Clinical Applications of Neuromodulation: Neurostimulation for Complex Regional Pain Syndrome

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Key Points

- Complex regional pain syndrome (CRPS) is defined, and criteria necessary to be satisfied for this diagnosis are addressed.
- A review of recent literature describing the use of spinal cord stimulation (SCS) in the management of CRPS is provided.
- The risk–benefit analysis, patient criteria, and conditions should be met before consideration of SCS is addressed including the need for psychometric testing and instruments that are used for this purpose.
- The multidisciplinary management of patients with CRPS is emphasized including how SCS may be introduced as either a temporary adjunct to functional restoration or its permanent implantation in cases that require the ongoing attributes of SCS as it serves to ameliorate pain and improve the microcirculation and functional improvement of motor function is emphasized.

Introduction

Complex regional pain syndrome (CRPS), formerly termed reflex sympathetic dystrophy (RSD), was introduced in 1994 by the International Association for the Study of Pain (IASP) [1, 2]. CRPS comprises two syndromes: type I, representing reflex sympathetic dystrophy, and type II referring to causalgia [3]. The hypothesis of sympathetically maintained pain (SMP), introduced by Roberts in 1986, represents a phenomenon that may be present in both syndromes and can be confirmed, when present, by sympathetic blockade [4].

As set forth by the IASP, the diagnostic criteria that must be satisfied comprise pain, impaired function in the region, trophic changes involving the nails, hair growth, and sudomotor dysfunction [2]. Sensory abnormalities such as hyperesthesia, hyperalgesia, and mechanical or thermal allodynia (or both) are also present (Table 63.1).

The fundamental signs and symptoms of CRPS entail sensory, motor, autonomic, and trophic changes. The IASP requires that these clinical features be identified under these four categories. No supportive clinical tests are included in the IASP classification. However, tests of sudomotor dysfunction, e.g., the quantitative sudomotor axon reflex test (QSART), quantitative sensory testing (QST), skin biopsy, and the use of sympathetic blocks to determine whether any significant autonomic dysfunction is evident, can be undertaken.

The differential diagnosis of CRPS requires the elimination of other clinical syndromes which share clinical features with CRPS but which are clearly distinct by virtue of their own unique constellation of signs and symptoms. Clinical features similar to those of CRPS include the pain, edema, and temperature asymmetry characteristic of trauma patients, but who nevertheless do not develop CRPS. Table 63.2 describes the clinical diagnostic criteria of CRPS, termed the "Budapest Criteria" and published in 2010.

Movement disorders, not previously associated with CRPS, are now well recognized (see Table 63.3) [8]. They include weakness, tremor, muscle spasms, dystonia, and inability to initiate movement. Occasionally sympathetic blockade, when undertaken soon after the onset of CRPS, may eliminate the movement disorder.

Contemporary thinking accepts that the initial clinical features of CRPS resemble a significant inflammatory disorder. However, this thinking has been shaped by studies revealing that free O_2 radical expression can sensitize activity in C and A-δ fibers. Continuous excitation of these

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Table 63.1 Diagnostic criteria for complex regional pain syndrome (CRPS)

Factor 1	Factor 2	Factor 3	Factor 4
Hyperalgesia signs (0.75)	Temperature asymmetry symptoms (0.68)	Edema signs (0.69)	Decreased range of motion signs (0.81)
Hyperesthesia symptoms (0.78)	Color change signs (0.67)	Sweating asymmetry signs (0.62)	Decreased range of motion symptoms (0.77)
Allodynic signs (0.44)	Color change symptoms (0.52)	Edema symptoms (0.61)	Motor dysfunction signs (0.77) Motor dysfunction symptoms (0.61) Tropic symptoms (0.52) Trophic signs (0.51)

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Table 63.2 Budapest clinical diagnostic criteria for complex regional pain syndrome (CRPS)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   Sensory: reports of hyperesthesia and/or allodynia
   Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in *two or more* of the following categories:
   Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

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nociceptors will in turn sensitize first-order and higher neurons in the central nervous system (CNS). Central sensitization can be demonstrated not only in the spinal cord but also at the supratentorial centers in the brain [9].

Rationale for the Use of Neurostimulation

Most pharmacologic treatments of CRPS target neurologic dysfunction. The treatments include membrane stabilizers, antidepressants, norepinephrine reuptake inhibitors, and NMDA antagonists—all of which are used to support a return of function by means of physiotherapeutic measures [10]. Two other measures used to support rehabilitation are (1) epidural infusions of local anesthetics with or without opioids and (2) the addition of alpha-2 agonists like clonidine. These techniques have proved very effective but are associated with a low incidence of infection as well as technical failure of the infusion system. They are also expensive because they require home health-care support and associated pharmaceuticals.

When sympathetically maintained pain (SMP) has been demonstrated by a sympathetic block, with almost complete symptomatic relief, a comparatively long duration of effect can be achieved by segmental radio frequency ablation (RFA) of the sympathetic trunk.

Increasing evidence now supports the use of neuroaugmentative procedures such as spinal cord stimulation (SCS) or peripheral nerve stimulation (PNS) [11–13]. This evidence includes randomized controlled trials (RCTs), several long-term studies, and several case studies. The first RCT, conducted by Kemler et al., was published in 2000 [14]. The patients in this study met the IASP diagnostic criteria for CRPS and were unresponsive to conventional medical management (CMM). Two randomly assigned groups comprised patients who undertook spinal cord stimulation (SCS) plus physical therapy and patients who received only physical therapy. All patients who successfully completed their trial underwent implantation of the neurostimulator. The subsequent intention-to-treat analysis demonstrated a significant reduction in pain in the SCS/physical therapy group [15]. Other measures showed that the SCS/physical therapy group experienced improvement both in the global perceived effect (GPE) and in quality of life (QOL). All patients underwent implantation of their SCS. The same authors demonstrated long-term improvement in pain relief and GPE among the SCS/physical therapy group, in comparison to the patients who received only physical therapy at 2 years. At 5 years, the GPE remained better than in patients who had received only physical therapy, although the "expressed" pain relief did not differ between the two groups. However, all the patients who had received an SCS stated they would repeat the treatment should the need arise.

In one study, carbamazepine and morphine were compared in patients previously implanted with an SCS [16]. This study,

Table 63.3 Prevalence of movement disorders in complex regional pain syndrome (CRPS)

N	Weakness (%)	Akinesia (%)	Dystonia (%)	Spasms (%)	Tremor (%)	Reference
200			22			Schwartzman and Kerrigan (1990)
829	95		36[a]	25	49	Veldman et al. (1993)
181	89	80			45	Blumberg and Jänig (1994)
123	75/76[b]				24/94[b]	Harden et al. (1999)
145	79	45	30[c]		48	Birklein et al. (2000)

From van Hilten et al. [7]. Used with permission
[a]Reflects involuntary movements
[b]Symptoms/signs
[c]Including myoclonia

divided into two phases, investigated the effect of administering carbamazepine or placebo in phase I and morphine and placebo in phase II after the patient's SCS system had been deactivated. Carbamazepine was superior to morphine in reducing the level of pain. However, only 2 of the 38 patients preferred to continue their treatment with carbamazepine; the remaining 36 preferred to continue their treatment with SCS. These results clearly demonstrated the successful symptomatic management of either neuropathic pain or CRPS.

Although most of the papers during the past 35 years have been case studies or retrospective reviews, a common thread of success runs through these works. The latest publication that supports the use of SCS is probably the 2009 Health Technology Assessment report, issued by the National Institute for Health and Clinical Excellence (NICE). This report reviewed 6,000 citations, including 11 RCTs of neuropathic pain and eight of ischemic pain [17], and concluded that SCS effectively decreases chronic neuropathic pain, and the results are more effective than those of conventional medical management (CMM). With regard to cost containment, the incremental cost-effectiveness ratio (ICER) described a range of $25,000–$30,000 per quality-adjusted life year (QALY), and if based on device longevity of 4 years, these figures were reduced to $20,000 per QALY.

It should be emphasized that most of the data reported so far have been obtained with comparatively unsophisticated systems. However, the efficacy of SCS, and in particular its effect on CRPS, has been improved by means of more modern neurostimulation systems with computerized programming capabilities, multiple arrays, and dual or multiple electrode systems. When the results of these latest systems are carefully studied, it becomes clear that early intervention is responsible for a much greater success rate in reversing or suppressing the symptoms.

The temporary use of SCS to provide analgesia in support of a physiotherapeutic program or a more comprehensive interdisciplinary treatment program was advocated by Prager and Chang in 2000 [18]. In this study, the authors described a triple-lead (tripolar) system that was temporarily implanted, and an "extended trial" was used to facilitate exercise therapy. The system was retained for 4 weeks, and if the patient required further analgesia after that time, it was implanted. A second set of 16 patients, who had failed 4 weeks of comprehensive therapy, underwent permanent implant of SCS with continuing interdisciplinary treatment. Patients who no longer felt that SCS was necessary underwent explantation. Five of the original eight patients showed improvement in their symptoms sufficient to warrant removal of the system. The authors noted that SCS is a fairly inexpensive treatment compared to CMM or multiple sympathetic blocks. Finally, it should be noted that an implanted SCS lead with an externalized pulse generator could always be converted to a totally implanted system, circumstances prevailing.

Patient Selection

Appropriate selection of patients for SCS is essential to a successful outcome [11]. Most published treatment algorithms describe the use of SCS after simpler and more conservative therapies have been tried in a stepwise fashion although usually in support of an exercise therapy treatment program [19]. Conventional wisdom would suggest that any patient who is likely to need an implantable device such as an SCS must undergo a satisfactory behavioral assessment [20]. Such an assessment is essential for precluding those patients who might believe that a simple or rapid intervention such as SCS is most likely to cure their clinical problem, or who may have unrealistic expectations regarding the management of their syndrome. Although SCS is a minimally invasive procedure, it should always follow an adequate screening trial. The trial should demonstrate to the patient and to the treating physician that the activities of daily living (ADLs) can be improved and that notwithstanding improved symptoms, the patient should maintain their exercise therapy (Table 63.4).

In this respect, convention requires a 50 % reduction of pain. If other comorbidities, or the possible anatomic anomalies, are suggested, preradiologic screening with MRI or CT scan is imperative. Additional selection criteria have been developed by several authors (see Table 63.3). In an effort to standardize criteria for the selection of patients for SCS, several scientific bodies, including the International Association for the Study of Pain (IASP), the International Neuromodulation

Table 63.4 Selection criteria for spinal cord stimulation in complex regional pain syndrome (CRPS)

Oakley [11]	
Inclusion	Exclusion
Diagnosis of CRPS	Absence of initial CMM
6-month pain duration	Previous failed SCS trial
Psychological clearance	Untreated axis I psychiatric disorder
Informed consent	Certain psychoses
Contraindications	
North et al. [21]	
Relative	Absolute
Medication dependence	Coagulopathy
Unresolved psychiatric disorder	Immunosuppressive therapy
Nonorganic signs (Waddell's)	Unacceptable surgical risk
Inconsistent history	Conflicting therapy diathermy
Anticoagulation therapy	Serial MRI requirements
Alternative therapy with lower risk/benefit ratio	Occupational risk

Minimally adapted from Prager [22]. Original used with permission

Society (INS), the North American Neuromodulation Society (NANS), and the American Academy of Pain Medicine (AAPM), are involved in the education and dissemination of guidelines to be met before patients are selected for neurostimulation. The requirement for psychological pretesting is addressed by the Centers for Medicare Services (CMS), the industrial commissions and state bureaus of workers compensation (BWC), and most health insurance agencies. Most contemporary psychological evaluation is based on an inventory of risk factors which, together with behavioral management, play a significant role in patient care that supports the use of SCS in selected patients [23, 24].

Risk–Benefit Analysis

The potential benefit of SCS as a treatment modality for CRPS has been described in the supporting literature. Table 63.5 identifies several observations that underscore the value of SCS; however, pain relief remains the most significant reason to consider SCS. For more than 30 years, success has been defined as a reduction of 50 % in pain [30]. However, pain reduction is subjective, and the level of pain is assessed by means of arithmetic scales such as the visual analog scale (VAS), verbal rating scale (VRS), and numerical rating scale (NRS). Unfortunately, because pain is subjective and is an exponential function, the values, expressed arithmetically, bear little resemblance to the constellation of symptoms about which the patient complains. Furthermore, chronicity and environmental factors materially impact the number chosen on any one of the above scales. Function should become the standard by which the impact of pain can influence a variety of functional markers (Table 63.5).

The Neuromodulation Therapy Access Coalition identified studies that demonstrate the ability of patients to undertake their activities of daily living (ADL) and to improve quality of life (QOL). Although there are quite extensive data from patients in whom failed back surgical syndrome (FBSS) has been treated by SCS, other functional markers used are the Oswestry Disability Index and the Hospital Anxiety and Depression (HADS) Scale [27]. All measures showed significant reduction. In the single RCT on CRPS by Kemler et al., the QOL improved by 11 % [14]. Although patient satisfaction has never been standardized, several authors have indirectly described patient satisfaction as those patients who choose to cross over from CMM to SCS, or who choose to repeat implantation to achieve the same result, indicating the success of SCS [25, 31]. An interesting aspect of SCS that often escapes comment is its effect on depression. Several authors have noted that SCS patients manifest fewer symptoms of depression such as those measured by the Beck Depression Inventory (BDI) [29, 32, 33].

The greatest impediment to successful treatment stems from complications due to technical failure, or from infection, which occurs in as many as 30 % of all cases [34].

Under the best of circumstances, the incidence of perioperative infection is between 4 and 5 % of all cases [11, 34]. North, describing 20 years of experience with spinal cord stimulation, found 0 incidence of spinal cord injury, meningitis, or other life-threatening infection. An incidence of spinal fluid leak, neurologic injury, or hemorrhage has been reported in 0–42 % of cases [11].

Electrode displacement occurs in approximately 24 % of cases [34]. The subsequent loss of therapeutic stimulation requiring surgical revision occurs in approximately 50 % of cases. However, many of the foregoing data have been derived from older and simpler systems. Modern multichannel systems with computerized implanted pulse generators (IPGs) are significantly more reliable. Accordingly, the future of SCS should markedly improve as a result of technological advances in contemporary equipment.

In a review of 126 cases, Oakley found that 26 patients (20 %) requested that their system be explanted or discontinued [11]. The main reasons for failure were progression of disease, loss of therapeutic paresthesia, and discomfort at the implant site (primarily IPG). On the other hand, four patients (3 %) experienced such successful analgesia that they no longer used their system. When patients are being prepared to consider SCS, the relative merits of its use should be placed in the context of their treatment to date. It is critical that the patient be informed of the shortcomings associated with SCS (as described above), of the nature of the screening trial, and the reasons for it. The specific endpoints a patient should assess during a trial are (1) the degree of pain relief, (2) what functional improvements are experienced on the affected side, (3) whether activity

Table 63.5 Potential benefits of spinal cord stimulation in treating complex regional pain syndrome (CRPS)[a]

Benefit	Comments
Pain relief [25, 26]	The primary outcome measure of SCS success is patient-reported pain relief, generally using a standard pain scale such as the visual analog scale (VAS), functional rating index, McGill Pain Questionnaire [21]
	A majority of patients may experience at least 50 % reduction in pain
Increased activity levels or function [12, 26, 27]	As demonstrated by activities of daily living, such as walking, climbing stairs, sleeping, engaging in sex, driving a car and sitting at a table [28]
	Measured by the Oswestry Disability Index (specific for low back pain), the Sickness Impact Profile (for general health), Functional Rating Index, Pain Disability Index
Reduced use of pain medication (Harke et al. 2005)	Patients in whom SCS is successful should be able to reduce or eliminate their intake of pain medication [21]
Improvement in quality of life [21, 27]	Would repeat treatment to achieve the same result [21]
Patient satisfaction with treatment (Alo et al. 1999; Bennett et al. 1999; [12, 21, 27])	
Fewer symptoms of depression [12, 21, 27, 29]	Measured by the Beck Depression Inventory

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[a]Original author's note: Consult "practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain" [21] for a comprehensive bibliography of studies that support the benefits of spinal cord stimulation in treating complex regional pain syndrome (CRPS) Selected long-term or seminal studies are cited here; short-term studies and case reports are not

is facilitated, and (4) whether circulation, as determined by temperature change and skin color in the region, is improved. It is also important to allow the patient to continue their routine medical management—in particular, medication—so that any reduction in use may definitively reflect successful SCS. Finally, patients should be encouraged to increase daily activities and, if appropriate, maintain their exercise program.

Obviously, a detailed description of the risk–benefit aspects of SCS that can be experienced should be discussed with each patient. Moreover, long-term efficacy should be placed within the context of our cumulative experience of SCS.

Multidisciplinary Care: The Role of SCS

Experience gained during the past 20 years has clearly highlighted the need for multidisciplinary or interdisciplinary management of patients with CRPS. It has been determined that neurostimulation, in its various forms, is the single most successful modality to use in most patients. In 2002, a physiotherapeutic continuum involving multidisciplinary management for CRPS was published (see Fig. 63.1) [35]. This algorithm underscored that psychological, rehabilitative, and interventional pain management should be implemented in a time-contingent manner—sequentially, or at times simultaneously. The various behavioral and/or interventional approaches are introduced only if or when progress slows or stalls during the course of psychotherapeutic measures. "Time contingency" as proposed by the international group that participated in the development of this algorithm was considered to be the sine qua non for promoting physical therapy and, when adopted, underscored the need to incorporate neurostimulation as a major component of therapy. In fact, during rehabilitation, desirable functional effects (e.g., vasodilatation and motor improvement) are most often conferred when interventions such as SCS are incorporated [36]. These effects obviously require validation.

Although SCS is usually introduced as an intervention during the course of treating neuropathic pain, contemporary experience would suggest that in some cases, because of its significant attributes, SCS should be introduced much earlier [37–42]. This point is already addressed in the treatment algorithm.

One thing is certain that previously used ablative measures such as sympathectomy—whether pharmacologic or surgical—have little part to play in the modern management of CRPS.

The SCS Trial

A trial of SCS offers patient and physician the opportunity to determine whether the patient's therapy can be continued without the restrictions of their disability and at the same time allows the physician to assess whether the patient might be able to successfully discontinue their medications if any. The trial should assess goals that the treating physician has proposed, and it

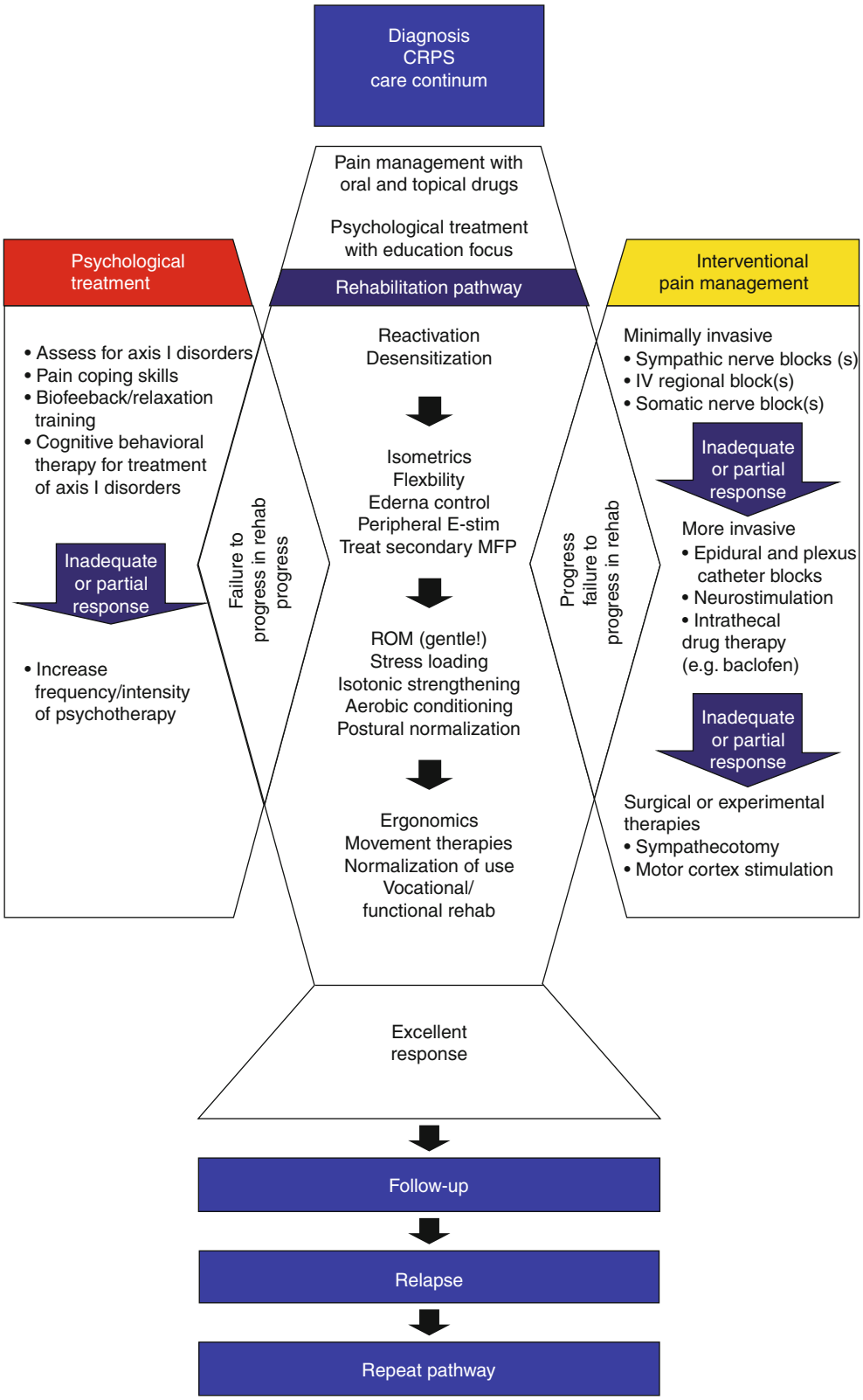

Fig. 63.1 Treatment algorithm suggested for the restoration of function using a stepwise approach and the introduction of behavioral or interventional measures that should be introduced in order to facilitate progress in treatment. With demonstrated improvement, the physiotherapeutic measures may be increased in intensity and frequency in order to achieve a final remission of this syndrome

should also aim to reduce pain symptoms by at least 50 %, while functional rehabilitation is still being undertaken [26, 29].

In addition to psychological assessment, a physical examination should be performed; this is also including a complete neurologic assessment to detect and evaluate other possible comorbidities [28]. Although many screening protocols are followed, a trial of SCS will be influenced by the site (upper vs. lower extremity), the patient's overall medical condition, the practice resources, geographic proximity to the patient's home, and economic issues related to the patient's reimbursement for their trial, e.g., private insurance, Medicare, BWC.

If the patient has certain anatomic abnormalities and/or prior adverse experience with neurostimulation, these aspects may require consultation with a neurosurgeon so that a percutaneous trial [28, 43, 44]. The customary duration of an SCS trial is 1 week, which is usually long enough for the patient and physician to evaluate the merits of SCS as a therapeutic modality. Longer periods are customary if a patient doubts the efficacy of their trial.

In certain cases, a so-called "extended" SCS trial is used to facilitate either rehabilitation or a comprehensive outpatient or inpatient multidisciplinary pain program [45, 46]. In such cases, the trial electrode is left in situ for periods of 6–8 weeks. In many of these cases, it is not intended that an SCS system be subsequently implanted; the trial merely serves as a means for facilitating their exercise program.

Surgical Implantation

Because SCS represents a radical departure from CMM, the patient should regularly be made aware that SCS will reduce, but in most cases will not completely eliminate, their pain. Patients must also understand that SCS will be a component of other therapies. Whenever practicable, patients should be followed at intervals of 3, 6, and 12 months so that any adjustments can be made prospectively or in response to the loss of therapeutic stimulation. Patients who are to undergo laminotomy placement of their SCS must be informed that greater discomfort and some morbidity are associated with the procedure but that within a reasonably short time, these symptoms should resolve [47]. Patients should also be counseled that lifelong exercise therapy will be needed to maintain optimal therapeutic support from the SCS. Moreover, they should be cautioned that over a 2-year period there will be about a 10 % loss in efficacy; after which, there will be no further loss for the life of the neurostimulator [48]. Finally, at no time should the relationship between the patient and the implanting physician be disrupted; for maintenance of the relationship allows subsequent technical issues or a breakdown in SCS efficacy to be addressed in a timely manner.

Cost-Effectiveness

Several studies in the USA, the Netherlands, the UK, Germany, and Canada have evaluated the cost of SCS treatment. Evidence from RCTs confirms the cost-effectiveness of SCS for treating CPRS. In the Netherlands, the 12-month cost of CRPS treatment by SCS was $4,000 greater than that for CMM but in an analysis over a lifetime; SCS was found to be $60,000 less than CMM per patient. In the UK, the lifetime cost savings was $60,800 for SCS compared to physical therapy alone. In Canada, Kumar et al. found that in a group of 104 patients, the cumulative cost of SCS was $29,123 compared to $38,029 for CMM [21, 48–53].

Summary

SCS is successful as an adjunct in the treatment continuum for CRPS. A trial of SCS is always necessary before implantation is considered or implemented. Not only analgesia but also improvement in function and in the ability to tolerate physical therapy should be determinants of a successful trial. Over the past 30 years, during which SCS has been used in the treatment of CRPS, no adverse effects have been reported on the central nervous system or neuroendocrine systems. SCS is cost-effective. Continuing improvements in the understanding of its mechanism of action, as well as improvements in technological developments, should anchor this modality as one of the most successful treatments for neuropathic pain. Thus, it plays a unique role in the management of and supportive of rehabilitation for CRPS.

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