Special Article

Complex Regional Pain Syndrome: Manifestations and the Role of Neurostimulation in Its Management

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Abstract
The hallmark of complex regional pain syndrome (CRPS) is excruciating pain (aching, burning, pricking, or shooting). Diagnosis should be established as soon as possible, as response to treatment is adversely affected by any delay. Treatment of CRPS is aimed at improving function, using an interdisciplinary, time-dependent, patient-dependent approach that encompasses rehabilitation, psychological therapy, and pain management. If no response to conventional treatment (e.g., pharmacotherapy) is noted within 12–16 weeks, a more interventional technique such as spinal cord stimulation (SCS) should be used. SCS has been shown to be highly effective in the treatment of CRPS type I, resulting in a significant, long-term reduction in pain and improvement in quality of life. SCS is particularly effective at helping to restore function in affected extremities, especially if applied early in the course of the disease. SCS is also cost effective and improves health-related quality of life. J Pain Symptom Manage 2006;31:S20–S24. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Complex regional pain syndrome, rehabilitation, pain management, psychological therapy, spinal cord stimulation

Diagnosis of Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a regional pain of unclear pathophysiology, usually occurring after an often minor precipitating event or trauma such as a fracture, sprain, or after surgery. When such symptoms can be traced to an identifiable nerve injury, the condition is referred to as CRPS type II; in the absence of an identifiable nerve injury, the condition is defined as CRPS type I (Table 1).[1] CRPS is a disease of relatively young people (the mean age of CRPS patients ranges from 36 to 42 years) and occurs more frequently in women. Excruciating pain is a hallmark of the disease. Although the sympathetic nervous system has been implicated in the pathophysiology of CRPS, and the term sympathetically maintained pain (SMP) was introduced to explain the response of sympathetic blockade, the presence of autonomic dysfunction in the context of CRPS does not guarantee that all patients will respond to such blocks. In fact, the term sympathetically independent pain (SIP) was introduced to explain the lack of response to a sympathetic blocking procedure as illustrated in Fig. 1.

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Table 1
International Association for the Study of Pain Diagnostic Criteria for CRPS I and II[1]

CRPS I (reflex sympathetic dystrophy)	CRPS II (causalgia)
1. The presence of an initiating noxious event, or a cause of immobilization 2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event 3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain 4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction Note: Criteria 2–4 must be satisfied	1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve 2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain 3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction Note: All three criteria must be satisfied

The intense pain that distinguishes CRPS is characterized as aching, burning, pricking, or shooting. Other symptoms include allodynia, hyperalgesia, hyperesthesia, edema, abnormalities of temperature, sudomotor dysfunction, skin color changes, and trophic changes.

The diagnosis of CRPS should be established as rapidly as possible, since the response to treatment appears to be adversely affected by any delay.

Treatment of CRPS

The goal of treatment is to improve function. While the syndrome has a complex pathophysiology involving both peripheral and central nervous systems, together with significant behavioral features, successful treatment is complicated by not only the precipitating pathology, but also the variety of clinical presentations. Treatment, therefore, is directed at the suspected pathophysiology: central nervous system (CNS) disturbance, peripheral nerve stimulation (PNS) disturbance, dysautonomia, nociceptor dysfunction, peripheral inflammatory changes, including ischemia, and the motor disturbance.

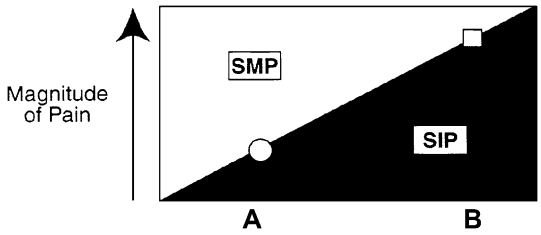

Fig. 1. The sympathetic component of pain. The diagram illustrates the relative contribution of SMP to SIP. A patient at A would be said to have a large component of SMP and therefore respond favorably to a sympathetic block; a patient at B whose symptoms are primarily SIP would have little or no response to a sympathetic block.

A panel of experts recently met to review the current pathophysiology of CRPS and its treatment to provide an updated algorithm for its management (Fig. 2).[1] It was determined that some cases of CRPS are refractory to conservative measures and require more flexible application of treatment options within the CRPS algorithm, as well as earlier consideration of such interventions as neurostimulation (spinal cord stimulation [SCS], PNS, deep brain stimulation, and motor cortex stimulation). The resulting clinical guidelines aim to optimize function and minimize pain using an interdisciplinary, time-dependent approach to therapy, based on the patient's response. Three core treatment elements are emphasized:

- *Rehabilitation* (the mainstay of CRPS treatment)—emphasizes the importance of functional restoration and reanimation. While the body of evidence for this is small, several recent studies now underscore this premise,[2,3] the point at which a patient enters the treatment algorithm and the speed with which they progress will depend on factors such as their clinical presentation and their response to therapy. Failure to progress will require a change in medications, in particular stronger analgesics, a reappraisal of the physical therapy (PT), and a need to address the many motor abnormalities such as weakness, lack of coordination, tremor, and dystonia that interfere with therapy.
- *Pain management*—pain is the fundamental symptom of CRPS and its management must be dynamic and flexible

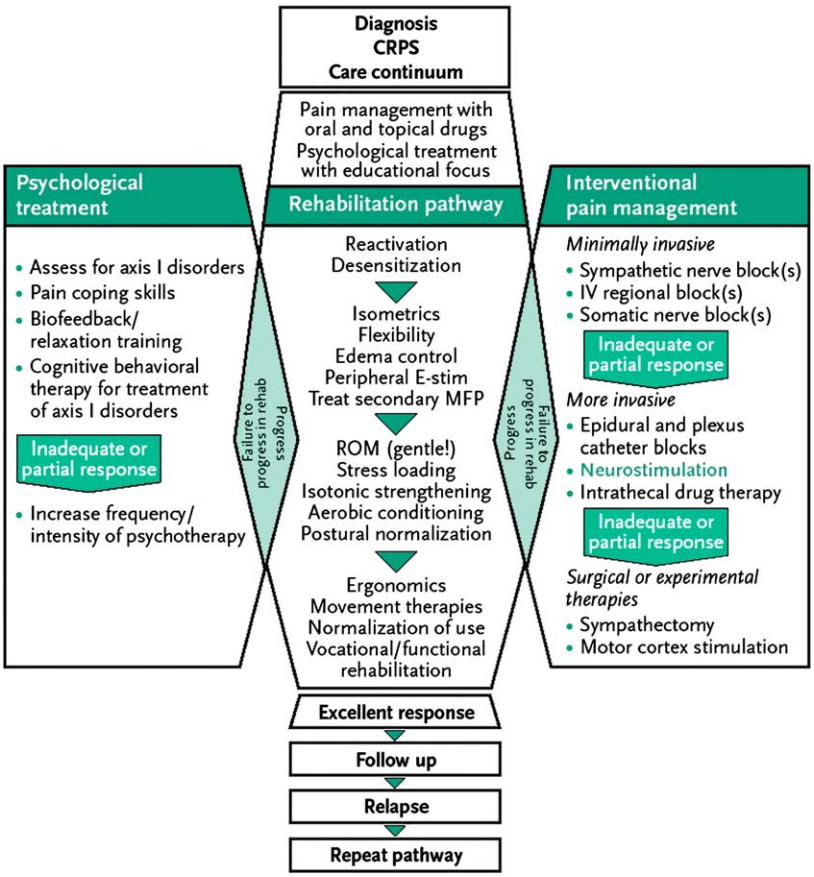

Fig. 2. Revised therapeutic algorithm for CRPS.[1] The algorithm emphasizes the use of therapeutic modalities in response to the patient's clinical progress during the course of his or her rehabilitation; adapted from the earlier 1998 Guidelines.

(corresponding to the disease progression) to provide symptomatic relief and enhance the patient's ability to optimize their function. To prevent a plateau in progress through the rehabilitation pathway, no longer than 12–16 weeks of a particular pharmacotherapy or regional anesthesia should be allowed before a change in therapy is undertaken. This may mean recourse to more invasive techniques such as continuous epidural analgesia or neurostimulation (SCS or PNS). Plainly stated, persistence with ineffective therapy in a syndrome such as CRPS should not be tolerated, and every endeavor to use all resources must be taken if a remission is to be achieved.

- *Psychological therapy*—focused on improving quality of life (QoL), developing pain-coping skills, cognitive behavioral psychotherapy, and facilitating progress through the rehabilitation pathway.

The Role of SCS in CRPS

SCS has been shown to be highly effective in the treatment of CRPS type I and its ability to successfully reduce pain, allodynia, and muscle dysfunction and to improve blood flow is the substance of many anecdotal reports and more recently prospective studies. Early evidence suggested that SCS resulted in the relief of pain in over 73% of CRPS patients and helped to reduce the edema associated with the condition (Fig. 3).[4–6]

More recent studies have supported these observations. In 2000, Kemler et al.[7] carried out a prospective, randomized, controlled study in patients with chronic CRPS type I to determine whether SCS plus PT ($n = 24$) was

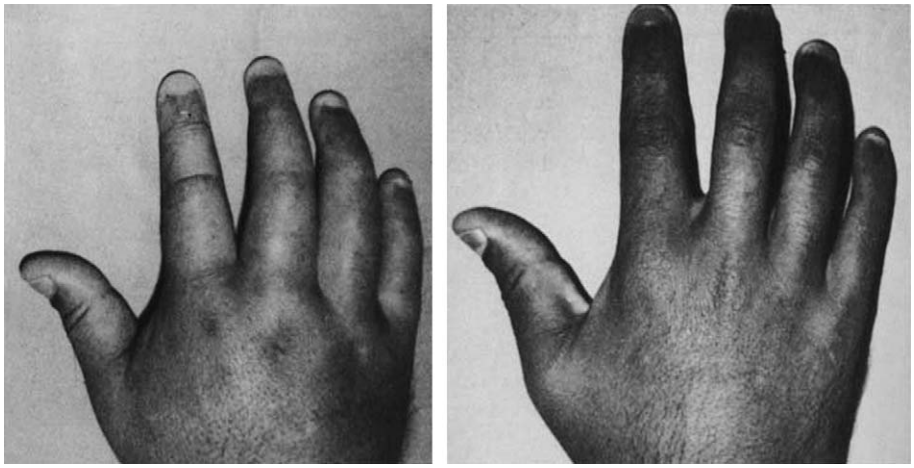

Fig. 3. Reduction of edema in the right hand of a patient with CRPS, 24 hours after treatment with SCS.[6]

more effective than PT alone ($n = 18$). Results showed that in patients treated with SCS + PT, pain intensity was significantly reduced by 3.6 cm on the visual analog scale, compared with an increase of 0.2 cm in the PT alone group ($P < 0.001$). In addition, a significantly greater proportion of SCS-treated patients (58%) described a "much improved" global perceived effect compared with the PT alone group (6%) ($P < 0.001$). Although there was no clinically important improvement in functional status, treatment with SCS improved the overall health-related quality of life (HRQL) score by 11%. Significant improvements in HRQL were seen for patients with an affected hand ($P = 0.02$) and those with an affected foot ($P = 0.008$). The results of the 2 year follow-up study confirmed the long-term efficacy of SCS in the treatment of CRPS.[8] Complications occurred in 38% of patients. These were of a technical nature, most occurring in the first year. Pulse generator replacements were the only significant recurrent expenditures.

In another prospective study, QoL assessments that included the McGill Pain Rating Index, the Beck Depression Inventory, and the Sickness Impact Profile[9] were used to evaluate the effect of SCS in the management of CRPS. The results determined that 80% of patients experienced at least 50% pain relief. All the patients treated with SCS experienced a statistically significant improvement in QoL over an 8 month period ($P \leq 0.05$) (Fig. 4).

Cost Effectiveness of SCS in CRPS

Several studies have demonstrated the cost effectiveness of SCS for CRPS. One study, in which a comparison was made between the use of SCS and other modalities in a group of patients with CRPS (60%) and failed back surgery syndrome (FBSS) (40%), showed a substantial reduction in the overall medical costs of patients treated by SCS.[10] After 3.1 years, the study showed a net saving of $48,464 per patient compared with other forms of therapy.

Similar results were reflected in the recent economic evaluation by Kemler and Furnée,[11] based on data from the randomized, controlled trial in patients with chronic CRPS type I.[7,8] Although SCS + PT incurred high expenditures in the first year (mainly a result of the implantation procedure, which formed 83% of the

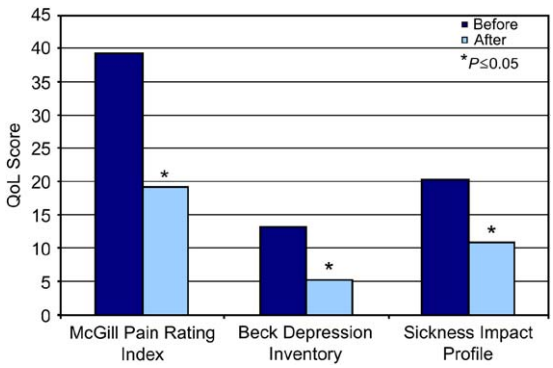

Fig. 4. SCS significantly improves QoL in patients with CRPS.[9]

expenditure), thereafter the mean annual maintenance costs for CRPS I were significantly reduced. Costs in the PT alone group remained the same and over the long term exceeded those for the SCS + PT group after 3 years. The mean lifetime saving was €58,471 per patient in the SCS + PT group.

Only patients in the SCS + PT group were noted to have an improved HRQL, corresponding to a mean cost per quality-adjusted life years (QALY) of €22,500 at 1 year follow-up. This cost per QALY demonstrates that SCS can provide a significant cost effectiveness in the treatment of patients with chronic CRPS type I. The study concluded that SCS + PT significantly reduced pain intensity and improved HRQL, which was less costly after 3 years in comparison with PT alone.

Conclusions

The clinical evidence has established the efficacy and cost effectiveness of SCS in the treatment of CRPS type I and prospective studies demonstrate a statistically significant, long-term reduction in pain and improvement in QoL. Moreover, SCS has proved to be particularly efficacious in supporting the restoration of function in affected extremities, particularly when applied early in the course of the syndrome. To enable patients to benefit from this cost-effective therapy, as required by the treatment algorithm, those who do not respond to an acceptable level of conventional treatment within 12–16 weeks should have the benefit of a trial of SCS.

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Appendix

Three videos showing the story of a CRPS patient implanted with a neurostimulator are available in the online version of this article in this issue at http://journals.elsevierhealth.com/periodicals/jps.