limitation. Occlusive peripheral vascular disease (PVD) or PAD, notably atherosclerosis, has a substantial fixed or static component, and this should be distinguished from the variable or dynamic component of vasospastic conditions, notably Raynaud's disease. Devulder et al. (131) recently published an algorithm for the treatment of critical ischemic pain, making this distinction. According to the authors, first-line therapy should be conservative using pharmacological treatment with analgesics, vasodilators, and anticoagulants, followed by SCS or sympathetic blocks as second-line therapy for patients refractory to medication. If first- and second-line therapies are inadequate, then SCS or sympathectomy should be considered as third-line therapy.

Evidence

A Cochrane review by Ubbink and Vermeulen on the effectiveness of SCS for treatment of nonreconstructable chronic critical ischemia compared with conservative treatment alone was published in 2005 and later updated (339). The authors identified ten papers, of which five focused on the Dutch epidural electric spinal cord electrical stimulation (ESES) study (175,340–343), each addressing a different endpoint or aspect. Ubbink and Vermeulen classified the ESES-related papers as one randomized trial. Thus, in total, five RCTs (ESES study, 344–346), and one nonrandomized controlled clinical trial (347) yielded a total of 444 patients, based on the inclusion criteria defined in the review (see review for full details). No study was blinded due to the type of intervention. In summary, it was concluded that SCS leads to fewer amputations, provides better pain relief, and restores more patients to Fontaine stage II status compared with conservative treatment. Patients receiving conservative treatment exhibited more adverse effects due to medication, including GI hemorrhage, nausea, and dizziness. Transcutaneous oxygen pressure ($TcPO_2$) measurements have been found to be useful in selecting the patients most likely to respond to SCS, particularly those having a foot $TcPO_2$ between 10 and 30 mmHg (347).

The conclusions in the Cochrane review have, however, been questioned. A Health Technology Assessment report on the clinical and cost-effectiveness of SCS in the management of chronic pain of ischemic (and neuropathic) origin pointed out that the existing ischemic pain trials had small sample sizes, and most may not have been adequately powered to detect clinically meaningful differences (179). Two of the studies referred to in the Cochrane Review did not show any significant difference in amputation scores between SCS-treated patients and patients receiving pharmacological treatment alone (346).

Discussion

Based on the available literature on SCS for treatment of inoperable chronic critical leg ischemia presented here, the conclusion should be drawn that SCS, compared with conservative treatment alone, may reduce amputation rate and pain in selected patients

Table 14. Summary of the Case Reports and Retrospective Case Studies on the Use of Spinal Cord Stimulation for Treating Raynaud's Phenomenon.

Authors	No. of patients	Range of follow-up	No. patients with prior sympathectomies (% of patients)	Microvascular monitoring to assess SCS effects	Anatomical location	Lead position	Outcome (% of patients)	Complications (% of patients)	Success defined by author (% of patients)
Fiume 1983 (355)	1	1 year†	0	None	Right leg	T9	PC, U	IR	S (100)
Francaviglia et al. 1994 (44)	15	1 to 6 years	5 (33)	None	Upper extremity	C4 to C7	E (86), F (86), M (83), PC (83), RE (93), U (100)	R (7)	S (100)
Neuhauser et al. 2001 (356)	1	1.5 years	1	CM, LDA	Bilateral hands	C5/C6	PC, RE, U	None	S (100)
Robaina et al. 1989 (43)	3	Mean 27 months	1	P	Upper extremity	C5 to C7	PC, RE, U	Not documented	S (100)
Raso 1989 (362)	40	2 to 30 months	4 (10)	P, CWD	Upper extremity	C6 to T2	PC, RE, U	I	S (100)
Sibell et al. 2005 (361)	1	>1 year	1	None	Upper extremity	C4	F, M, PC, U‡	I	S (100)

Table adapted and updated from: Provenzano et al. (357).
†SCS removed at three months due to infection.
‡Patient experienced some healing; nonhealing ulcers required distal phalanx amputation.
CM, capillary microscopy; CWD, continuous-wave Doppler; E, reduced edema; F, functional improvement; I, treated infection; IR, infection requiring SCS removal; LDA, laser Doppler anemometry; M, reduced pain medication; PC, pain control; R, lead replacement; RE, Raynaud's episode improvement; S, successful treatment; $TcPO_2$; transcutaneous oxygen pressure monitoring; U, ulcer healing.

refractory to conservative and reconstructive surgical treatment. SCS for treatment of ischemic neuropathy merits grading as a level B therapy according to the evidence grading outlined by the INS in the Practice Parameters for the Use of Spinal Cord Stimulation in the Treatment of Chronic Neuropathic Pain (191).

Recommendations

Patients with pain due to PAD initially receive conservative therapy that aims at treating the cause as well as the symptoms. In persistent disease, reconstructive vascular surgery is a straightforward choice in appropriate candidates, although it sometimes fails even in optimal candidates (348). Ischemia due to structural lesions (peripheral arterial occlusive disease) or due to vasospasm (viz., Raynaud's disease, see below) are well treated by SCS; however, venous engorgement has not been shown to respond. In the SCS-EPOS study, Amann et al. selected patients with a fair microcirculation on the basis of their local $TcPO_2$ (10–30 mmHg) and those with poor $TcPO_2$ (<10 mmHg) who still showed at least some reserve capacity (increase to at least 20 mmHg) after test stimulation (347). They found that SCS treatment for nonreconstructable critical leg ischemia provides a significantly better limb survival rate compared with conservative treatment. The NACC feels that the evidence supporting sympathectomy is very poor and recommends SCS be utilized prior to the irreversible approach of sympathectomy.

Raynaud's Syndrome

Background

Raynaud's disease is a vasospastic disorder primarily affecting the distal resistance vessels and causing ischemia. It may occur independently (idiopathic or primary Raynaud's) or present as a manifestation of a systemic disease, such as scleroderma, CREST syndrome (CREST is an acronym for the five manifestations of the syndrome: calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia), or systemic lupus erythematosus (secondary Raynaud's) (349,350). The incidences of primary and secondary Raynaud's phenomenon range from 0.2% to 5% (131). Initial symptoms include a burning sensation in the affected area, usually fingers, accompanied by allodynia and painful paresthesias with vasomotor changes (cold; white or cyanotic discoloration).

In patients with refractory pain, sympathetic nerve blocks have been used, although these have a short duration of action. Both sympathetic nerve blocks and surgical sympathectomy lack long-term studies that might indicate positive long-term outcomes (351–354).

Evidence

Current evidence for the use of SCS for Raynaud's phenomenon is based chiefly on case reports, which suggest that SCS could be a promising treatment (355–361) (Table 14). Raso (362) followed 1048 Raynaud patients for ten years, including 40 with critical ischemia who were treated with SCS. The results in those 40 patients were positive in 60%, with 18 reporting excellent results and six reporting good results. Patients with Raynaud's for less than five years had better results than those with Raynaud's for more than five years. Robaina et al. (43) treated 11 patients with severe vasospastic disorders of the upper limbs with SCS; three patients had idiopathic Raynaud's disease. A total of ten patients had good to excellent results, and thermographic and plethysmographic changes were observed. Francaviglia et al. (44) treated 15 patients with progressive systemic scleroderma and Raynaud's phenomenon using SCS. Their study showed beneficial effects of SCS on pain, ulcers, vascular sclerosis, and hand function.

Recommendations

Using the evidence-grading criteria set forth in the Practice Parameters for the Use of Spinal Cord Stimulation for the Treatment of Chronic Neuropathic Pain (191), SCS for treatment of patients with Raynaud's syndrome would be graded as level C. That means that SCS for this indication might be useful but has an undetermined validity due to lack of RCTs and well-designed clinical studies.

In a recent review, an algorithm for the treatment of Raynaud's phenomenon was presented by Devulder et al. (131), which recommends that neuromodulation for this disorder be used earlier in the algorithm of care. Their analysis showed that many medical treatments have disappointing long-term efficacy. Conservative treatment is often disappointing in individuals with secondary Raynaud's phenomenon, and sympathectomy for the treatment of Raynaud's phenomenon is associated with mixed results (351–354).

The NACC recommends using SCS as an early intervention in the first 12 weeks of symptoms in patients with Raynaud's syndrome and other painful ischemic vascular disorders.

Chronic Refractory Angina

Background

Chronic angina resistant to therapy (CART) is defined as a "clinical diagnosis based on the presence of symptoms of stable exercise induced angina, caused by myocardial ischemia due to advanced coronary disease, and which is not controllable by a combination of maximal tolerable medical therapy, bypass surgery and percutaneous intervention" (363). The current European guideline definition of CART is "chronic stable angina that persists despite optimal medication and when revascularization is unfeasible or where the risks are unjustified" (364). Included are patients inappropriate for revascularization due to unsuitable anatomy, sometimes resulting from one or several previous bypass or percutaneous transluminal coronary angioplasty procedures, lack of suitable grafting material, significant extracardiac comorbidity, and/or advanced age.

In recent years 6.8% of all patients who underwent coronary catheterization were categorized as "no-option," which means an incidence of at least 150,000 patients with CART each year in the USA (365) and about three patients per 100,000 inhabitants in Europe (366). In contrast to the impressive halving of mortality from ischemic atherosclerotic heart diseases during the past decades, angina-associated morbidity has not decreased. Thus, more and more patients are surviving ischemic heart diseases, and antianginal therapies will be ultimately exhausted. Furthermore, annual mortality in this group of patients is relatively low, varying from 4% to 6%, as they usually maintain their left ventricular function without serious arrhythmias (365,366). Hence, an increasing number of patients are refractory to standard conventional therapies (363). In this respect, any adjunct therapy that improves QOL for patients with CART without unfavorably affecting their prognosis is worth considering.

Invasive electrical neuromodulation therapies like SCS have been used to treat angina pectoris since 1967 (367). The original researchers used a radiofrequency-coupled device (a modification of which was used in the earliest SCS systems) to stimulate the carotid sinus. In 1982, neuromodulation for angina was administered with TENS (368). In 1986, the first SCS implants for angina were reported (369).

SCS is considered to act by a combination of electroanalgesia at the spinal cord and antianginal mechanisms (370), resulting in improved QOL (371). Although SCS modifies the perception of ischemic-sensitized nociception and so elevates the angina threshold, development of angina symptoms still occurs to warn of an acute myocardial infarction (372).

Evidence

Patients with CART experience severe pain leading to frequent hospitalization and poor health-related QOL (371). These patients are offered a number of therapies for which evidence is limited. As summarized earlier in the section on cost-effectiveness, SCS has the best efficacy/safety profile and is applicable to almost all patients with chronic CART.

The beneficial effects of neuromodulation have been shown to last for over ten years (373,374). In 2002, the European working group on CART summarized the evidence and concluded that SCS is one of the best adjuvant therapies (363). In concert with the NICE recommendations and in addition to numerous observational studies for the treatment of CART, several comparative randomized studies have been performed. Unfortunately, the majority of these randomized studies are small, ranging from 12 to 104 patients. A total of 12 original randomized studies and two meta-analyses of the first seven RCTs, evaluating a total of 270 patients, have strengthened the evidence regarding efficacy of SCS for angina (375,376).

A recent systematic review of the use of SCS in CART (375) identified seven RCTs including a total of 270 patients with refractory angina. Five studies compared SCS stimulation (SCS on) to either subthreshold or no SCS stimulation (SCS off). One study compared SCS with usual care, and two studies compared SCS with an alternative therapy (i.e., CABG or PMR). The risk of bias of five trials was judged to be high (i.e., two of five criteria met) and that of three trials to be low to moderate (i.e., three or more of five criteria met). These observations corroborated another meta-analysis (376).

The benefits of SCS in treating CART were also noted in the European Angina Registry Link Study (EARL) (371), where patients from ten European centers were entered prospectively. Implanted patients reported significantly fewer angina attacks, significantly reduced short-acting nitrate consumption, and significantly improved Canadian Cardiovascular Society class (all $p < 0.0001$) as well as QOL (SF-36 and Seattle Angina Questionnaire).

In an attempt to make SCS more accessible and less invasive for patients, some observational studies in the past decade have reported that subcutaneous electrical nerve stimulation can produce outcomes comparable with those of SCS (377).

SCS modulates the autonomic nervous system, decreases exaggerated intrinsic cardiac nerve activity independent of beta-sympathetic nervous system activity, improves exercise capacity and time to angina, and reduces ST-segment depression at comparable workload (370). Many observational and randomized studies have shown that there is a significant reduction in myocardial ischemia using different measures that include exercise stress testing, ambulatory electrocardiogram monitoring, right atrial pacing, radionuclide myocardial perfusion techniques, and coronary flow measurements. The anti-ischemic effect of SCS is the consequence of a combination of recruitment of collaterals and a preconditioning-like effect, making the myocyte more resistant to ischemic challenges. The combination of both phenomena may reduce myocardial demand (370,378).

Discussion

Although there is abundant evidence for SCS as a successful and safe therapy in the treatment of CART, the cardiology community in general has not accepted neuromodulation as a treatment option. A multidisciplinary team approach is certainly warranted if patients are to find relief from the disabling symptoms of angina with SCS.

Recommendations

In accord with a patient care pathway for CART (379), electrical neuromodulation is recommended as a reversible and safe therapy. The evidence level for SCS as therapy for refractory angina was reported as 2b in 2002 (380). Based on recent comparative randomized studies and two meta-analyses reporting significant improvements, SCS can now be recommended as evidence level 2a, degree of recommendation A. Based on the accumulated evidence, SCS for angina treatment is accepted in both the European (European Society of Cardiology) and US (American Heart Association/American College of Cardiology) guidelines (380).

The National Institute for Health and Clinical Evidence (NICE) of the UK recommends further research to generate robust evidence about the durability of benefits in the use of SCS (including pain relief, function, and QOL) executed by comparative studies, preferably RCTs (381).

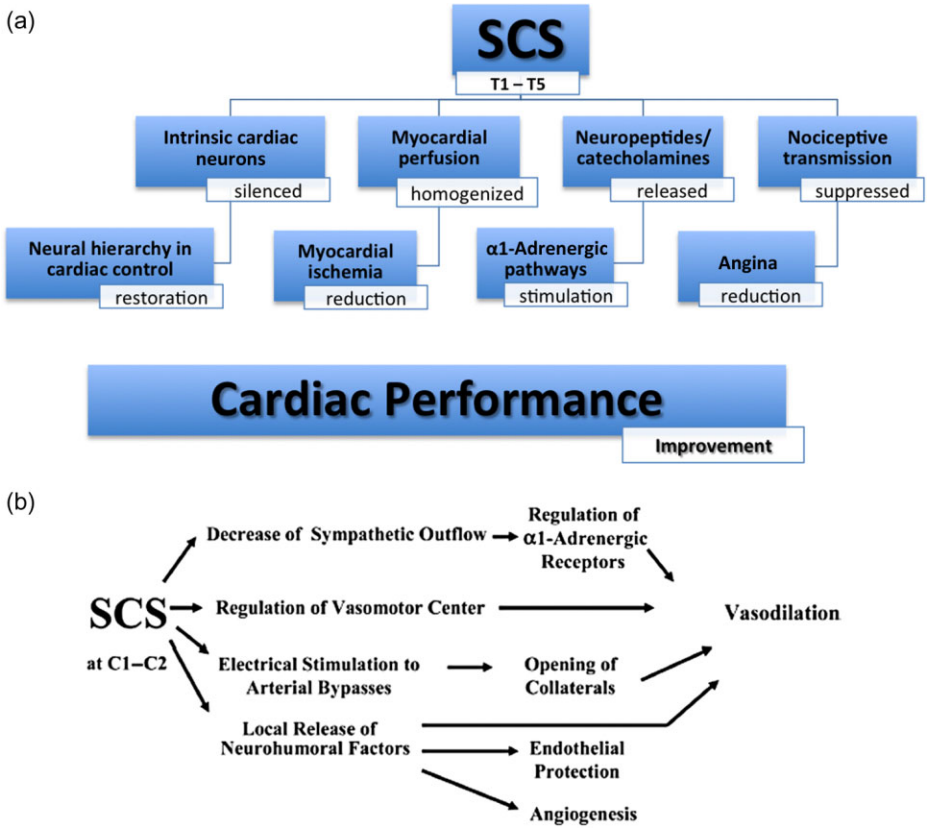

Figure 5. Potential mechanisms of spinal cord stimulation–improved heart function and vasodilation in the brain. a. Improved heart function may be due to locally increased or redistributed blood flow, regulation of the intrinsic cardiac nervous system, release of neuropeptides, and suppressed nociceptive transmission. b. Vasodilation may be due to decreased sympathetic outflow, regulation of the vasomotor center, electrical stimulation and opening of collaterals, and local release of neurohumoral factors, which may contribute to endothelial protection and angiogenesis.
Source: Figure adapted from Wu et al. (386). Used with permission of the authors.

Congestive Heart Failure

The use of electrical neuromodulation for congestive heart failure has drawn interest from both cardiologists and neuromodulators, partially because the positive results noted with SCS for the treatment of chronic refractory angina were also reported to improve reduced ventricular function (382). In basic research models, investigators have demonstrated that left ventricular ejection fraction improved with epidural SCS. The mechanism is thought to be induction of alpha-sympatholytic activity under stress (278), which results in myocardial protection and realigning of the ischemia-induced exaggerated activity of the intrinsic cardiac nervous system (383) (Fig. 5).

The effects of SCS vary with the spinal levels that are being stimulated. At the upper cervical levels (C1–C2), SCS increases cerebral blood flow, decreases sympathetic activity, increases vasomotor center activity, and releases neurohumoral factors. At C3–C6, SCS increases blood flow in the arms. In the thoracic spine (T1–T2), SCS relieves pain and reduces the frequency and severity of angina attacks. In the lower thoracic and lumbar spine (T11–L3), SCS may produce vasodilation in the legs and feet, and this effect, depending on the applied output of the neurostimulation device, can be mediated by antidromic activation of sensory fibers and decreased alpha-sympathetic outflow. In treating congestive heart failure, T1 to T3 stimulation has been successful in preliminary human work. Additional studies are under way to further define the targets and stimulation parameters.

In a canine heart-failure model, SCS significantly improved left ventricular ejection fraction ($p < 0.001$) compared with SCS plus concurrent medication (carvedilol plus ramipril, 2.5 mg PO QD) or no therapy (384). SCS also significantly decreased spontaneous nonsustained ventricular tachyarrhythmias and ischemic ventricular tachyarrhythmias ($p < 0.03$) compared with medication or no treatment. In a canine model of healed myocardial infarction and heart failure, SCS reduced sinus rate and systolic blood pressure, which are indicative of antisympathetic effects (385,386). In a porcine model of ischemic heart failure, thoracic SCS significantly increased left ventricular ejection fraction ($p < 0.05$) and decreased myocardial oxygen consumption without elevating norepinephrine levels ($p = 0.006$) (387,388).

Recently, human clinical studies have been initiated in an open-label manner in patients with heart failure to assess changes in left ventricular function and New York heart classification status among those who received implantable SCS devices in the upper thoracic or lower cervical spine (389).

NEW ADVANCES AND EMERGING TECHNOLOGY

Neuromodulation therapies continue to evolve at an increasingly rapid pace (390). Emerging therapies in pain treatment focus on novel implantable power technologies or skin-based power sources

(391), novel programming techniques to further optimize desired paresthesia capture, novel frequency bandwidths to stimulate subthreshold perception (20,22), and novel targets for stimulation, such as the DRG (25,68), the medial branch of the dorsal ramus, or the cluneal nerve. New microwave power technology may change the cost and profile of PNS, PNfS, and SCS in some settings. The 10-kHz-frequency system and DRG stimulation have been found to be safe and effective in prospective studies and have been approved in Europe for clinical use. The best indications for new approaches and technologies remain the subject of intense study. Beyond the pain treatment arena, a virtual explosion of neuromodulation therapies is happening in both clinical and preclinical phases to treat many disease states and indications. Table 5 presents some current devices under study.

The choices available, both in recently approved and in "over-the-horizon" technologies, give the practitioner more flexibility to determine the optimal neuromodulation construct in any given individual, but there are limited data sets to inform the process. Prospective, randomized, and masked (if using subparesthetic stimulation) studies are needed, and many are ongoing.

CONCLUSIONS

Neurostimulation—SCS, PNS, and PNfS—can be a life-changing therapy for many patients. Reversibly stimulating neural structures to reduce pain, improve function, and change QOL has obvious advantages in medical care. The NACC strives to enhance the quality of patient care. The recommendations made by this consensus panel are intended to improve safety, selection of implant candidates, efficacy, and cost-effectiveness. To this end, the NACC will update these recommendations in the future. We encourage implanting physicians to strive to provide the best and most informed care possible in this quickly evolving and exciting area of medicine.

NOTE

The Boston Scientific Precision Spectra SCS System has received Food and Drug Administration approval for MRI-conditional head scans. The ImageReadyTM Guidelines and Patient Eligibility Checklist are available from the company. St. Jude Medical is planning MRI compatibility submissions in the European Union in 2014.

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Dr. Deer served as primary author, project organizer, and editor; Drs. Provenzano, Pope, and Krames served as a primary authors and editors; Dr. Mekhail served as senior manuscript editor. The remaining authors contributed sections of the manuscript or provided critical reviews. Opinions expressed herein are not necessarily shared by all authors.

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COMMENTS

This is an ambitious project. The idea is to create a series of documents that will be reviewed, updated and added to over time in an effort to avoid the misleading advice offered by historical guideline groups. Our field is rapidly evolving at technological and clinical levels but the accumulation of copper-bottomed evidence is slow and incomplete. This is not because there is lack of efficacy of our therapies but that we have, as a group, found it difficult to organize ourselves into an evidence-producing cooperative. There are many new neuromodulation companies with new devices but often an inadequate resolve and budget to make not only the case for "approval" but also the case for reimbursement. The data required is different. Unless we find a way to resolve this our patients will not get access to the therapies that they need. The NACC will help to show the gaps. I just hope that other INS initiatives will help to encourage and support the evidence provision that we need.

However the NACC also shows us where there is not only the clinical evidence but also the consensus support. We must use this to drive SCS uptake in global healthcare systems.

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This manuscript reviews the levels of evidence available for a variety of forms of neurostimulation. The work is a result of the Neuromodulation Appropriateness Consensus Committee, and reports the levels of evidence available for the safety, efficacy, and indications for these procedures. Although evidence is lacking for some areas of neuromodulation, and clearly needs to be augmented, some good evidence does exist. This work represents a good summary of these data.

Some of the strongest evidence available is for the use of spinal cord stimulation to treat failed back surgery syndrome and complex regional pain syndrome. Less robust evidence is available for several other indications such as trunk neuralgias, facial pain, and postherpetic neuralgia. This work will be useful for implanters who are trying to make sense of a vast literature, and likely for payers who are critically assessing whether sufficient evidence is present to justify coverage of a particular procedure. Most importantly, reports such as this highlight the most obvious gaps in the evidence base, and will hopefully guide the creation of future evidence to fill in these gaps.

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Excellent and comprehensive article that will be for sure useful to all implanters to better select candidates for neurostimulation, reduce complications and convince payers thanks to a robust and detailed review of the available literature.

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Comments not included in the Early View version of this paper.

