Neuromodulation: Technology at the Neural Interface

Received: February 19, 2024 Revised: April 2, 2024 Accepted: April 22, 2024

https://doi.org/10.1016/j.neurom.2024.04.006

The Neurostimulation Appropriateness Consensus Committee (NACC)®: Recommendations for Spinal Cord Stimulation Long-term Outcome Optimization and Salvage Therapy

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ABSTRACT

Introduction: The International Neuromodulation Society (INS) has recognized a need to establish best practices for optimizing implantable devices and salvage when ideal outcomes are not realized. This group has established the Neurostimulation Appropriateness Consensus Committee (NACC)® to offer guidance on matters needed for both our members and the broader community of those affected by neuromodulation devices.

Materials and Methods: The executive committee of the INS nominated faculty for this NACC® publication on the basis of expertise, publications, and career work on the issue. In addition, the faculty was chosen in consideration of diversity and inclusion of different career paths and demographic categories. Once chosen, the faculty was asked to grade current evidence and along with expert opinion create consensus recommendations to address the lapses in information on this topic.

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Results: The NACC® group established informative and authoritative recommendations on the salvage and optimization of care for those with indwelling devices. The recommendations are based on evidence and expert opinion and will be expected to evolve as new data are generated for each topic.

Conclusions: NACC® guidance should be considered for any patient with less-than-optimal outcomes with a stimulation device implanted for treating chronic pain. Consideration should be given to these consensus points to salvage a potentially failed device before explant.

Keywords: Best practices, closed loop, dorsal root ganglion stimulation, high frequency, spinal cord stimulation

INTRODUCTION

Neuromodulation for pain control has witnessed major technologic advances over the past few decades, translating to improved pain relief, function, and quality of life. In long-term randomized controlled trials (RCTs), the efficacy of spinal cord stimulation (SCS) has been indicated for treating persistent spinal pain syndrome (PSPS, formerly failed back surgery syndrome), refractory angina pectoris, peripheral neuropathies, and complex regional pain syndrome (CRPS). Newer paresthesia-free or paresthesia-independent SCS modalities have been introduced, including burst SCS (B-SCS) and high-frequency SCS (HF-SCS). Compared with traditional SCS, these modalities provide both improved pain relief and improved affect, and are more commonly used than the more traditional tonic stimulation in treating chronic pain conditions.[1–3] Moreover, the quest for new therapeutic targets and stimulation delivery methods has led to the development of dorsal root ganglion stimulation (DRG-S), exploration of potential nonneuronal targets such as glial cells,[4] and closed-loop stimulation.[5]

Despite these technical advances, loss of efficacy (LoE) over time is a major limitation of neuromodulation procedures and is the leading cause of discontinuing neuromodulation therapy and device explantation. LoE refers to the decreasing effects of neuromodulation over time unrelated to device malfunction and may present early, including in the first year of therapy.[6] LoE remains a poorly understood phenomenon. Underlying mechanisms may involve psychologic issues, secondary gain, habituation, over- and understimulation, peripheral neuroplasticity, and central cortical reorganization.[7] Explant rates due to LoE are approximately 5% at one year after implantation and nearly 10% at two years after implantation.[8] Overall explantation rates may be as high as 43% to 73%,[9–11] although this number has been suggested to be much lower with the more recent SCS modalities.[1,3,5,12,13]

Novel waveforms and anatomic targets for neuromodulation have caused greater therapeutic outcomes of neurostimulation and may have a lower risk of losing efficacy over time. In addition, these newer approaches provide further opportunity to restore therapeutic relief if initial neuromodulation therapy loses effectiveness. Neuromodulation therapy aimed at restoring and potentially improving outcomes after a previous neurostimulation therapy has lost efficacy is termed "salvage therapy." Two scenarios apply: The first seeks to restore effective pain relief using the existing system, and the second involves the replacement of the existing device with one that works using a different type of stimulation or a different therapeutic target. Both should proceed only after a thorough patient evaluation dedicated to determining the possible reasons for therapeutic LoE. If both strategies fail, a patient, in conjunction with the physician, should decide to cease stimulation and either leave the system in situ with system turned off (also known as a "virtual explant") or explant it. Minimally invasive therapies as an alternative may offer pain relief to selected patients.

Traditional tonic SCS shows cost-effectiveness over conventional medical management in Canada at approximately 2.5 years after implantation[14] in patients with chronic pain syndromes such as PSPS.[15,16] The use of salvage therapy early in the course of initial neuromodulation treatment or on more than one occasion in a patient could lead to concerns of increased costs and thus decreased cost-effectiveness.[17,18] Physicians who perform neuromodulation procedures need to balance their ethical duty to the

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Source(s) of financial support: This Neurostimulation Appropriateness Consensus Committee publication was supported by the International Neuromodulation Society (INS), and no authors were paid for their contributions. Sarah Staples, MA, ELS, assisted with manuscript preparation as a parttime contractor for INS.

individual patient with their fiduciary responsibility to society. In fact, these issues are seldom in conflict given careful patient selection and maximizing neuromodulation outcomes are imperative for both the initial neuromodulation therapy and the proposed salvage treatments.

Thorough evaluation of ongoing neuromodulation therapies with optimization of programming is vital to limit LoE and the resulting discontinuation of potentially effective therapy. This guidance document outlines programming optimization for various neuromodulation therapies to maximize or regain effective therapy when clinical improvements have decreased over time. Furthermore, in cases in which LoE necessitates discontinuation of therapy, we provide a current evidence-based approach to restore therapy with alternative neuromodulation technologies. Considering the 2.5-year mark to reach cost-effectiveness and the inevitable decrease in patient satisfaction with LoE, therapy must be carefully optimized before abandoning a given neuromodulation therapy, and subsequent restoration options should be in place to recoup patient satisfaction and cost-effectiveness with another neuromodulation procedure.

MATERIALS AND METHODS

Development Process

As part of its mission to improve patient care and access to advanced neuromodulation techniques, the International Neuromodulation Society (INS) formed the Neurostimulation Appropriateness Consensus Committee (NACC)®, comprising INS members worldwide who were chosen for their recognized clinical expertise, familiarity with the peer-reviewed literature, research capabilities, and previous publications. At regular intervals, NACC members have evaluated the level of current evidence in the peer-reviewed literature for topics identified as critical for improving neuromodulation efficacy and safety.

Working groups were convened to conduct literature searches and examine the evidence for the topics developed by lead authors in outline form. After the literature search was completed, each author was asked to provide a list of cited references and a ranking of their level of evidence. On the basis of the literature cited within the preceding section, the section leaders then formulated the recommendation grade, which was reviewed by at least three different, nonconflicted NACC working group members. If conflicts of interest were identified, recusal was required. The section leaders then created consensus points, which were agreed on by in-person meetings, teleconference, or other electronic or audiovideo communications to define the consensus; agreement by ≥80% of the contributing authors was considered consensus. Consensus strength was defined as described in previous NACC[19] and Polyanalgesic Appropriateness Consensus Committee publications.[20] If a recommendation was proposed with <50% consensus, based on assigned evidence rank and recommendation grade, no consensus was achieved.

As a consensus guideline, this document provides recommendations in the form of consensus points regarding practices for salvage therapy and outcome optimization. However, these recommendations should not be construed as a standard of care but represent best practices. This guidance is based on several factors and peer-reviewed evidence, and regardless of the strength of the evidence, requires interpretation for clinical application based on physician judgment and specific patient circumstances.

Management of Conflict of Interest

The INS policy for guidelines development determined the disclosure process, which complies with the International Committee of Medical Journal Editors standards. One of the coprimary authors is without conflict and is the adjudication determination official for any issues of potential conflict. All authors were asked to recuse themselves from any recommendation potentially affected by a disclosed conflict. In addition, authors without conflict vetted all recommendations for bias. At least 50% of the authors had no potential conflicts of interest.

Literature Search, Evidence Ranking, and Consensus Development

The world literature in English was searched using Medline, EMBASE, Cochrane CENTRAL, BioMed Central, Web of Science, Google Scholar, PubMed, Current Contents Connect, Meeting Abstracts, and Scopus to identify and compile the evidence for neurostimulation therapies for treating pain. Search words included "spinal cord stimulation." Identified peer-reviewed literature was critiqued using the United States Preventive Services Task Force (USPSTF) criteria for quality of evidence,[21] with modifications for neuromodulation studies (Table 1). After USPSTF letter grading was assigned, the working subgroup assigned the "level of certainty regarding benefit" as described in Table 2.

For each major section or topic, the NACC formulated consensus points. Consensus points should be distinct from recommendations based on consensus alone, which were rendered as clinical guidance owing to the lack of evidence-based literature (such as RCTs, prospective observational studies, or retrospective cohort/case series).

SCS HABITUATION AND TOLERANCE

Tolerance is a well-defined pharmacologic term. It refers to the need for increasing doses of an agonist to accomplish the same physiologic effect and/or the reduced response of the body to the effects of the agonist with repeated exposure to the substance.[22] Tolerance can be a complex phenomenon involving the concentration of the drug, the changing number of specific types of receptors, the changing affinity for the receptors to the drug, etc. The field of neurostimulation has adopted the term "tolerance" from the pharmacologic literature, but the underlying nature of this decreased response to neurostimulation over time is not as well understood. The first reference of tolerance to SCS was by Kumar et al in 2006.[7] The authors astutely recognized the limitation of such nosology: "We also considered causes of long-term failures and have identified a group in whom, after initial pain relief, pain control eventually fades despite a fully functional stimulating system. We have labeled this phenomenon 'tolerance,' for lack of a better descriptive term."[7] However, unlike pharmacologic tolerance, tolerance to SCS is not defined physiologically or clinically. There are no molecular or laboratory/radiologic markers for SCS tolerance. Furthermore, when patients no longer receive analgesia from a functioning SCS system, increasing the "dose" of stimulation may or may not improve response. Levy et al have recently referred to this phenomenon as "therapy habituation."[6]

Habituation is described as "a behavioral response decrement that results from repeated stimulation and that does not involve sensory adaptation/sensory fatigue or motor fatigue."[6] Habituation or tolerance has been reported to occur in 13% to 34% of patients treated

Table 1. Quality of Evidence Ranking Using the USPSTF.

Grade	Definition	Suggestions for practice
A	The NACC recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The NACC recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The NACC recommends selectively offering or providing this service to individual patients on the basis of professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The NACC recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I (Insufficient Statement)	The NACC concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

with SCS.[6] Management can be challenging and labor-intensive. At the very least, it may involve significant reprogramming efforts and at the most may require revision with implantation of an alternate SCS system and/or system explantation.[6,7,11,23–25] Pathophysiology and etiologies notwithstanding, tolerance to stimulation is one of the commonly attributed causes of LoE with SCS,[26] and is the most common cause of device failure over time,[10,11] responsible for approximately 40% to 80% of SCS explants.[9,11,27,28] New discontinuous dosing strategies are hypothesized to slow the progression, but there is as yet no evidence of such.[29]

Tolerance to electrical stimulation occurs in every part of the nervous system in animals and humans. It is described in the peripheral nervous system,[30] dorsal root ganglion (DRG),[6] spinal cord,[6,8,31] brainstem,[32] deep brain nuclei,[33] and cerebral cortex.[34,35] It occurs in the clinical setting of chronic pain,[6,36] tinnitus,[35] and movement disorders,[37] and therefore likely is the consequence of a general (patho) physiological mechanism. The exact mechanisms of developing tolerance to electrical stimulation are not known, but some hypotheses have been advanced. Although one cause may be scarring around the implanted lead, with resulting changes in

Table 2. Levels of Certainty Regarding Net Benefit.

Level of certainty	Description
High	The available evidence includes consistent results from well-designed, well-conducted studies in representative primary care 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. Evidence Level: I-A - At least one controlled and randomized clinical trial, properly designed
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 the following factors: • the number, size, or quality of individual studies • inconsistency of findings across individual studies • limited generalizability of findings to routine primary care 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. Evidence Level I-B—Well-designed, controlled, nonrandomized clinical trials (Prospective Observational studies conforming to STROBE criteria) or Evidence Level I-C—Retrospective cohort or large case studies (>20 subjects)
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the following: • 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 primary care practice • lack of information on important health outcome Evidence Level II—Expert opinion based on risk to benefit or based on case reports

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

impedance,[38] most cases seem to be idiopathic[31] and are often not responsive to treatment. Tolerance at a clinical level may result from habituation at a synaptic level. This results from the predictability of a repetitive signal because an organism learns to stop responding to a stimulus which is no longer biologically relevant (by being monotonous).[39] As far back as the 1960s, Thompson and Spencer characterized habituation in the spinal cord[40] in the following ways:

1. If stimuli are stopped, recovery of the response develops.
2. If repeated, habituation develops faster.
3. Higher frequencies cause more habituation.
4. Weaker stimuli cause more habituation.
5. Repetitive habituation may cause prolonged residual inhibition.
6. Habituation may generalize.
7. Other stimuli may cause dishabituation.
8. Repeated dishabituation produces habituation.
9. In marine mollusk studies, burst stimulation prevents habituation.[41]
10. In marine mollusk studies, burst stimulation can partially reverse habituation.[41]

Regarding a measured closed loop decreasing habituation, it should be understood that an electrical current depolarizes several nerve cells; it can create an objective measure of activation, which is the evoked compound action potential (ECAP). A fixed output system would have no measurement or control of the ECAP intensity, but the addition of a closed-loop system leads to a larger adherence to a neural dose and subsequent reduction of overdosing, believed to be a major factor in nerve response reduction.

These facts suggest that low-frequency bursts, intermittent stimulation, measured stimulation, or unpredictable stimulation may treat or prevent tolerance to stimulation, although this has yet to be shown clinically.

Consensus Point 1. Tolerance or habituation to stimulation, defined as the loss of pain relief from an otherwise functioning SCS system, is common, with a reported frequency of 13% to 34%.

USPSTF grade A, level of certainty high, evidence level I-A

Consensus Point 2. Tolerance to therapy is a leading cause of therapy failure and the need for system explant.

USPSTF grade A, level of certainty high, evidence level I-A

Consensus Point 3. The term "tolerance" is not synonymous with loss of therapeutic efficacy. The failure of a device may be multifactorial and unrelated to the dosing or habituation of the dosing. Factors including targets, disease progression, neural target changes, and device malfunctions are all potential causes of failing therapies. Going forward, we could recommend the term "loss of efficacy."

USPSTF grade is not applicable because this is a statement on nomenclature, not therapy. Level of certainty high, level of evidence II

PATIENT EVALUATION IN THE SETTING OF LOSS OF SCS EFFICACY

Pain Evaluation for Worsening or New-Onset Pain

One of the challenges facing physicians who manage patients with chronic pain with implanted neuromodulation devices is worsening pain that can contribute to the loss of perceived benefit. Consistent follow-up can often identify changes in pain and address them promptly with further programming or other medical interventions. Patients with implanted devices also can, and often do, develop new areas of pain. New-onset low back pain (LBP) with or without leg pain not only affects those patients with neuromodulatory devices placed for LBP but also individuals who have the device for other pain etiologies. The increasing prevalence of primary LBP in addition to that secondary to comorbid psychologic disorders and medical risk factors such as obesity, advancing age, smoking, and lack of exercise will render the need for pain reevaluation more common.[42] Moreover, as the number of patients with implanted neuromodulatory devices increases, the incidence of patients needing other types of therapy or procedures also may increase.[43]

In the case of a new pain generator in any location, it is recommended that the patient be evaluated in the same manner as in all other pain evaluations. This includes a detailed history, physical examination, and any necessary diagnostic studies. The history is regarded as the most valuable tool for establishing a differential diagnosis. Using a broad differential diagnosis for the new pain is paramount for establishing the proper diagnosis. Patients may report that the device hardware is the source of their pain. For example, worsening buttock pain may be blamed on the implantable pulse generator (IPG). Although pocket pain is not uncommon and can affect up to 8% of patients, physical examination can often clarify whether the hardware is the true source of pain or simply coincides with the region of new referred pain.[44] Inspection of the device insertion sites also is valuable in reducing suspicion of infection. Patients also may blame the stimulation of the device for the "new pain," which can be evaluated by simply turning the device off.

In addition to LBP, which has numerous possible sources,[45] other symptoms may include headache, pain in the neck, shoulder, hip, knee, and/or upper and lower extremities. Although the physical examination is of variable validity and value in evaluating pain reports, it remains the most common standard tool for guiding further testing when combined with history. The diagnostic study that usually imposes the greatest challenge for patients with implanted neuromodulatory devices is magnetic resonance imaging (MRI). When the SCS system is not MRI compatible, computed tomography or ultrasound may suffice. If MRI is deemed necessary, knowledge of MRI conditional labeling among the different manufacturers' devices is fundamental. Consideration for conversion to a conditionally MRI-compatible system may be reasonable in those patients who are likely to have ongoing MRI needs for relapsing conditions; it is hoped that this consideration will be made before the initial device implantation.

Using the existing implanted system to control a new pain symptom is ideal. However, if the pain is outside the treatment field of the stimulator, potential therapeutic options include physical therapy (PT), medication management, and diagnostic and therapeutic blocks. New-onset back or leg pain may have an inflammatory component and may thus be best treated with injection-based therapies (Table 3) using antiinflammatory steroids. Persistent nociceptive facetogenic pain may be managed by radiofrequency lesioning of the medial branches.

In addition, before explant, the physician should consider other pain generators that may not be within the common indications of neurostimulation devices. These issues may create a clinical scenario that mimics habituation but is not a therapy failure; rather, it is the presentation of a new treatment need. For example, these issues have been outlined in publications that generated the successful continued use of neuromodulation devices after treatment of sacroiliac disease or spinal stenosis.[46,47]

Table 3. Factors to Consider With Antiinflammatory Steroid Injection Therapy for a Patient With a Neurostimulation Device.

- Injections are not contraindicated solely because a patient has an SCS device implanted.
- Consider image guidance for injections when the implanted system is close to the location of treatment.
- Extreme caution must be taken to prevent infection. The degree of sterile precautions will depend on the proposed procedure and proximity to the implanted device.

Consensus Point 4. The NACC recommends consideration of new pain generators that may need treatment other than neuromodulation before deeming a device to be an ineffectual stimulation system.

USPSTF grade B, level of certainty moderate, evidence level I-C

If interventional procedures are deemed necessary for diagnostic and/or therapeutic purposes, carefully considering the implanted device is necessary. Proper sterile technique becomes particularly important when injecting in or around an implanted device to avoid infection that may force removal of the implanted system. In addition, any planned procedures need to consider placement of the IPG and leads to avoid physical harm to the implanted system; image guidance is recommended. When using radiofrequency lesioning near an IPG, it is first suggested that the grounding pad be placed on the opposite side of the IPG when possible.[48] This keeps the current path as far away from the generator and leads as possible. In addition, bipolar lesioning should be considered to minimize current spread. Recently, guidance was published to advise on dealing with radiofrequency in those with indwelling devices.[49]

Consensus Point 5. Proper precautions should be used when using radiofrequency ablation in patients with indwelling devices.

USPSTF grade A, level of certainty moderate, evidence level 1-C

In addition to new pain generators, patients may have other chronic pain symptoms that the implanted device was not intended to treat. The decision to implant a neuromodulation device should address pain etiologies that are generally responsive to the therapy. Patients who have pain that is known to be unresponsive to neuromodulation should be treated with other modalities. In such cases, injection therapies may be indicated. It is important that the physician understand the pain generators for each patient and set appropriate expectations for them as they relate to neuromodulation. Although the long-term safety and efficacy of injection use in patients with neuromodulation devices have not been adequately studied, rational selection of injections in these patients can offer valuable diagnostic insight and effective pain relief.

Consensus Point 6. Identifying new pain generators and differentiating between acute, subacute, and chronic pain issues require clinical assessment. Clinicians should balance maximizing therapy for long-term issues with appropriate assessment and treatment of acute/subacute issues with modalities such as percutaneous interventions and adjunctive medications.

USPSTF grade A, level of certainty high, evidence level II

MRI IMAGING FOR IMPLANTED NEUROMODULATION SYSTEMS

One great advancement in neurostimulation has been the development of MRI conditionally compatible devices. With such devices, patients may undergo MRI scanning after permanent implantation. At the time of this writing, MRI conditional SCS systems are widely available from multiple companies.[50] As described by Sayed et al, all approved implanted devices are cleared by the Food and Drug Administration (FDA) for MRI under very strict conditions and settings. In January 2024, a DRG-S device was added to the FDA-approved list.[51] Although many techniques for SCS salvage can involve the use of electrodes, adapters, and IPGs from different systems and vendors, MRI imaging after salvage therapy would likely not be allowed. Such cross-vendor systems have thus far not undergone the proper safety testing required for FDA clearance of MRI imaging.[52] Certain situations may exist in which existing percutaneous or paddle leads may be salvaged with upgraded IPGs from the same manufacturer, but this must be referenced and confirmed by safety data provided by the manufacturer. If MRI scanning in the future is of high priority, SCS salvage may require full explant of the existing device and reimplantation with a different MRI conditionally compatible SCS system.

Consensus Point 7. MRI compatibility should be a consideration when contemplating SCS salvage therapies. Cross-vendor compatibilities are not established in most cases, and this can lead to a currently MRI-compatible system no longer meeting MRI standards. Clinical judgment and discussion with the patient are key in decision-making.

USPSTF grade B, level of certainty low, evidence level II

DEVICE EVALUATION IN THE SETTING OF LOSS OF SCS EFFICACY

The loss of previously effective SCS therapy is an unfortunate complication that should be investigated and addressed expeditiously. A six-year review in patients who experienced LoE with 10-kHz dorsal column SCS found that a one-month stimulation holiday produced significantly greater pain relief ($p < 0.001$) and a significantly higher response rate (>50% pain relief, $p < 0.001$) after stimulation resumed.[53] Thus, some pain practitioners recommend suspending and restarting stimulation before abandoning the therapy.

Device Interrogation

The loss of previously effective SCS therapy is an unfortunate complication that should be investigated and addressed expeditiously. A range of factors may be responsible for a patient not receiving an acceptable level of pain relief from the neurostimulator despite successful therapy during the trial period or immediately after permanent implantation. These factors can be categorized as device, programming, or patient related (Table 4). By working in conjunction with the device manufacturer's representative, physicians can identify the source of the problem and take steps to regain pain relief for the patient.

Lead Migration

Migration of leads from their ideal position is a leading cause of a reduction or loss of pain relief. Published rates of migration vary

Table 4. Likely Causes for Inadequate Pain Relief After Neurostimulator Implantation.

Device-related issues	Programming issues	Patient-related issues
• Lead migration • Lead breakage • High impedance • Battery malfunction • Charging issues • Remote/programmer malfunction • End of service/implant life • Difficulty in entering MRI (magnetic resonance imaging) mode • Difficulty in entering surgery mode • Failure to respond to remote monitoring • Failure to respond to video remote programming	• Inappropriate programming • Incorrect therapy choice • Over- or understimulation • Failure to elicit ECAPS (evoked compound action potentials)	• Worsening of pain condition • New pain areas • Device nonuse/compliance issues • Habituation or therapy inadequacy

widely. A literature review in 2753 patients with SCS over 20 years gave a migration rate of 13.2%.[54] Rates are likely to be higher when leads pass over areas experiencing more movement; thus, migration may be more common in cervical than in thoracic SCS; occipital neurostimulation leads seem particularly vulnerable to migration.[55] When migration is significant enough to compromise coverage of the desired neural target, the patient experiences a loss of pain relief. This may initially be reported as a change or loss of coverage in the case of paresthesia-based therapies, or as a sudden or gradual loss of relief when paresthesia-free or paresthesia-independent programs are in use. Some systems can run diagnostic checks that alert programmers to certain types of lead migrations. Ultimately, radiologic techniques are used to visualize lead migration. Large displacements will be obvious on x-ray imaging alone; more subtle shifts are detected by comparison with fluoroscopy obtained at the end of the initial implantation procedure. Slight movements may be enough to lose therapy when the target is small, for example, with DRG-S, and may occasionally be compensated for using different contacts on the lead. However, lead revision is often required to restore adequate therapy. Careful and secure lead anchoring, strain-relieving measures, and good patient education and compliance with movement restrictions greatly minimize the risk of lead migrations. There has, however, been no definitive study comparing anchoring techniques to determine which is best.[55]

Lead Fracture

A lead fracture can cause stimulation to move from the desired target or more likely to be lost entirely, even if the lead remains in the same position. This damage can occur owing to trauma, sharp positional changes, anatomic stresses on the leads, intrinsic fragility of the leads, or wear and tear over time. Interrogation of the IPG provides information on the current programming and program use, in addition to the impedance of the electrodes. Fractures are suspected when impedance is >2 to 3000 Ω, although fractures are not the only possible cause of high impedance.

If there are no fractures, and impedance is normal, it is recommended to recheck the stimulation using paresthesia mapping, if this was performed during the initial implant. Fractured leads may be discontinuous when viewed on x-ray. In some cases of subtotal damage, the lead may appear intact on x-ray examination, and some contacts may remain functional. Therapy may then be salvageable by programming adjustments, although the partial failure of a lead often presages complete failure. Ultimately, lead replacement is often necessary to recapture stimulation. In addition, if a lead is only partially functional, it may not be within the parameters for MRI compatibility. This alone may lead to a need for revision or explant.

Battery Malfunction

Malfunction of the device battery can occur owing to intrinsic device-related faults; however, stringent manufacturing and quality-control processes overseen by government-controlled administrative bodies mean that this is a rare occurrence. More frequently, a battery might malfunction because of external factors, such as impact, trauma, or high electromagnetic fields (eg, those caused by radiofrequency ablation, electrocautery, or arc welding) near an implanted device, which may cause damage to the internal components. Damage to the battery-charger coupling or other charging issues can lead to irreversible battery depletion with some batteries and cause permanent battery failure.

Charging Issues

Some devices are primary cells, which means recharging a device is not needed. For all other devices, recharging is needed to maintain use of the device. Inadequate or improper charging can cause loss of device efficacy. Charging issues are most commonly due to faults with the external charging apparatus. Several other factors also may be responsible, including the use of programs with high power demands, high impedance leads, and battery-charger coupling issues. Other, patient-related issues include incorrect charging protocols, changes in battery position or depth due to changes in subcutaneous fat or scarring, and incorrect placement of the device during implant. When appropriate, replacing a faulty external charging device or reeducating a patient on correct charging protocols are quick and easy solutions. Relocating, anchoring, or changing the implanted depth of a battery may sometimes be required. If left unaddressed, charging issues can sometimes lead to permanent discharge of the battery, requiring replacement of the IPG.

Remote Control or Programmer Malfunction

Malfunction of the remote control or programmer can cause therapy failure by limiting patients' ability to correctly set and change their programs. This in turn can lead to under- or overstimulation, which either reduces the effectiveness of therapy or increases pain. Replacement of these peripherals should immediately rectify these problems.

End of Battery Life

A nonrechargeable battery will reach the end of its life after its stored charge has been depleted. Thereafter, only IPG replacement will allow the resumption of effective therapy. Some rechargeable IPGs reach their end of service after a predetermined number of years set by the manufacturer, at which time replacement also is necessary to maintain therapy.

Consensus Point 8. The NACC recommends new imaging and device interrogation to evaluate the possibility of lead migration, lead fracture, generator failure, or other mechanical disorders when LoE occurs.

USPSTF grade B, level of certainty low, evidence level II

USER ISSUES IN THE SETTING OF LOSS OF SCS EFFICACY

Inappropriate Program Usage

When LoE is observed, one of the first considerations should be inappropriate program usage or inappropriate application of a correct program, and the problem may be remedied in some settings. Monitoring levels of pain relief and optimizing program usage after implant are essential to maintaining consistent therapy outcomes. Follow-up appointments to reevaluate programming parameters or waveform selection are standard best practices for pain management using an implanted device. This follow-up is often performed in collaboration with a device manufacturer representative. Newer cloud-based tools are being introduced to assist in this process. In addition, US billing codes have been recently added for video-assisted teleprogramming through remote internet interaction.[56]

Incorrect Therapy Choice

Incorrect choice of therapy by the patient can cause immediate or early failure, or in an effort to optimize therapy, a reduction of previously experienced relief. Inadvertently switching to an alternative or ineffective program can cause over- or understimulation or a different mechanism of action effect, which produces loss of pain relief. Patient education on remote programmer use, good naming and organization of programs, and routine follow-up can minimize or quickly address this issue.

Understimulation or Overstimulation

Both understimulation and overstimulation cause increases in pain, either by not adequately downregulating pain pathways or by upregulating them, respectively. In many devices, the precise dose to create an impact cannot be easily determined and may make it difficult to identify understimulation or overstimulation; however, the latter is typically reported by the patient almost immediately as painful/uncomfortable, overly intense stimulation. In some devices, positional or electrical feedback can be used to adaptively maintain optimal stimulation, and in other settings, dosing studies have been performed. Again, good patient education, consistent follow-up, and optimization of programming minimize and mitigate this potential issue.[12,57]

Patient Noncompliance with the SCS Device

Patients may stop using their devices for various reasons, including loss of confidence in the device, lack of real or perceived benefit, or fears or anxieties after adverse events such as overstimulation, or other compliance issues. Noncompliance may be addressed by patient education, support, and routine follow-up. In some cases, this loss of compliance leads to a virtual or real explant. This signifies the need for ongoing follow-up and may be improved with future remote monitoring of device use.[58]

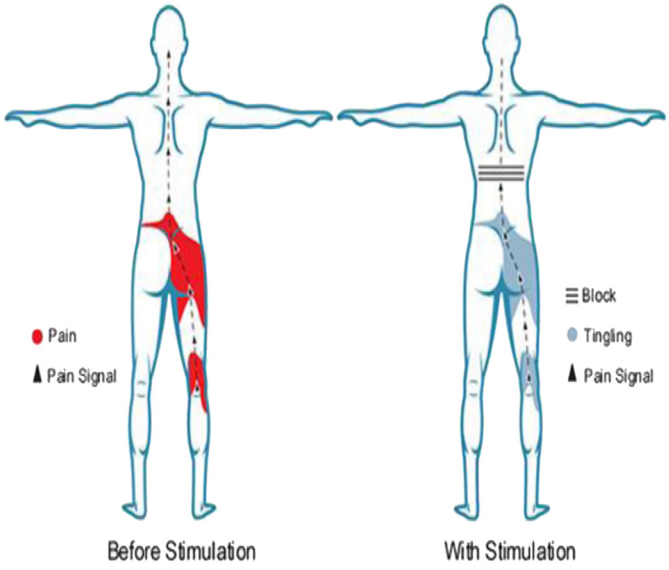

Figure 1. Paresthesia coverage of painful area. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

THERAPY OPTIMIZATION STRATEGIES WITH EXISTING SYSTEMS

Optimizing Tonic SCS

For decades, the goal of tonic SCS programming has been to generate stimulation-induced paresthesias in the area of pain (Fig. 1). In older studies, the degree of pain relief was observed to correlate strongly with the extent of the area(s) of pain that were overlaid with paresthesia as created by the stimulation itself.[59] At the interface between the epidural lead and the patient, an electrical impulse is transduced from the lead into the central nervous system, which ultimately causes an action potential within the

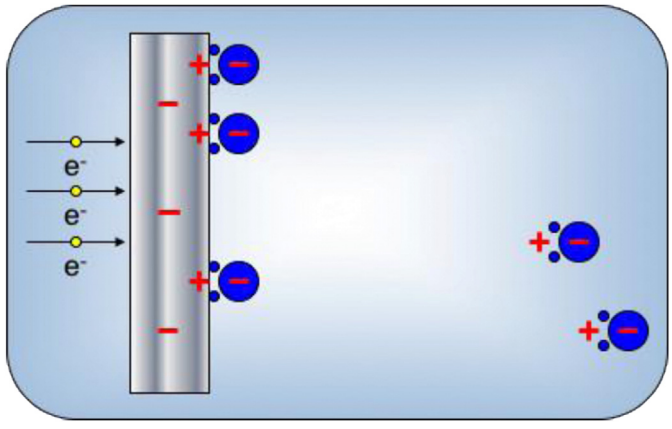

Figure 2. Flow of electrons in the lead alters the ionic orientation within the surrounding milieu. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

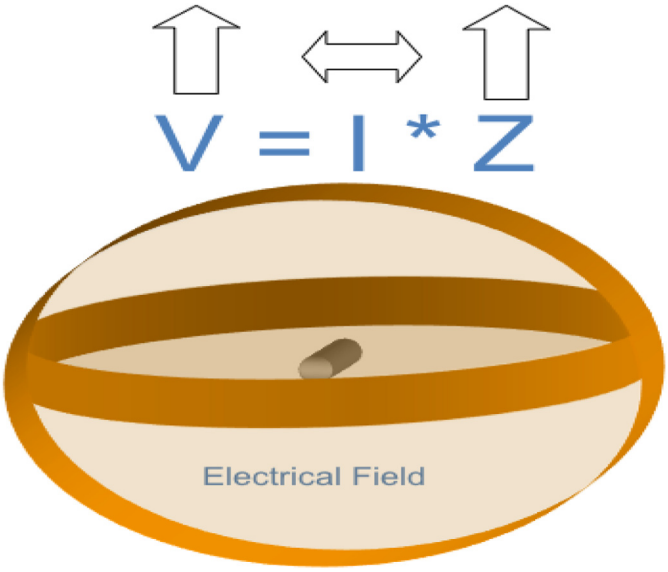

Figure 3. Voltage, current, and impedance interplay to create and shape the electrical field. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. I, current; V, voltage; Z, impedance. [Color figure can be viewed at www.neuromodulationjournal.org]

targeted neurons and the perception of a paresthesia in the corresponding body part(s) (Fig. 2).[60] The physics of a constant voltage SCS system indicates that as impedance increases, current decreases as voltage is held constant (Fig. 3). Conversely, in constant current systems, voltage increases as impedance increases to keep the flow of charge (current) constant. Before device advances, the debate on which of these engineered systems had the best outcome was a common topic, but there is literature to suggest constant current as a salvage mechanism is not upheld in high-level evidence studies.[61]

The output of a traditional tonic IPG can be modulated using three independent parameters: amplitude, pulse width, and frequency[60,62] (Fig. 4). When increasing amplitude from zero, the programmer initially encounters the patient's perception threshold when the stimulation is first detected. As the amplitude is increased, the patient will report the discomfort threshold when the stimulation becomes unpleasant. The range between the perception and discomfort thresholds defines the therapeutic window within which pain relief is usually obtained.

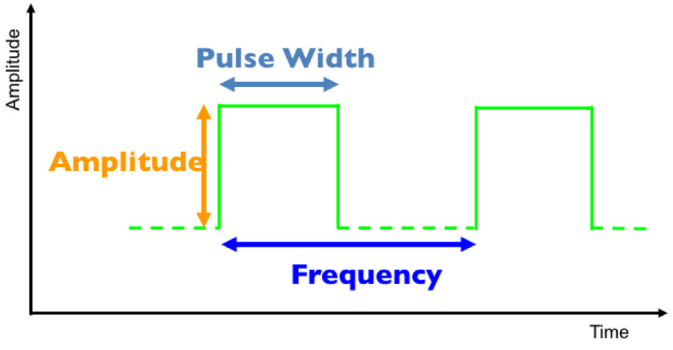

Figure 4. Amplitude, pulse width, and frequency. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

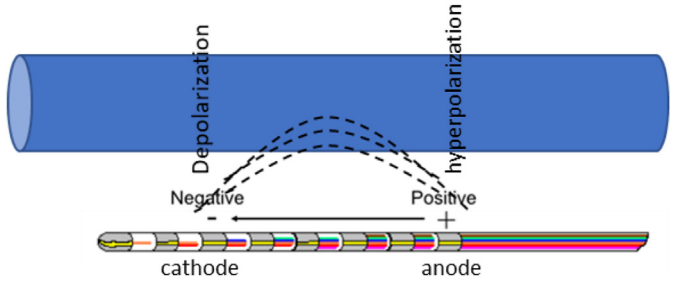

Figure 5. Electron flow. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

Because pulse width is increased using tonic SCS, patients tend to report a spread in the area covered by stimulation-induced paresthesias.[60,62] Frequency modulation tends to change the perceived nature of the stimulation from "buzzing" to "tingling," and at a higher frequency, all sensation of stimulation may be lost.

At the SCS lead level, electrons flow from the anode to the cathode (Fig. 5). The placement of charge along the electrode from negative to positive and the configuration of the active electrodes allow shaping of the electrical field and subsequently determine biological effect (Fig. 6a). For example, in Figure 6b, the simplest arrangement of cathode-anode generates an electrical field. However, using a "guarded array cathode" arrangement (a cathode flanked on either side by an anode) drives the electrical field deeper into the target zone of the dorsal column. Similarly, shallow but elongated electrical fields can be generated using a dual cathode adjacent to an anode arrangement (Fig. 6c). Lead arrangements and pulse widths can be maneuvered to target different areas within the dorsal column.

Finally, the more advanced concept of interleaving tonic stimulation uses the notion that stimulation parameters on one section of the lead (stimulation A) may have differing therapeutic effects from those using a different stimulation pattern (stimulation B) on another part of the lead. Alternating between these may allow a summation of biological effects that are synergistic and more effective than either stimulation pattern A or B alone (Fig. 7). This concept, known as interleaving, has been used to great effect in selected patients.[62]

Consensus Point 9. In patients with paresthesia-free systems, the modification in programming to a paresthesia-based program with or without closed loop could lead to salvage in a potentially failed system.

USPSTF grade B, level of certainty moderate, evidence level I-C

High-Frequency Stimulation (>10 kHz)

High-frequency stimulation was developed using high frequencies at low amplitudes to provide paresthesia-free stimulation. Frequencies of ≥1000 Hz have been studied, including the 10-kHz proprietary system.[63] Studies have shown 10-kHz stimulation to be superior to tonic SCS in treating both back and leg pain.[1,64] A patient who experiences LoE with tonic SCS can be considered for salvage therapy with 10-kHz stimulation. Several recent studies have shown impressive rates of therapy salvage using 10-kHz stimulation in patients with LoE, using lower frequencies.[65] In a multicenter retrospective review in 105 patients with ineffective pain relief from traditional SCS, most had a primary diagnosis of PSPS or CRPS. The average visual analog scale (VAS) pain score

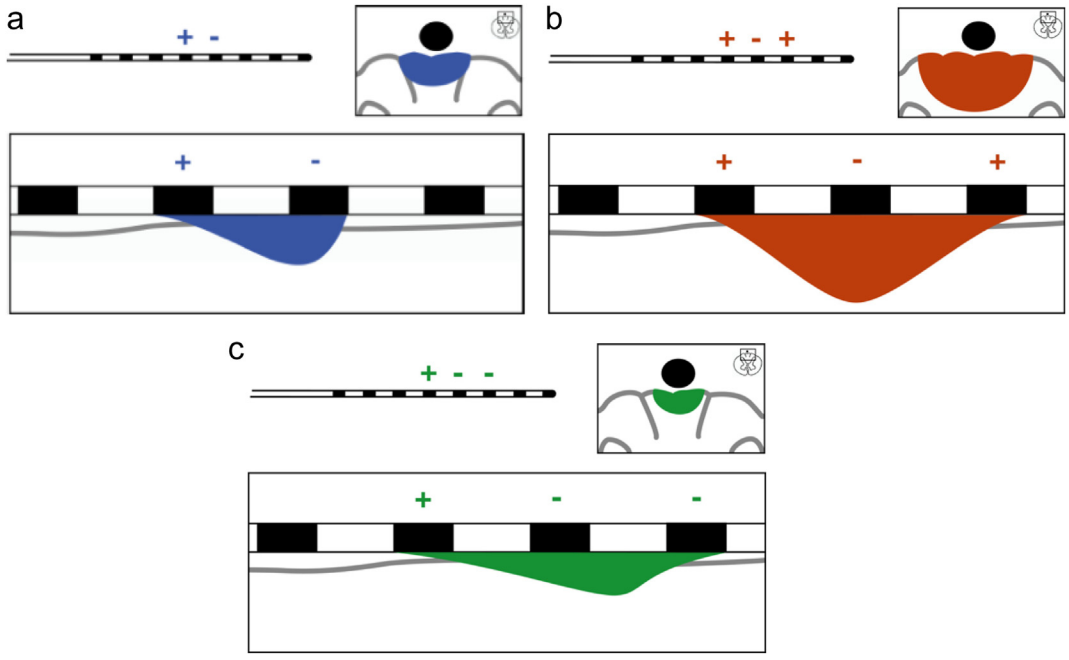

Figure 6. a. Flow of charge and generation of electrical field in a simple anode-cathode configuration. b. Flow of charge and generation of electrical field in a guarded cathode configuration. c. Shallow elongated field. Illustrations courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

before salvage with 10-kHz SCS was 8; after salvage to 10-kHz SCS, the average pain score decreased to 3 at both 12- and 24-month follow-up. The study also documented a decrease in the use of opioids; morphine equivalent usage decreased from 60 mg to 32 mg. The results of this multicenter review support the use of 10-kHz SCS as a salvage therapy for patients with decreased efficacy from traditional tonic SCS. A more recent observational European case series suggests that upgrading to a more versatile SCS device capable of delivering a variety of stimulation algorithms, including high-frequency (<1.2 kHz) stimulation, can reestablish efficacy for patients who experience LoE.[66] In the rescue subgroup ($n = 51$), the responder rate was 58.5% at last follow-up, and pain scores had decreased significantly ($p < 0.0001$) compared with scores with the previous device.

From a practical standpoint, there are a few nuances to using 10-kHz SCS as a rescue therapy. First, as noted previously, one must understand the reason for the loss of therapeutic efficacy. LoE due to uncomfortable paresthesias or failure to cover areas of pain with stimulation-induced paresthesias, as is often the case with PSPS, seems a promising indication for attempting salvage with 10-kHz SCS.[67] Another important consideration for 10-kHz salvage therapy is the electrode location of the existing system; 10-kHz stimulation of the lower back and legs targets a midline location around T9–T10, whereas tonic SCS is driven by paresthesia mapping to the

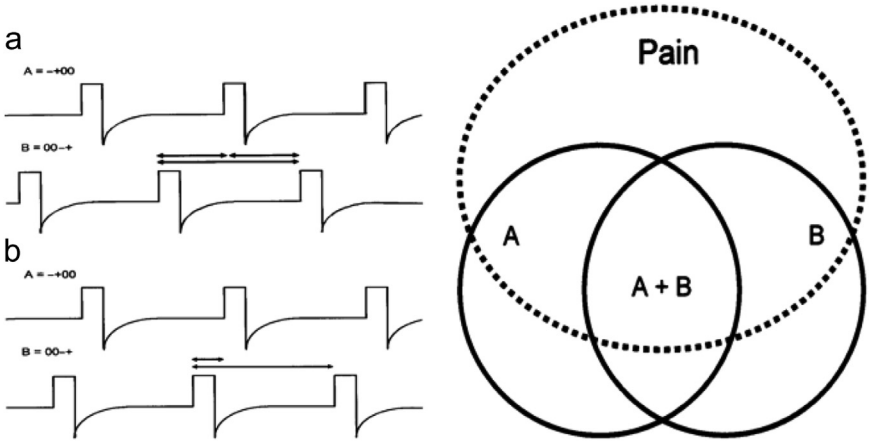

Figure 7. Interleaving pulses. Illustration courtesy of North RB, Kidd DH, Olin J, Sieracki JM, Boulay M. Spinal cord stimulation with interleaved pulses: a randomized, controlled trial. *Neuromodulation*. 2007;10:349–357 and used with permission from Elsevier.

patient's typical pain pattern. Existing SCS electrode placement will allow a conversion to 10 kHz if there are electrodes spanning T9–T10 near the anatomic midline. It should be noted that exact midline placement is not entirely essential for effective therapy with 10-kHz SCS, and that lead location both slightly right or left of midline can still produce effective therapy. If the preexisting electrode configuration does not span the ideal anatomic target (T9–T10 for lower back and leg pain), surgical revision of the existing leads must be considered in addition to replacement with an IPG capable of delivering 10-kHz SCS. In situations in which conventional stimulation is failing owing to axial pain, use of a higher frequency may be attempted before explant.[68]

Consensus Point 10. Modification to a system capable of delivering 10 kHz could lead to salvage of a potentially failed system. The electrode array must span the T9–T10 disk interspace.

USPSTF grade A, level of certainty high, evidence level I-B

Burst SCS

Burst stimulation was introduced by De Ridder et al in 2010 as an alternative to continuous low-frequency tonic stimulation.[69] Burst stimulation has been shown to be superior to tonic stimulation for patients with new implantations.[2] In addition, patients who have experienced tonic stimulation had reported reduced pain when switched to burst stimulation.[70] In a separate study, 62% of patients not responding to tonic SCS had increased analgesia when converted to burst stimulation.[69]

B-SCS activates the dorsal columns in stimulus bursts comprising five 1-millisecond pulses with an intraburst frequency of 500 Hz, delivered with a frequency of 40 Hz in a passive recharging paradigm; ie, the charge balance occurs at the end of the five monophasic pulses, to maintain charge balance across the electrical contacts.[71] The B-SCS system comprises one or two octopolar leads positioned in the epidural space to target the chronic neuropathic pain. If a patient with burst stimulation has lost the expected degree of pain relief, the suggested first step is to stop the stimulation for two weeks and then reassess the patient. This allows the clinician to investigate differences with and without stimulation and to determine whether the perceived loss of effect results from unrealistic expectations on the part of the patient.

For any paresthesia discrepancy, or if the lead(s) were placed anatomically, an x-ray may help confirm the electrode position and potential lead migration. Any lead migration will require either reprogramming, if the lead is still within the target areas, or a surgical revision of the electrode(s). If both anatomic and paresthesia-mapped burst programs at low amplitudes have been attempted unsuccessfully, a tonic program can be delivered before concluding that LoE has occurred.[72]

There are several nuances to programming B-SCS. In contrast to tonic stimulation, B-SCS suppresses pain more effectively at lower rather than higher amplitudes.[73] Cycling of stimulation, to improve battery life, should be considered given burst stimulation has a carry-over effect, and recent research has shown that lower burst doses with cycling had very good results. With burst, less stimulation seems more effective; stimulation as low as 0.1 mA with up to 360 seconds of off time seems as effective as other stimulation paradigms.[74] In addition, for burst stimulation, either anatomic or paresthesia-mapped programming can be used. The recent Clinical Reasoning in Spine Pain (CRISP) study showed programming based on both anatomic and physiologic criteria.[75]

Consensus Point 11. Modification to a burst waveform as described by De Ridder et al could lead to salvage in a potentially failed system. Burst has been shown to be superior to tonic waveforms and may be dosed at very low power intervals to reduce the burden of charging.

USPSTF grade A, level of certainty high, evidence level I-B

DRG Stimulation

DRG-S applies an electrical field over the DRG cell bodies to exert potential orthodromic effects in the dorsal horn and antidromic effects on distal afferent terminals. Owing to the proximity of the DRG lead to its target and the lack of significant intercalated cerebrospinal fluid, DRG-S requires a total charge that is a small fraction (as low as 1%) of that required for conventional SCS and as low as 0.1% of that required for HF-SCS. Again, minimal cerebrospinal fluid (CSF) surrounding the DRG combined with a minimal depolarization threshold provides a unique direct gateway to activate Aβ, Aδ, and C fibers and has transformed paresthesia-free neuromodulation. Recently, Chapman et al reported in 60 patients who had failure of SCS therapies and were successfully salvaged with DRG-S. This group contained patients with CRPS, PSPS, and other nerve injuries.[76] The median follow-up was 34 months, with a significant decrease in pain scores and oral morphine equivalent dose, and improvement in Oswestry Disability Index score. This seemed successful regardless of stimulation device or brand. Despite this, a narrow therapeutic window exists such that movement of the lead may cause loss of therapy, which may require additional imaging or device evaluation.

General Principles of DRG-S

DRG-S is a low-amplitude neurostimulation therapy that delivers energy through quadripolar contact lead(s) positioned closely to the target DRG. Given the close anatomic proximity of the lead to the target, the electrical stimulus is delivered at lower frequencies, pulse widths, and amplitudes than when SCS is used. In contrast to SCS, DRG-S amplitude can be adjusted at 0.025-mA intervals compared with 0.1-mA intervals for tonic SCS. Although tonic SCS does not usually relieve pain at subthreshold levels,[77] DRG-S has indicated efficacy at both supra- and subperception levels. Furthermore, studies have shown that most patients prefer paresthesia-free therapies and experience superior pain relief with them.[1,3] Although many practitioners titrate stimulation parameters using a sensory feedback-independent method, the challenge of this approach is that without feedback, stimulation may be programmed outside the therapeutic window, and thus, patients may experience suboptimal pain relief. Patient education is a vital step in management owing to the smaller subperception window when the patient could easily be under- or overstimulated.

The ability to fine-tune stimulation dosage is paramount to DRG-S success given the parameters used are a fraction of those used with SCS. Chapman et al showed maintenance of efficacy at frequencies as low as 4 Hz.[78] Frequency may change the total charge delivered to the DRG over time but not necessarily affect nerve fiber recruitment. Therefore, pulse-width adjustments can be leveraged to capture additional nerve fibers.

The long-term prevalence of LoE with DRG-S has yet to be established; however, the incidence seems less than that of SCS.[6,79] Thus, a patient reporting recurring pain should first be evaluated with a thorough history and physical examination to rule out a

change in the clinical scenario and confirm that worsening symptoms are strictly device related. As noted, device evaluation and reprogramming should be exhausted before considering alternative options such as medication changes or further interventional procedures as salvage therapy.

The patient programmer is first used to confirm that the device is in the "therapy on" mode. Next, if the patient may be outside their therapeutic window, stimulation amplitude can be increased using the current active program to recapture paresthesia, which may restore pain relief. As stated previously, superior results were reported when paresthesias were not perceived; therefore, one of the first steps in evaluating LoE with DRG-S is to inquire whether the patient is feeling paresthesias because the device may have inadvertently been adjusted by the patient to deliver an amplitude that is too high. If stimulation-induced paresthesias are not identified at higher stimulation amplitudes, impedance measurements may confirm a suspicion of lead fracture or disconnection from the IPG. If the patient programmer cannot connect to the IPG, the healthcare professional should confirm that the operating system and patient controller software are up to date. The patient should be asked about possible recent procedures using electrocautery or MRI, and whether the device was set to either the surgery or MRI mode given these may thwart the function of the DRG-S.

Should the patient programmer not identify the reason for the LoE, the clinician programmer becomes necessary. Individual electrode impedances should be checked to evaluate for lead fracture. If an electrode impedance is >7000 Ω, there is a significant probability of lead fracture, and this should be further investigated. Nonetheless, if more than two electrodes on the lead have normal impedances, the lead may still be functional. Programming using the valid electrodes is then performed to recapture effective stimulation. If effective stimulation cannot be restored, lead revision is required. If multiple electrodes have high impedances, the risk of further lead deterioration is high. In contrast, if all electrode impedances are normal, the clinician should attempt reprogramming and further assess for lead migration.

The first step in assessing lead migration is obtaining anterior/posterior and lateral x-rays or fluoroscopic images. Comparison with immediate postoperative images can be helpful. If a lead has migrated, the clinician should assess the electrode location to determine whether reprogramming to reestablish therapeutic coverage will be possible (ie, proximity of contacts to the suspected location of the DRG). Reprogramming should be attempted even in the setting of significant out- or inward lead displacement because the available contacts may stimulate portions of the nerve root, DRG, or dorsal root to provide adequate pain relief. Should this not be the case, the clinician should consider lead revision. If possible, efforts should be made to optimize any adjacent lead placements to improve the adjacent lead's potential pain coverage; this may be possible because of the convergence of DRG fibers in the spinal cord.

DRG-S Programming

Clinical experience suggests that initial programming is best performed using the electrodes that are located under the pedicle in the neural foramen. A "skip-bipole" configuration, in which the anode is separated from the cathode by an inactive contact, is capable of effective stimulation in most cases. If no imaging is available, lead location can only be assessed by lead mapping. This can be performed using a bipole configuration with the cathode most distal, the distal two contacts, the middle two contacts, and the proximal two contacts. If initial programming fails to provide desired coverage and pain relief, a "double guarded array," using two middle cathodes flanked on either side by an anode, although energy inefficient, may cover the broadest area and provide both coverage and pain relief. Initially, the amplitude should be zero and slowly increased until the sensory threshold is reached. After reaching this threshold, the pulse width can be adjusted to obtain the desired dermatomal paresthesia coverage. Occasionally, at levels just above threshold, pulse width adjustment may not capture full dermatomal coverage, and increasing amplitude or frequency may be required. Achieving stimulation-induced paresthesias throughout the entire dermatome is not usually necessary to obtain pain relief.

Consensus Point 12. Optimization of DRG-S programming, as with all neuromodulation forms, is a crucial factor for long-term success. The significantly lower electrical charge requirement and subsequent narrower therapeutic window provide less leeway for subtle stimulation changes. Proper education and counseling empower patients to control their therapeutic dosing and minimize preventable loss of pain relief and unnecessary office visits.

USPSTF grade B, level of certainty moderate, evidence level II-C

Closed-Loop SCS

Conventional SCS therapy is delivered using patient feedback. The US FDA recently approved a novel neuromodulation system that can record in vivo spinal cord neurophysiology in real time and use these signals as feedback control for SCS therapy.[12,80] Evoked compound action potentials (ECAPs) are recorded after each SCS pulse is delivered, reflecting the degree of spinal cord activation. These ECAPs are used not only to program the device but to continuously compare the degree of spinal cord activation with the optimal degree obtained in the clinic and to adjust the stimulation amplitude to maintain this optimal degree of activation.

General Principles of Closed-Loop SCS

The newly available commercial closed-loop system uses two 12-contact leads attached to an IPG. The electrodes are typically placed to identify the best position to achieve paresthesia coverage of the painful area. Once the ECAP is measured, the closed loop is activated to keep the stimulation within the therapeutic window and avoid over- or understimulation. If, after the therapy has been established, the clinical outcome has not been achieved, the system is interrogated.

Closed-Loop SCS Programming

The IPG stores information that is useful to evaluate patient compliance and to determine the percentage of time that stimulation remained within the patient's therapeutic window (Fig. 8). When the device is interrogated, the following information is available:

- therapy—the amount of current being delivered in mA
- patient therapy adjustments—any increases or decreases in stimulation and any interactions with the remote and the system's responses to the changes
- spinal cord response to therapy—the ECAPs recorded over time and how well the feedback loop is tracking any changes
- the current required to activate the spinal cord
- the active program used
- a histogram of ECAPs measured over time and the current required to evoke this response

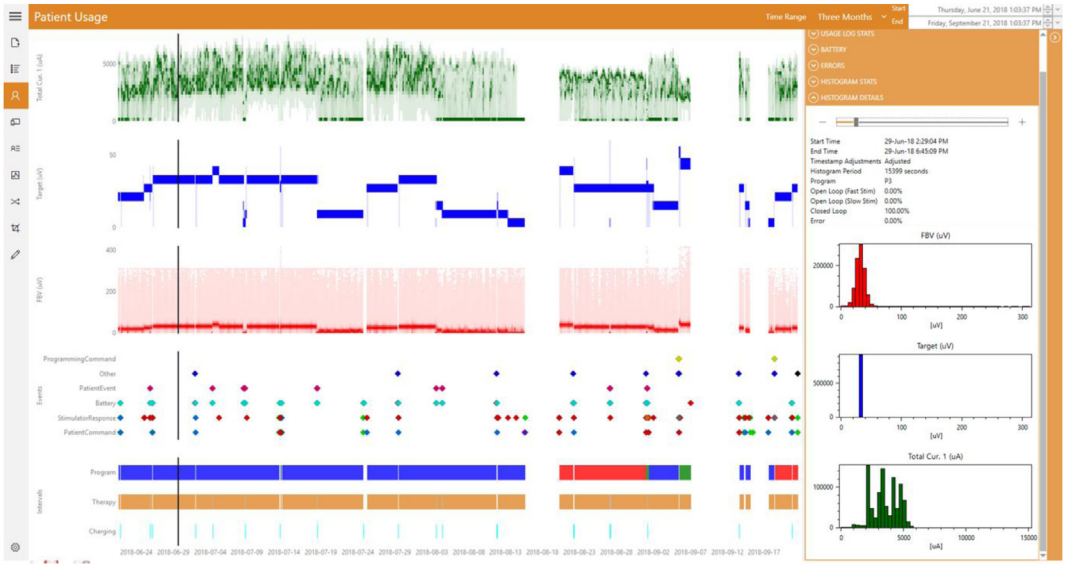

Figure 8. Records stored in the IPG. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

When closed-loop therapy loses efficacy, and after initial device interrogation, it is important to evaluate for potential lead fracture. First, system impedance is evaluated. Usual electrode impedances range from 200 to 1000 Ω. If any electrode shows an impedance >4000 Ω, a fracture is possible, and further evaluation must be performed. At this point, the programmer should attempt to program the device while avoiding the high impedance electrode(s). If all impedances are high, the patient requires a revision surgery to replace the lead and evaluate the connection of the lead to the IPG.

If increased impedance is not a problem, the programmer should evaluate for lead migration. If there is a difference between paresthesia mapping performed at the time of implantation and after a loss of pain relief, migration of the lead may have occurred. An x-ray image of the lead will confirm its migration. Despite lead migration, adequate pain coverage might be obtained with reprogramming. If not, revision surgery will be required.

The CAFFE programming algorithm has been proposed (Fig. 9). The initial step of this algorithm involves "Confirmation and Converge." This involves first checking the device impedance and then programming a guarded cathode (+−+) configuration at the top, middle, and bottom of the lead to determine the area of the lead to focus on. The standard parameters for stimulation are a frequency of 30 to 50 Hz, a pulse width of 240 milliseconds, and an amplitude ranging up to 20 mA. As with other paresthesia-based

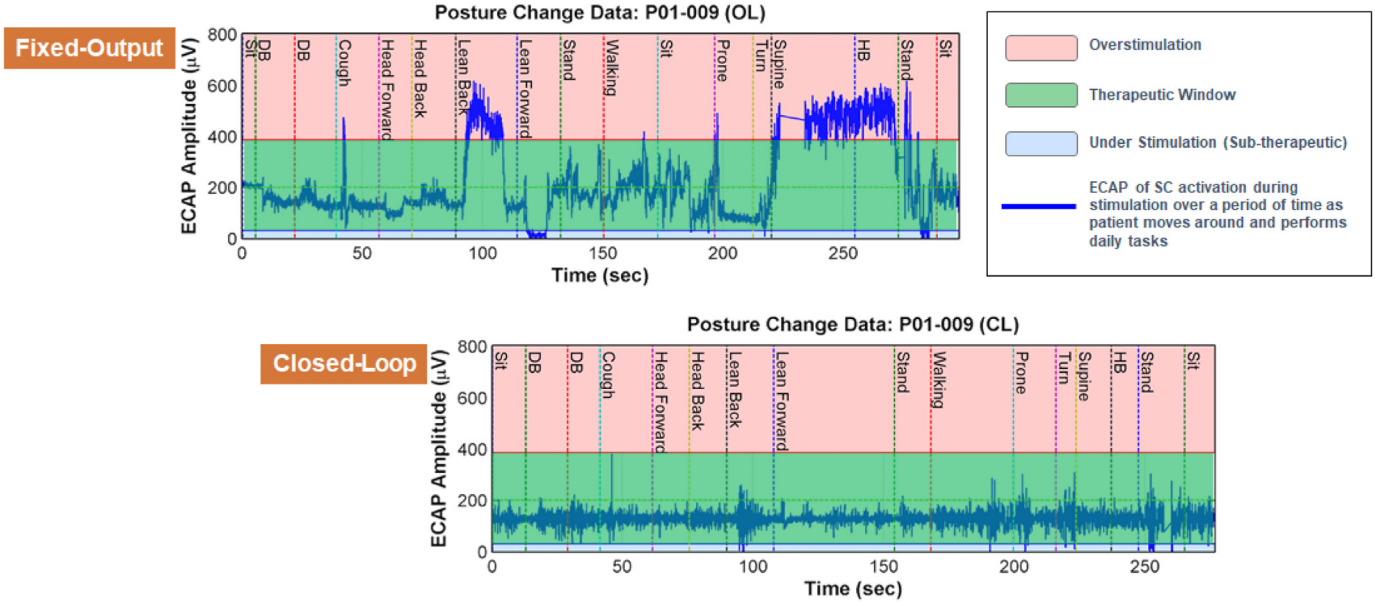

Figure 9. Troubleshooting programming with closed-loop stimulation systems. Illustration courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. CL, closed loop; OL, open loop; SC, spinal cord. [Color figure can be viewed at www.neuromodulationjournal.org]

therapies, the goal is to cover ≥80% of the pain areas with stimulation-induced paresthesias.

The second step involves the acquisition and optimization of the ECAP. The programmer moves the reference and the reading electrode to obtain the best ECAP signal. Obtaining the optimal ECAP recording is the key to closed-loop therapy; this can sometimes be achieved by either reducing the pulse width and frequency or moving to a new contact for paresthesia mapping. This optimization of the ECAP creates a dose-response curve that can be modified and narrowed to give a specific dosing table for an individualized patient. This dosing algorithm uses ECAPs, modified by the patient and involving patient feedback into the computer software to generate dose accuracy based on the patient's activity, physiology, and changes in neural response, which may vary with illness, medications, and other factors. The neural panel concept can lead to the potential of capturing a successful dose ratio owing to accuracy when other systems have failed.

The third algorithmic step is to fit the filter properly so that a clear and reliable ECAP measurement is obtained to provide an accurate measure of spinal cord activation. Finally, the programmer must evaluate the settings in various patient positions including sitting, standing, and lying down.

If all the adjustments have been made and the patient has spent >90% of the time within their therapeutic window with good ECAP and closed-loop readings, the system is functioning technically, and the patient is not responding to the stimulation (therapeutic failure). Further changes will not improve efficacy. Given closed-loop therapy is in its first few technologic iterations, one might expect that further refinements are possible.[12,81] Three refinements are currently being investigated in a clinical study, with results expected later this year.

Consensus Point 13. Modification to a closed-loop stimulation system capable of sensing and responding to changes in ECAPs could lead to salvage of a potentially failed system. Optimization of the closed loop may produce a significantly higher percentage of time in the therapeutic window.

USPSTF grade A, level of certainty high, evidence level I-B

Differential Targeted Multiplex Therapy

Although there is no published evidence supporting the use of differential targeted multiplexed (DTM) therapy in patients who have lost SCS effectiveness, anecdotal evidence exists for its potential use in this setting. The hypothesized mechanism of action of DTM therapy involves the observation that at the spinal level typically used for SCS, >90% of the cells are glial cells.[82] This suggests that stimulation that modulates both glial cells and neurons might be more effective in providing pain relief. Using a spared nerve injury rodent model and genetic expression profiling, the DTM algorithm was optimized to show the highest conversion back to the nonpain state of both glial cells and neurons. The genetic expression profiles surrounding proinflammatory mediators were sequenced and suggested a reversion of spinal glial cells and neurons to a noninflammatory phenotype.[83] These preclinical data led to the execution of a parallel-arm RCT comparing DTM with tonic stimulation, which showed an 84% responder rate and a 69% profound responder rate, and reported VAS scores of <2 for back and leg pain at 12 months.[84] DTM as used in this trial and on its clinical release uses an anatomically based programming algorithm that includes a base and prime signal based on a cephalad lead, with its top electrode at T8 and a caudad lead with its top electrode at mid-T8. This is presented in Figure 10.

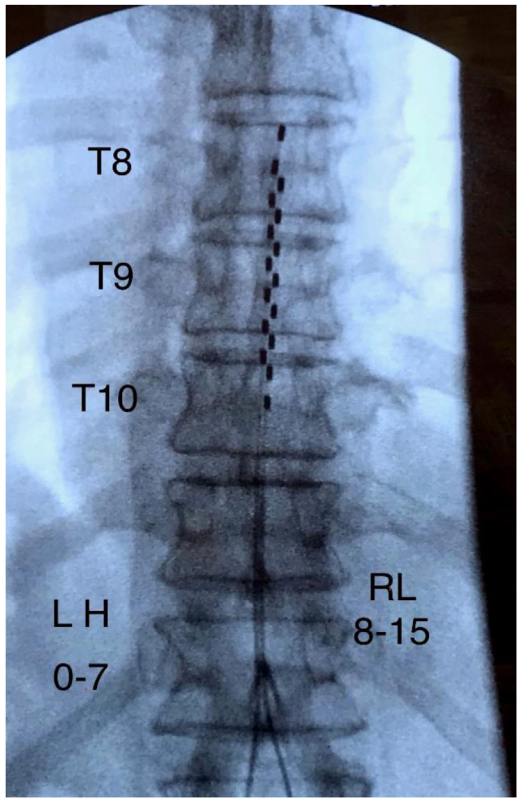

Figure 10. Positioning of leads for differential targeted multiplex therapy. Radiograph courtesy of University of Kentucky College of Medicine, Lexington, KY, USA and used with permission. [Color figure can be viewed at www.neuromodulationjournal.org]

This anatomically based algorithm allows three therapy options corresponding to different locations on the T8–T10 span of the leads. Each therapy option comprises multiplexed 50-Hz to 1200-Hz combinations, at a defined pulse width and amplitude determined by each patient on the basis of their perception thresholds. In salvage, updated imaging is required to ensure the appropriate anatomic location of the cephalad and caudad lead before consideration of DTM therapy. This may necessitate the adjustment of the existing leads to these anatomic locations before initiating DTM therapy.

Consensus Point 14. Modification to include additional stimulation of the glial target cells could lead to salvage of a potentially failed system based on eliciting a different neural response. However, there is no current peer-reviewed evidence to support this hypothesis.

USPSTF grade C, level of certainty low, evidence level II

Sequential Bipolar Cascade Programming

In 2013, Tiede et al published a study on the use of subperception SCS using a frequency of 10 kHz to treat neuropathic low back and leg pain.[85] Early studies suggested that the optimal lead placement for LBP using 10-kHz SCS was at T9–T10.[75,85,86] This was more caudal than at T8–T9, which was typical for low-frequency tonic stimulation for back pain.[87] An RCT has indicated superior outcomes of 10-kHz SCS to those of tonic SCS in a population of patients predominantly with PSPS.[64] There was, however,

little information on the specific programming parameters and the radiographic level of the stimulated electrodes at which the stimulation was applied in the 10-kHz SCS group.[64] Multiple prospective studies in SCS have failed to describe programming parameters and thus ways efficacy was obtained.[64,75,88–92] Subsequent studies have suggested that there is considerable patient variability concerning the best anatomic target for 10-kHz SCS.[93,94]

When the T9–T10 disk space is the suggested anatomic stimulation target, 73% of patients in a study in 1660 patients using 10-kHz SCS required further optimization.[95] In this study, as many as 50% of patients required multiple bipolar configurations to achieve adequate therapy. This finding emphasizes the frequent need for a broader area of stimulation than that provided by single bipolar stimulation with 10-kHz SCS. A recent study of the treatment of neck and arm pain showed that it could take up to seven different programming sessions to optimize the anatomic site for 10-kHz SCS.[94]

Complex Programming for 10-kHz SCS

Issues with 10-kHz SCS have led to alternate programming strategies to obtain better and more uniform results. Al-Kaisy et al have developed a duty-cycled, bipolar-configured programming algorithm using every electrode on a single eight-electrode lead to provide 10-kHz SCS over a significantly larger area of the dorsal surface of the spinal cord. This sequencing programming uses four successive bipoles, each having a duty cycle of 5 seconds ON and 15 seconds OFF.[95]

Al-Kaisy et al report in a cohort of patients with neuropathic back pain, with or without leg pain, who had a trial of SCS.[95] Pain assessments using numerical rating scales (NRS) and Patient Global Impression of Change (PGIC) scores were collected at baseline, six months, and last follow-up beyond 12 months (mean 15.1 months). Patients were programmed with 10-kHz SCS using complex programming during the trial, which was continued unless they reported inadequate pain relief. At six months, 87 of 97 patients (90.6%) with active devices were using complex programming, and 58 of 72 (81%) continued at the last follow-up >12 months. There was a significant reduction in back NRS [8.3 vs 3.9 ($p < 0.0001$), $n = 97$] and leg pain NRS [7.53 vs 3.83 ($p < 0.0001$), $n = 77$] at six months. At the last follow-up of >12 months, back NRS [8.3 vs 3.95 ($p < 0.0001$) $n = 72$] and leg NRS [7.53 vs 3.534 ($p < 0.0001$), $n = 58$] decreases continued to be highly significant. The PGIC score was 6 of 7 or 7 of 7 in 72% of patients (70/97) at six months and 68% (49/72) at the last follow-up beyond 12 months.

The study concluded that this new complex programming comprises effective methods that may have benefits over a single bipolar configuration for 10-kHz SCS, particularly during a trial of stimulation.[95] Results from this study suggest it is a durable program for patients with neuropathic back and leg pain. The other benefits include mitigating issues with lead migration, excessive reprogramming sessions, and overstimulation. The recharge burden of this program should be considered when selecting patients for this therapy.

SYSTEM REPLACEMENT AND UPGRADE AFTER FAILURE OF CONVENTIONAL SCS WITH AXIAL BACK PAIN

PSPS is one of the most common indications for SCS and one of the most common device explant diagnoses.[9–11,13] Emerging data also indicate the role of varying SCS waveforms for the treatment of nonoperative back pain[96,97] and the salvage of failed stimulation.[67,97,98]However, such advances have not had a correlative improvement in device explant rate with SCS, regardless of the waveform.[8,13,95]

Ten-kHz SCS

It is estimated that close to 30% of patients who receive permanent implants with traditional paresthesia- based SCS will require an explant of their SCS devices for reasons including LoE, hardware discomfort, mechanical failures, and infection.[1,10] In case series, the potential of 10-kHz SCS therapy to rescue patients who do not respond to paresthesia-based SCS (PB-SCS) has been shown in treating neuropathic back and leg pain. A retrospective multicenter evaluation in 76 patients with primarily spinal-related pain for whom PB-SCS and/or failed peripheral nerve field stimulation (PNFS) had failed found that 68% had a positive 10-kHz SCS trial result and a 60% reduction in pain intensity at six-month follow-up after implantation. This preliminary clinical experience reported among three Australian pain centers suggests that 10-kHz SCS may be used successfully as an alternative to paresthesia-based treatment modalities.[88]

Verrills et al report on a cohort of patients with chronic back pain who did not experience pain relief withPB-SCS[88] or PNFS and were then treated with 10-kHz stimulation.[99] In both cases, the improvement in pain relief was substantial, with pain NRS reduced from a mean of 7.1 ± 1.3 before the 10-kHz trial to 3.1 ± 1.8 afterward for failed SCS, and from a mean of 6.5 ± 1.8 before the 10-kHz trial to 2.4 ± 1.6 for failed PNFS. There were trends toward improvement in patient medication use, Oswestry Disability Index, ability to function, and psychologic state for both patient groups. This result confirms the European study subgroup analyses that patients for whom traditional neurostimulation therapies failed may still have success with 10-kHz SCS.[100]

A multicenter, retrospective review evaluated the 10-kHz therapy efficacy in 1660 patients with chronic trunk and/or limb pain.[94] At least 70% of patients reported response to therapy throughout 12 months of follow-up. This sustained responder rate was corroborated by the last visit value (74.1%). Most patients reported concomitant improvements in function (72.3%), sleep (68.0%), and quality of life (90.3%) at their last visit vs baseline. Moreover, 95.0% of patients with previous PB-SCS ($n = 382$) experienced better pain improvement with 10-kHz SCS.

Twenty-six consecutive patients in whom PB-SCS therapy had failed were trialed with 10-kHz SCS using a "pocket trial" technique.[101] The technique involved accessing the previously implanted PB-SCS leads in the IPG pocket and externalizing the leads using a connected adapter, thereby allowing delivery of the trial 10-kHz signal. Patients who reported ≥50% pain relief during the trial received a new 10-kHz IPG. At the last visit, minimal clinically important change (MCI ≥30% pain relief), responder rate (≥50% pain relief), and overall change in function, sleep, quality of life, and medication intake vs baseline were recorded. All patients with implants were followed up (median 12.5 months); 61.9% (13/21) reported >50% pain relief and 76.2% (16/21) reported MCI ≥30% pain relief. Moreover, there were improvements in sleep 62% ($n = 13/21$), quality of life 52% ($n = 11/21$), and function 71% ($n = 15/21$), and medication intake decreased by 52% ($n = 11/21$). The authors concluded that 10-kHz SCS, with minimally disruptive trialing through the IPG pocket, can be a potential salvage strategy for patients with failed PB-SCS. The therapy can provide long-term

pain relief and symptom improvement in these patients without requiring lead revision.

Burst Stimulation

Salvage therapy of initially successful SCS for pain that has failed at some point has been studied with burst stimulation.[63,97] In a study in 102 patients from two countries, Belgium and The Netherlands, 24 of 102 patients developed tolerance, with 0.85% pain suppression, ie, complete failure of the tonic SCS.[69] When switched to burst stimulation, 62.5% of these nonresponders did respond, with 43% pain suppression on average. This was a retrospective study, not yet confirmed by other studies. In this study, the Belgium group had a higher responder rate than that of The Netherlands group (83% vs 55%), which could be related to different reimbursement systems in the two countries. The amount of pain reduction obtained by tonic and burst stimulation being very similar in the two independent centers suggests that the benefit of burst salvage may be a true effect. Yet further similar studies, preferably randomized placebo-controlled trials, are needed to confirm these promising results. These data should be differentiated from studies in which patients who never responded to tonic stimulation (ie, <10% pain suppression, rather than tolerance) were converted to burst stimulation. These patients also responded poorly to burst, with only 23% pain suppression.[70]

This European study was replicated and extended in a larger retrospective multicenter USA-based study.[97] A total of 307 patients with ongoing SCS therapy underwent a conversion to the same B-SCS used in the European trial. However, although in the European group, only failures to tonic stimulation were analyzed, in the USA, tonic, rate-cycling, or 10-kHz stimulation was studied. Similarly, two groups were analyzed, one group who were experiencing failure of their SCS (salvage) and a second group who were reporting success with their SCS system but were looking for increased pain relief (upgrade). There were statistically significant and clinically relevant reductions in NRS, 1.74 and 3.51 points, respectively, for the salvage and upgrade group. A statistical reduction in opioid dosing was seen in the overall population and the salvage group.

Consensus Point 15. In patients with decreased efficacy from SCS, a pocket-based trial of burst stimulation can help assess patient responsiveness to a change in therapy.

USPSTF grade B, level of certainty moderate, evidence level 1-B

Dorsal Root Ganglion

Using the principles already outlined, DRG-S has been shown in several studies to be an effective salvage therapy for traditional SCS that has lost efficacy. Of course, the nature of the pain and its distribution must be amenable to DRG-S treatment.[76,102–105]

DRG-S is FDA approved for treating CRPS and has been identified as a treatment for focal, dermatomal pain.[3,106] However, there is mounting evidence that DRG-S effects are not only at the DRG itself[107] but rather that DRG-S may inhibit diffuse pain syndromes through orthodromic propagation of inhibitory signals onto convergence points within the dorsal horn (DH).[108,109]

Because the ACCURATE study was first published in April 2017,[3] the number of peer-reviewed studies on DRG-S therapy is low. For the treatment of LBP, DRG-S was first used at the L2 level on the basis of sympathetic convergence.[110] However, the inclusion of patients with radicular pain led to mixed results.[111] Two prospective studies after this indicate the efficacy of DRG-S at L2 for LBP, DRG-S for diskogenic, nonsurgical LBP,[112] and postdiskectomy axial LBP.[113] A 17-patient retrospective study with leads at T12 for LBP showed efficacy for diverse, instrumented patient populations.[114] The authors postulated that LBP fibers converged at the T8-to-9 level, and the activation of inhibition of the T12 spinal nerve inhibits pain at this convergence point.[109] The group performed two subsequent studies on frequency titration and sensory testing with 20 and 15 patients with leads at the T12, and had similar results.[78] HF-SCS used in a small cohort treated with T9 and L2 lead placements also showed efficacy.[115]

As an alternative target for neuromodulation, DRG-S is revealing mechanisms separate and distinct from SCS, from potential filtering at the T-junction,[116] less γ-amino butyric acid (GABA) involvement,[117] prolonged washout at frequencies compatible with DRG-S,[118] efficacy at very low frequencies,[78] and the ability to directly activate all nerve fiber types, including those in the superficial DH.[119]

Although the current body of literature on DRG-S as a salvage therapy has been positive, it is scant and limited to case reports and data mined from other studies.[102,104,111,114,120,121,122] With the benefits of better dermatomal coverage of DRG-S, a new subcategory of salvage known as "additive" therapy, in which DRG-S is used to supplement SCS, has emerged.[102,120,123,124]

Given habituation occurs with all forms of dorsal column neuromodulation, the DRG offers another target, with alternative underlying mechanisms that may not have been previously exposed to neurostimulation. Although lacking an RCT, DRG-S has shown impressive improvements in pain, function, quality of life, and mental health in treating nonsurgical and postsurgical axial LBP. As such, patients with failed SCS secondary to LoE, failed SCS with multiple waveforms, inadequate axial LBP coverage with SCS, or a failed SCS trial for any of the preceding reasons would be candidates for DRG-S as a salvage method.

Consensus Point 16. DRG-S has shown efficacy as salvage therapy in treating axial back pain and can be considered when other neuromodulation techniques have failed or need augmentation. Further studies will be required.

USPSTF grade C, level of certainty moderate, evidence level I-C

Multifidus Stimulation

Axial LBP of neuropathic genesis may be amenable to SCS; however, if the pain is predominantly nociceptive, this treatment modality is not deemed appropriate.[125] If axial LBP is of mixed nociceptive and neuropathic genesis, it is conceivable that although effectively treating the neuropathic pain component, SCS treatment exposes mechanical LBP as the underlying nociceptive chief symptom.

In patients with intractable mechanical chronic LBP, symptoms are frequently linked to impaired motor control and degeneration of the multifidus muscle, the primary local stabilizer of the lumbar spine.[126–131] Consequent functional segmental instability causes ongoing, mechanically induced nociception in the facet joints, intervertebral disks, ligaments, fascia, and muscles. Surgery is not indicated for most of these patients, and although nonsurgical therapies, including PT, nonopioid medications, opioid analgesics, injections, and rhizotomy, may provide transient relief, they rarely produce long-term improvements.[132–134]

Bilateral stimulation of the L2 medial branch of the dorsal ramus causes episodic contractions of the lumbar multifidus muscle, which override the underlying inhibition, elicit proprioception, and

facilitate restoration of neuromuscular control and functional spine stability, which produce consequent symptom relief.

Long-term restorative neurostimulation was determined to be an effective, durable, and safe treatment for patients with disabling, intractable, mechanical chronic LBP that caused pain at least half of the days in the past 12 months and had evidence of impaired neuromuscular control of the multifidus (FDA premarket approval).[135]

Because restorative neurostimulation relies on viable multifidus musculature and substrate innervation, patients with previous low back surgery were excluded from the clinical trials. Therefore, the efficacy of restorative neurostimulation in patients with previous low back surgery remains to be investigated. It is possible to hypothesize that patients who have had anterior lumbar interbody fusion may respond to the therapy, but patients who have had posterior lumbar surgery may or may not be suitable candidates, depending on the subsequent anatomic presence of non-denervated multifidus muscle (a far lateral microdiskectomy may respond; a laminectomy may not, for example). However, for patients with chronic LBP in whom SCS provides inadequate relief, restorative neurostimulation could be considered for salvage if the chief pain symptom predominantly stems from multifidus muscle dysfunction, is refractory to medication and PT, and is not amenable to spine surgery. There are currently no outcome reports for patients with both a multifidus muscle stimulator and an epidural spinal cord stimulator.

Specific scenarios when restorative neurostimulation might be considered for salvage include the following:

- patients who were implanted with an SCS for axial chronic LBP but are receiving inadequate pain relief owing to a mechanical (nociceptive) etiology
- patients who were implanted with an SCS for mixed chronic LBP and are receiving relief of the neuropathic pain component but have significant residual mechanical (nociceptive) pain. If the chief symptom is of mechanical etiology, replacement with restorative neurostimulation may be indicated. Safety of the restorative neurostimulation system has not been evaluated when used in combination with SCS or other implanted systems. Similar considerations can be made for patients who were implanted with intrathecal drug pumps for chronic LBP.

FOCAL NEUROPATHIC PARESTHESIA COVERAGE AFTER FAILURE OF CONVENTIONAL SCS THERAPY

At times, conventional SCS to control focal neuropathic pain will lose efficacy for a variety of reasons such as tolerance, habituation, neuronal fatigue, plasticity, and cortical reorganization.[7] After the lead location is verified as unchanged and optimized programming is ensured, LoE or a failure of the particular type of stimulation is likely but not necessarily failure of neuromodulation altogether. Development of novel waveforms and stimulation delivery in recent years makes it possible to take advantage of modern non–paresthesia-based therapies to salvage neuromodulation treatment, in which a subset of patients who have lost efficacy with tonic SCS benefit from conversion to alternative stimulation.[63]

Dorsal Root Ganglion

One study found that after two years, traditional, tonic SCS is no better than PT concerning the treatment of CRPS.[136] As it pertains to the treatment of CRPS, there are several known shortcomings that have plagued traditional, tonic SCS[136–138]:

1. inability to provide focal stimulation
2. inability to consistently capture the foot, groin, and pelvic region
3. dependency on paresthesias
4. position-dependent variations in stimulation due to distance changes between the cord and lead in addition to CSF volume
5. waning efficacy over time

In the case of items 1 and 2, traditional, tonic SCS is at a particular disadvantage given that the foot is the most common area affected with CRPS in women and the second most common for men.[137,138] As such, there was considerable room for improvement with neuromodulation with respect to CRPS. DRG-S is particularly suited in this regard given it is specifically designed to provide focal coverage over specific parts/regions of the body (such as the foot). When one considers the level of involvement of the DRG in the modulation of chronic, neuropathic pain, its ability to act at the level of the T-junction of the DRG to reverse allodynia right at the source is valuable.[3,139] DRG-S has shown advantages over traditional, tonic SCS in the treatment of CRPS (and several other complex neuropathic pain conditions), in addition to its ability to provide focal stimulation to the area of need, rather than a widespread region.[3,104]

Consensus Point 17. LoE due to incomplete paresthesia coverage in the setting of focal neuropathic pain can be salvaged with DRG-S.

USPSTF grade B, level of certainty moderate, evidence level I-B

Closed-Loop Stimulation

Paresthesias are an expected and intended effect of neurostimulation. In the case of traditional, tonic SCS, paresthesias are believed to be the therapeutic element per the gate theory—the goal of the operator is to target and stimulate the right portion of the dorsal columns to deliver as much paresthesia coverage as possible to cover the entire area(s) of pain.

Three of the most common reasons for explant are 1) uncomfortable paresthesias, 2) incomplete coverage of paresthesias over the affected area(s), or 3) unwanted paresthesias in the unaffected area(s).[8,9] In common pain conditions that involve generalized pain in the back and legs, creating paresthesias in the involved areas is fairly straightforward. However, in other situations in which the pain is localized to the axial low back or in a focal region such as the foot or pelvis, tonic-based neurostimulation therapies are at a tremendous disadvantage. It is challenging to reliably capture these areas and keep consistent stimulation owing to the location of those fibers within the cord—consequently leading to therapy failure and eventually an explant due to incomplete coverage. The most common means to overcome this hurdle is to increase the pulse width and amplitude; however, this comes at the expense of creating paresthesias in unaffected areas in addition to more intense paresthesias overall. Although this practice is sometimes effective in recapturing the affected area(s), it can lead to uncomfortable or unwanted paresthesias.

These scenarios led investigators to search for solutions whereby one could mitigate, control, or minimize the variability of paresthesias[2,106] and in some cases find therapies that were paresthesia-free altogether.[1,65] The first iteration of this undertaking was to develop an IPG that could sense positional movements and alter stimulation intensities to match those changes.[140] Although this addressed the major issue of overstimulation with the patient prone, this still did not address the other issues of poor coverage or unwanted paresthesias. High-frequency stimulation at 10 kHz and burst stimulation were major steps forward that allowed modulation of the dorsal columns without the need for paresthesias, thus mitigating all three of the previously mentioned reasons for explant. DRG-S, also paresthesia-free, was another major step forward in providing focal stimulation to targeted areas, particularly those areas that were known to be hard to capture (ie, foot, groin, and pelvis).

A major drawback of the previously mentioned platforms is that all three stimulate neural tissue statically and cannot self-regulate the amount of energy delivered to the central nervous system. Although there is no clear cause for LoE with SCS, tolerance and overstimulation are believed to play a major role.[97] Although overstimulation was no longer an issue on a conscious level with these three therapies, paresthesias serve as a barometer to alert to the presence of "too much" stimulation. Positional changes that move the stimulator lead closer to the cord, thus causing overstimulation, are not limited to lying supine—they can occur with sneezing, coughing, bearing down, or even a heartbeat, thus suggesting that the cord is potentially overstimulated countless times per day.

The most effective method for overcoming this shortcoming is a closed-loop system that can sense changes in the ECAP as a means to interpret stimulation intensity—thus limiting the probability of overstimulation and potential tolerance.[12] When the central nervous system is intact and the spinal cord is not damaged, explant of a failed system and implant of a feedback-controlled ECAP SCS can be considered in patients with low back and leg pain. There are no current studies to document the salvage rates that occur with this approach.

TRIALING TECHNIQUES WITH EXISTING SYSTEMS

Percutaneous Trial

Percutaneous trialing enables patient and clinician assessment of novel stimulation options through the placement of new electrodes without a surgical incision or modification of the indwelling pulse generator or leads. Preprocedural assessment of risks and benefits of any trialing approach incorporates imaging of the indwelling device, spinal anatomy, and previous operative summaries. The ability to place electrodes adjacent, proximal, or distal to an existing system may not be technically feasible; thus, other approaches, such as pocket trialing or electing to proceed with system replacement without a trial, can be considered with potentially equivalent outcomes.[141] In the event that paresthesia mapping or therapeutic benefit during percutaneous trialing is suboptimal, a pocket trial may permit coverage of a more optimal target using the preexisting system's indwelling leads for trial assessment. Trialing DRG-S or closed-loop stimulation for salvage requires specialized leads to enable stimulation of the DRG or ECAP sensing, respectively, and thus necessitates percutaneous trialing or when trialing is not feasible, system exchange without a trial. [76]

Pocket Trials

In patients with an ineffective SCS system, a salvage trial with a new system can be performed. In these instances, before performing the IPG externalization (or "pocket") trial, programming options with the existing system are maximized, and evaluation of the lead location and possible technical issues is completed to ensure no other less invasive options are possible to recapture relief. Patients may be considered for a more modern generator from the same manufacturer or a generator from another manufacturer offering other programming options (eg, 10-kHz or burst stimulation). Because patients often have some pain relief benefit, switching to an entirely new waveform without a trial may carry a risk of loss of all benefit. Therefore, a trial window using the newer modulation paradigms may be a low-risk option for confirmation of benefit before permanent implantation of a new IPG. The procedure also can be thought of as a staged SCS removal, in which before removal of the epidural leads, one more attempt at accomplishing SCS benefit is offered. This practice has proved effective, with evidence of reduced VAS scores in many of the patients in a recent series.[142]

In an externalization trial, the current SCS generator is removed, and the existing epidural array is connected to temporary extensions, which are externalized to the new trial system (Fig. 11). In some cases, manufacturer-specific adapters are required to convert the connection of one epidural array to another's extensions. Because the extensions are in continuity with the epidural array, careful attention to an occlusive dressing and infection prevention is essential. After externalization, patients are discharged and undergo a trial period with evaluation of VAS, medication usage, quality of life, and functional relief in pain that mirrors the usual temporary SCS trial. Adjustments to stimulation settings are performed as needed. If effective relief is not achieved and if clinically appropriate, a patient may be offered the option of a trial with an additional manufacturer's device during the trial window to exhaust all options. These patients return to the operating room

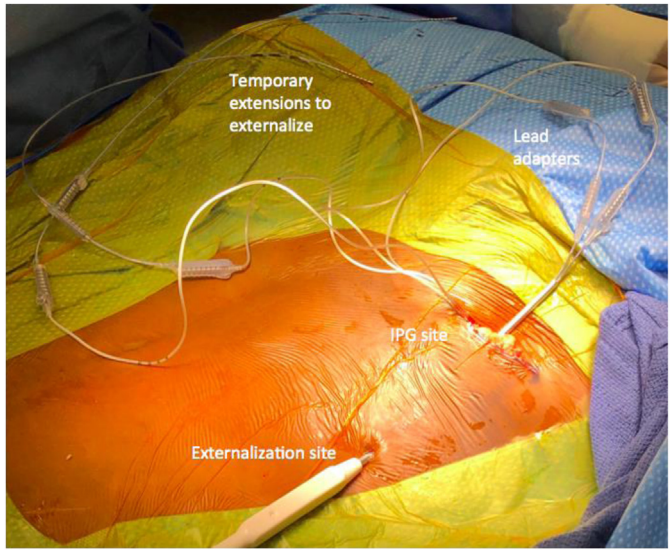

Figure 11. Intraoperative demonstration of connection of the previous epidural lead bodies to manufacturer-specific adapters and then to externalizable extensions. The extensions are tunneled to an exit site 12 cm from the IPG incision and away from the path of the exiting tunneled epidural leads. [Color figure can be viewed at www.neuromodulationjournal.org]

after the trial period in approximately one week for either permanent implantation or removal of the remainder of their former system. If the trial is successful, the salvage was accomplished without the added risk of epidural lead revision while preserving SCS benefit.

New stimulation paradigms such as burst and HF-SCS offer a new avenue of pain treatment for those with an ineffective SCS system without the additional risk of epidural access. Performing an externalization trial is one of the least invasive salvaging techniques and provides the opportunity to verify patient benefits before the implantation of a new device. Personalization of SCS therapy remains the goal, although no available device appears to deliver all options to each patient. When a patient's device cannot deliver these paradigms, an IPG externalization trial may be a low-risk option for salvaging therapy. These externalization trials also allow trialing of multiple systems, if necessary, before the implantation of the generator.

Consensus Point 18. When considering salvage therapy, converting conventional SCS to a different modality using an IPG pocket-based trial with trial lead extensions could be considered.

USPSTF grade B, level of certainty moderate, evidence level I-C

Consensus Point 19. Existing pocket trialing can be a safe and effective way to evaluate the efficacy of new or differing stimulation modalities in patients experiencing decreased efficacy with an existing system.

USPSTF grade C, level of certainty low, evidence level II

Consensus Point 20. With already implanted leads, a new system may be indicated that has a different spinal target. In this setting, a percutaneous trial can be an effective way to analyze the appropriateness of adding a second system.

USPSTF grade C, level of certainty low, evidence level II

No Trial

Trialing of patients with temporary SCS has been a long-standing standard before permanent implantation.[143,144] A recent comprehensive narrative review evaluates the evidence for trial stimulation during patient selection for SCS therapy and concludes that trialing lacks a consistent approach but complements patient selection by helping to exclude patients who may not tolerate or benefit from SCS.[145]Another recent prospective trial has shown no patient outcome benefit in undertaking an SCS screening trial in appropriately selected patients who were assessed at 36 months after permanent implantation.[146,147] Although these results pose an interesting conclusion, the utility of not trialing patients on new waveforms and technology in the setting of a previously failed SCS system poses a more challenging dilemma than do the patients implanted "de novo" in this study.

Limited evidence suggests that moving to a novel salvage waveform may be appropriate and lead to acceptable treatment success. A retrospective review in 105 patients with suboptimal pain control with traditional SCS were switched to 10-kHz SCS with a >80% success rate (pain relief >50%).[65] Bypassing a trial in a patient who has already experienced failure with a previous version of SCS may warrant trialing in most circumstances. Inherently, this patient population may have challenging pathology or underlying disease in which even newer waveforms and technology may fall short in providing adequate pain relief. Other circumstances such as previously implanted paddle electrodes, challenging anatomy, and infection risk may warrant moving to a newer SCS target or waveform without a temporary trial in carefully selected individuals.

Consensus Point 21. Bypassing a trial and salvaging to a new waveform, hardware, IPG, or target may be appropriate in carefully selected individuals.

USPSTF grade C, level of certainty low, evidence level II

SYSTEM REPLACEMENT

Lead Revision and Replacement

The SCS lead considerations for restoring therapy fall into three major categories: lead malfunction, lead migration, and lead compatibility if a generator swap (different vendor) is being considered along with the possibility of using the patient's current in situ leads.

Within the discussion framework regarding SCS salvage, the SCS lead is a fundamental contributor to the number of cases requiring revision/replacement.[63] Eldabe et al reviewed the complications of SCS, reporting a lead migration rate of 15.59% (CI 9.21%–21.77%) across ten studies (three RCTs, three systematic reviews, and four retrospective reviews) and a lead fracture/malfunction rate of 6.37% (CI 2.63%–-10.10%) across six studies (two RCTs, three retrospective reviews, one systematic review).[55] These data suggest that lead migration and fracture/malfunction are not an insignificant reason historically for patient and clinicians to consider revision surgery, which is in essence SCS salvage given the need to correctly position functional leads for therapeutic benefit.

The literature base has continued to expand concerning evaluation of lead contribution to SCS revision/replacement/explantation. In their 7.5-year SCS service review, Thomson et al reported 13 cases of lead revision (4.4%) whereas Van Buyten reported six cases in 955 implants.[8,148] More recently, Nissen et al and Patel et al reported lead migration rates of 4.4% (ten cases, with five ultimately leading to explantation) and 14%, respectively.[28,149] Lead malfunction preventing systems from converting to MRI-compatible mode is an underdocumented but relevant reason for revision and perhaps is captured in the data identifying MRI as a reason for revision.[9]

IPG Replacement and Lead Adapters

At times, revision for salvage is considered even when all components of the patients' existing systems are intact and functioning within normal parameters. One example is when a patient with a traditional paresthesia-based tonic SCS system develops therapy habituation and no longer receives pain relief despite maximal reprogramming. One option that can be considered is to keep the current system's leads in situ but surgically swap the generator with a new IPG that offers the option of expanded waveforms. When considering IPG replacement, lead compatibility must be considered. If an in situ lead is to be used, ensuring that the component will accomplish the clinical objective is key. For example, lead adapter kits that accommodate different manufacturers' leads into the IPG may alter the MRI capability of a system because occasionally, these adapter products are not MRI compatible. Similarly, different SCS therapies require differing lead arrays and differing spinal targets. The implanting physician should, well before the day of the procedure, map out the surgical steps and component parts needed for a given therapy to eliminate unanticipated issues on the day of operation.

Consensus Point 22. Lead compatibility, including MRI compatibility and the requirement of component parts, should be considered with any salvage procedure.

USPSTF grade B, level of certainty high, evidence level II

Paddle Replacement

Only retrospective data analyses exist for paddle lead replacements. A large retrospective data analysis in 13,744 patients has revealed that the implantation of paddle leads is associated with slightly higher initial postoperative complication rates than those of percutaneous leads (3.4% vs 2.2%, respectively). However, paddle leads are associated with significantly lower long-term (>five years) reoperation rates (22.9% vs 8.5%).[150] Reoperation rates for paddle leads, however, differ tremendously between centers, with reoperation rates varying between 0%[151] and 27.8%.[152] Revision of paddle leads is associated with younger age, male sex, associated neuromuscular pain, and severity of the pain (≥8).[24]

Thus, paddle leads are used for replacement of both percutaneous leads and paddle leads. Replacement of percutaneous leads by paddle leads can cause a long-term three-point pain reduction in 50% of patients.[153] Pain relief is superior in patients with better pain coverage and only one revision.[152] There is no reported literature on the best approach to reoperation of paddle electrodes, nor is there any comparative literature on which device to use in replacement surgery. However, considering the large intercenter differences, some guidelines may benefit the field. The data also may be difficult to interpret owing to the complexity of paddle lead revision.

Removal of an Existing Paddle

Paddle electrodes are held firmly in place by scarring around the region where the tails meet the paddle, and this is the key point that must be accessed to release them. It may be reached by following the tails from the subcutaneous layer down through scar tissue to the fenestration in the ligamentum flavum, staying on the dorsal aspect of the wires as the vertebral canal is approached to avoid any risk of entering the theca. If the caudal end of the paddle is slightly above the fenestration, removal of the lower edge of the lamina above may be needed to expose it. Once the caudal end of the paddle has been located, incising the collagenous capsule around it will allow the paddle to slide out without resistance.

Occasionally, the implanting surgeon may have passed the paddle a significant distance rostrally within the canal from the level of entry. If this is the case, it may be preferable to approach from a higher level to avoid an unnecessarily long laminectomy in pursuit of the paddle from the insertion site. It is advisable to obtain radiographs preoperatively to confirm the location of the caudal end of the paddle.

Selection of a New Paddle

If the paddle was removed because of LoE due to lead fracture, replacement with the same type of lead would be the most straightforward option. The capsule formed around the old paddle can be expected to be a precise fit, and the electrical contacts will be in identical locations. However, this may only be possible sometimes, for example, if the paddle has been in place for a long time and is obsolete. There may be other reasons to switch to a newer type of paddle, for example, to make the system MRI conditional.

SCS systems are sometimes changed to try new technology, such as a different waveform, as a means of salvage in cases in which the original therapy has lost its effect. Often, this will mean a change of manufacturer. It should be noted that the new technology is generally a feature of the IPG, not the paddle, and several manufacturers supply devices with headers or pocket adapters that can mate with other manufacturers' leads; frequently, therefore, the paddle does not need to be changed.

If it is necessary to replace a paddle with one of a different type, the use of a type whose outline fits entirely within that of its predecessor is straightforward and should therefore be the default option. If a larger paddle must be used, the procedure will be significantly more complex.

Replacement With a Larger Paddle

Accommodating a paddle that is significantly longer in its rostrocaudal axis will require an opening to the upper end of the capsule. It is unsafe to do this from within the capsule by passing instruments up from below. Instead, the upper pole of the capsule is approached through the most appropriate interspace above, typically one to two levels above the original insertion site, and incised. As little bone as possible should be removed because the laminae are important in retaining the paddle apposed to the dura.

Accommodating a paddle that is wider than its predecessor presents greater problems and is not generally advisable. Opening the capsule along one side would likely require significant ligament and bone removal, causing the paddle to sit off-center in the canal. Depending on the amount of scar tissue in the epidural space, it may be possible to lay the new paddle dorsally outside the capsule, but scar tissue is relatively insulating, and this would cause excessive power consumption.

Insertion of a New Paddle at a Different Level

If the new paddle is larger than the old, in view of the extra dissection necessary to enlarge the capsule, consideration may be given to siting the new paddle in virgin territory above or below the previous site. Trials have shown that with paresthesia-free stimulation, paresthesia mapping and anatomic placement give similar results[154,155]; moreover, the patients with paresthesia mapping were often stimulated at different vertebral levels from the anatomically chosen stimulation site. This suggests that for paddles implanted in the low thoracic region, there is a range of several vertebral levels in which results are equivalent.

Nonrechargeable vs Rechargeable SCS Systems

Early SCS devices were nonrechargeable, operating on a primary cell battery within the IPG. The observation that some patients needed frequent IPG changes led to the development of rechargeable SCS devices. Charge per second is the product of amplitude × pulse width × frequency and is expressed as coulombs per second. If the device is set at a high value, it will cause early battery depletion. However, the value is not proportional to the clinical outcome. Paz et al[156] and Thomson et al[92] have shown in the HALO and PROCO RCT studies, respectively, with a frequency range from 10 Hz to 10,000 Hz of subperception SCS, that there is a large reduction in charge delivery for the same clinical effect as the frequency is lowered. In these studies, frequency reduces by two orders of magnitude, but pulse width only increases by one order, with amplitude staying little changed. At the lower end of this frequency range for subperception SCS (SP-SCS), the charge per second is similar to that of PB-SCS.

Most cost-effectiveness studies are modeled on a four-year survival of a nonrechargeable device as the base case value for device longevity. These cost-effectiveness analyses use a Markov model and estimate the therapy utility over longer time horizons by cycling through this model every four years, considering the costs and changing utilities of the SCS therapy. The incremental cost-effectiveness ratio is highly sensitive to the device battery longevity and cost.[157]

Nonrechargeable and rechargeable SCS devices have benefits and challenges that affect cost- effectiveness, clinical effectiveness, patient satisfaction, service provider burden, and therapy complications.

Nonrechargeable Devices

These are easier for patients to use because the recharging burden is removed from the therapy. However, careful programming, regular monitoring, and judicious use of "on-time" are required. The programmer should use the lowest charge per second and duty cycle commensurate with an optimal clinical outcome. Monitoring of the device and patient is required because electrode and biological interface impedances change. A constant current control system will increase its voltage output if the impedance increases to maintain the current, placing more drain on the battery. A change in electrode array may return the system to better efficiency.

It has long been known that a patient does not need SCS therapy continuously. Poststimulation analgesia (also sometimes referred to as carry-over effect), in which a patient may remain pain free for minutes, hours, and occasionally days after a period of stimulation, is commonplace. Good clinical outcomes can be achieved with the on-time being reduced. Some patients tolerate the cycling of PB-SCS, whereas others do not. However, with SP-SCS modes such as burst[29] or probably tonic mode, the on-time cycle can be reduced without the patient being aware when stimulation is on or off.

Many early SP-SCS programming options required high energy and were outside the possibility of use with a nonrechargeable SCS device.

In general, the following are accepted:

1) A lower charge per second can achieve as good a clinical outcome as higher charge per second (neural dosing).
2) Lower amplitudes in burst stimulation achieve better outcomes, which are unaltered even if the on-time is reduced to one-sixth (microdosing).

It is estimated that nonrechargeable device longevity, even with SP-SCS, can be preserved for more than four years, making the therapy with nonrechargeable devices cost-effective.

Unfortunately, this perfect scenario at the outset may not be maintained in the future real world; sometimes, a patient requires different settings and modes of SCS that require higher energy, which can only feasibly and economically be delivered by a rechargeable SCS device. The need to replace the IPG predisposes the patient to a risk of device infection around the time of device replacement surgery.

Rechargeable Devices

SCS device recharging is a burden for each patient. The acceptability of that burden will vary among individuals. In some, it can contribute to an overall failure of SCS therapy. However, if the device is well implanted, with the ideal distance between external charging device and IPG, and the recharging technique is optimal, this aspect of SCS therapy is easily incorporated into the patient's routine. Some prefer to charge daily for short periods, others weekly, occasionally at longer intervals. HF-SCS can only be delivered by a rechargeable system. The patient should accept this fact before considering this mode of stimulation for salvage therapy.

Rechargeable devices are more expensive, so for them to remain cost-effective, one expects them to provide good clinical outcomes (utility) over a longer period. Recently published large data sets have reported on SCS explant rates due to inadequate pain relief. In one retrospective multicenter chart review of 955 SCS implants, 19% at five years were explanted for inadequate pain relief; rechargeable systems showed a higher rate than did non-rechargeable systems.[8] However, in a single-center retrospective chart review of 298 SCS implants over a 7.5-year follow-up period that used rechargeable systems from a single manufacturer, only 3.4% were explanted owing to inadequate pain relief.[148] The true picture needs to be clarified given there are many covariables that can account for this variation.

The use of nonrechargeable devices may be dictated by governmental or insurance carriers' decisions. In clinical experience, when both options are available, it may be best to occasionally use nonrechargeable systems in patients who may lack the physical ability to manage their recharging. Many practices in Europe are burdened with replacing nonrechargeable devices rather than treating new patients. Some patients face therapy interruption as they await device replacement or surgical complications, such as replacement device infection, that can end the otherwise successful SCS therapy. Conversely, many patients find the recharging process to be a dissatisfier to SCS therapy and prefer to have a nonrechargeable system. This works well with some SP-SCS systems that deliver less charge per second and concomitantly have longer IPG lifespan.

Consensus Point 23. Rechargeable and recharge-free systems are currently in a state of transition. The best therapy will depend on the mechanism of action and required energy requirements. At present, a recommendation cannot be made regarding a general battery type for patients receiving neurostimulation.

USPSTF grade B, level of certainty moderate, evidence level II

Other Disease-Based Causes of Stimulation Failure

When determining whether the device is failing, it is important to consider other disease processes that may appear as tolerance but are actually disease progression. In recent years, literature has been produced showing salvage of neurostimulation systems with treatment of comorbidities, including progressive lumbar spinal stenosis with neurogenic claudication, sacroiliac joint disease, and vertebrogenic pain secondary to degenerative inflammatory disk disease. Peer-reviewed literature suggests that treating these issues may lead to salvage of a perceived failing device.[46,47]

FAILURE OF SCS AND DEVICE EXPLANTATION

After a system has definitively failed to meet the pain relief objectives and has failed a troubleshooting paradigm, a patient, in conjunction with their physician, should make the decision to either leave the system in situ or seek to have it explanted. This decision may be influenced by whether the SCS system causes any

local discomfort or restriction in activities, which would favor explant, or whether the system is software upgradable, which may allow future salvage through new waveform applications and would favor retention of the system. We recommend an individualized decision based on the patient's circumstances.

CONCLUSIONS

To date, SCS therapy salvage has been an exercise in admitting the lack of efficacy in a patient and then trying to find a solution. This has often been based on physician or patient preference, with little focus on evidence. This NACC consensus is the initial process for creating a potential roadmap based on the best available evidence to restore therapy effectiveness. The recommendations should be combined with guidance on patient and device selection for initial implant, and with guidance on risk mitigation to create solutions that enhance neuromodulation, therapy efficacy, and patient safety.

Authorship Statements

Timothy R. Deer is responsible for primary authorship and coordination; Marc Russo is cofirst author; Jay S. Grider and Tim J. Lamer are responsible for grading and evidence; Fabián Cremaschi, Adnan Al-Kaisy, Ganesan Baranidharan, and Salim M. Hayek are editors; Robert M. Levy is senior editor. Olivier De Coster, Paul J. Christo, Vishal Varshney, and Stana Bojanic reviewed the manuscript for commercial bias. Dawood Sayed, David M. Dickerson, Jonathan M. Hagedorn, Erika A. Petersen, Michael A. Fishman, James FitzGerald, Dirk De Ridder, Krishnan V. Chakravarthy, Corey W. Hunter, Eric Buchser, Kenneth Chapman, Chris Gilligan, Simon Thomson, Natalie Strand, Jessica Jameson, Thomas T. Simopoulos, and Ajax Yang conducted literature searches, wrote sections, wrote consensus statements, or reviewed/edited sections they did not draft, and all authors approved the submitted manuscript.

Conflict of Interest

Timothy R. Deer consults for Abbott, Saluda, Painteq, Cornorloc, Spinal Simplicity, Spinethera, Nervonik, Biotronik, and SPR Therapeutics.

Dawood Sayed reports personal fees from Abbott, Medtronic, Flowonix, Nevro, and Boston Scientific, outside the submitted work.

David M. Dickerson reports research support from SPR Therapeutics and Abbott; consulting fees from Abbott, Vertos, SPR, and Biotronik; speaker's fees from Abbott, Vertos, Biotronik, and SPR Therapeutics; and meeting and travel support from Vertos, SPR, and Abbott. He is a committee chair for the North American Neuromodulation Society and the American Society of Anesthesiologists, and a board member of the Midwest Pain Society. He serves as a clinical advisory member for National Median Arcuate Ligament Syndrome Advisory and National Rx and Drug Abuse Summit.

Erika A. Petersen reports research support from Mainstay, Medtronic, Nalu, Neuros Medical, Nevro Corp, ReNeuron, SPR, and Saluda, in addition to personal fees from Abbott Neuromodulation, Biotronik, Medtronic Neuromodulation, Nalu, Neuros Medical, Nevro, Presidio Medical, Saluda, and Vertos, outside the submitted work. She holds stock options from SynerFuse and neuro42.

Michael A. Fishman reports honoraria from Abbott, Biotronik, Medtronic, and Mainstay Medical; consults and advises for Biowave, Biotronik, Medtronic, and Thermaquil; conducts funded research for Abbott, Biowave, Biotronik, and Medtronic; receives royalties/patent from Brixton Biosciences, Medtronic, and Vyrsa (acq Nevro); and has stock options from Brixton Biosciences and Thermaquil, an equity position in Celeri Health, and ownership in Brixton Biosciences.

James Fitzgerald reports personal fees from Medtronic and Abbott, and grants from Abbott, outside the submitted work.

Ganesan Baranidharan reports grants and personal fees from Nevro Corporation, Abbott, and Boston Scientific; and personal fees from Nalu Medical, outside the submitted work.

Dirk De Ridder reports other from Abbott during the conduct of the study, and he has a patent pending with Abbott.

Krishnan V. Chakravarthy reports other from Medtronic, Mainstay Medical, Vertos, NXTSTIM, Accufix Medical, Newrom Biomedical, and Douleur Therapeutics, outside the submitted work.

Corey W. Hunter reports other from Saluda Medical Pty Ltd; grants, personal fees, and other from Abbott; and grants from Biotronik, outside the submitted work.

Eric Buchser reports personal fees from Medtronic, Switzerland, outside the submitted work.

Chris Gilligan reports other from Mainstay Medical and Sollis Therapeutics; and personal fees from Medtronic, Saluda, and Abbott, outside the submitted work.

Simon Thomson reports consulting agreements with Boston Scientific Neuromodulation, Galvani Bioelectronics, Mainstay Medical, and Saluda Medical.

Jessica Jameson reports personal fees from Nevro, Boston Scientific, and Abbott, outside the submitted work.

Thomas T. Simopoulos reports personal consultant fees from Nevro Corp, outside the submitted work.

Robert M. Levy is an uncompensated consultant for Nalu, Saluda Medical, and Mainstay Medical; and has stock options from Nalu and Saluda Medical obtained before 2019 and not exercisable through the duration of his term as International Neuromodulation Society president and editor-in-chief of the journal *Neuromodulation: Technology at the Neural Interface.* The remaining authors reported no conflict of interest.

How to Cite This Article

Deer T.R., Russo M., Grider J.S., Sayed D., Lamer T.J., Dickerson D.M., Hagedorn J.M., Petersen E.A., Fishman M.A., FitzGerald J., Baranidharan G., De Ridder D., Chakravarthy K.V., Al-Kaisy A., Hunter C.W., Buchser E., Chapman K., Gilligan C., Hayek S.M., Thomson S., Strand N., Jameson J., Simopoulos T.T., Yang A., De Coster O., Cremaschi F., Christo P.J., Varshney V., Bojanic S., Levy R.M. 2024. The Neurostimulation Appropriateness Consensus Committee (NACC)®: Recommendations for Spinal Cord Stimulation Long-term Outcome Optimization and Salvage Therapy.
Neuromodulation 2024; ■: 1–26.

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COMMENTS

Traditional SCS systems are reported to have a significant explant rate due to loss of analgesic benefit. This manuscript provides a roadmap and rationale on ways newer SCS technologies can be implemented to salvage failing SCS therapies and provide a return to analgesic benefit for patients who would otherwise be considering explantation of their SCS system.

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I now have more options and ideas when we lose effect in patients. This overview is a beautiful article describing causes and solutions.

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