

NEUROSTIMULATION

For Complex Regional Pain Syndrome

Literature Review*

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Neurostimulation Therapy, commonly called Spinal Cord Stimulation (SCS) is indicated for the management of chronic, intractable pain of the trunk and/or limbs. Please see the brief summary on Page 8. The intent of this summary is to present data from published scientific literature relating to clinical and cost-effectiveness of SCS for complex regional pain syndrome (CRPS).

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Overview

Forty years ago, Shealy and coworkers reported that electrical stimulation of the dorsal columns of the spinal cord can be used in a clinical setting to inhibit pain.¹ Spinal cord stimulation (SCS) has since become a widely used neurostimulation therapy for chronic, intractable, non-malignant pain.^{2,3,4} SCS works particularly well when a specific area of the body is affected by pain, and the cause of the pain is neuropathic, rather than mechanical.^{3,5}

SCS is supported by the gate control theory of Melzack and Wall and the results of recent studies, suggesting that stimulation of an afferent nerve where it enters the dorsal column of the spinal cord can inhibit pain transmission and suppress sympathetic activity through the release of local neurotransmitters.^{6,7} Moreover, SCS elicits paresthesia in the area innervated by the afferent nerve, which also has a suppressive effect on pain.⁷

In SCS, an implantable electrical pulse generator is connected to leads with electrodes that are positioned in the epidural space on the dorsal aspect of the spinal cord at the levels of the nerve roots for the painful area. If a trial period of SCS gives a positive response, the SCS system is implanted.

In recent years, SCS has become increasingly successful in the long term due to refined patient selection criteria, greater accuracy in electrode placement, and improvements in multipolar and multichannel systems.⁴ However, hardware-related complications, such as electrode displacement or fracture, and biological complications, such as infection, still occur.^{4,8} Economic studies of SCS have shown that it is more cost-effective than conventional medical management.⁴

The second most common use of SCS in the United States is for the symptomatic management of complex regional pain syndrome (CRPS). In this paper, results of studies of SCS for CRPS, published in the peer review scientific literature, are summarized and reviewed to determine the effectiveness and cost of this use of SCS.

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Effectiveness of SCS for CRPS

CRPS is a neuropathic pain syndrome, the pathogenesis of which appears to involve the sympathetic nervous system.^{9,10} CRPS type I, formerly known as “reflex sympathetic dystrophy,” occurs without a definable nerve lesion, and CRPS type II, formerly known as “causalgia,” occurs with a definable nerve lesion.¹¹ The precipitating cause of CRPS is usually limb trauma, most commonly minor.^{4,11} Continuous, severe pain occurs in the limb outside the territory of a single nerve, and is disproportionate to the inciting event.^{4,11,12} Other clinical features include allodynia,* hyperalgesia, skin color changes, edema, stiffness of involved joints, and eventually bone demineralization.^{4,11} The upper limb is affected twice as often as the lower limb.¹¹

Table 1 summarizes five studies of the effectiveness of SCS for CRPS, reported from 1999 to 2006. All of these studies applied the visual analog scale (VAS) to determine pain intensity, where a mark is placed at the appropriate distance along a 10 cm line between the endpoints of 0 cm for “no pain” and 10 cm for “worst possible pain.” A “good” or “successful” response to SCS would be pain relief of 50% or more as measured with the VAS just before trial SCS and at follow-up after SCS system implantation. Moreover, three of these studies also determined global perceived effect, categorized as “best ever,” “much improved,” “improved,” “not improved/not worse,” “worse,” “much worse,” “worst ever.” An “improved” response to SCS would be considered a treatment “success.”¹³

* Allodynia is pain resulting from stimulation of the skin by a stimulus that is not normally painful.

Table 1: Studies of the Effectiveness of SCS for CRPS

Author(s)	Description	Results
Kemler MA, et al., 2000, ¹⁴ 2001, ¹⁵ 2004. ¹⁶	<p>Prospective, randomized, controlled study of 54 type I CRPS patients who were randomized by a 2:1 ratio, respectively, to receive SCS plus a standardized physical therapy (PT) program or only the PT program. The CRPS had to have lasted \geq 6 months, been restricted to a hand or foot and involved the entire hand or foot, did not have a sustained response to standard therapy for a 6-month period, and had a mean pain intensity of 5 cm on a 0 – 10 cm VAS. Exclusion criteria included a serious psychiatric disorder, substance abuse, possible secondary gain, Raynaud's disease, current or previous unrelated neurologic abnormalities and another condition affecting the affected or contralateral extremity. Thirty-three patients had CRPS in a hand and 21 had CRPS in a foot.</p> <p>The patients who were randomized for SCS received trial SCS for at least 7 days, and could receive SCS system implantation if they reported \geq 50% pain relief on the VAS during the last 4 days of the trial period or much improvement for the global perceived effect of SCS.</p> <p>Physical therapy consisted of graded exercises designed to improve the strength, mobility and function of the affected hand or foot, administered uniformly for 30 minutes twice weekly for 6 months, with further PT being optional.</p> <p>Effectiveness of implanted SCS plus PT and only PT was evaluated at 1, 3, 6, 12 and 24 months after SCS implantation. Pain intensity, global perceived effect, comparative functions of the affected hand or foot, health-related quality of life, and complications were reported.</p>	<p>Of the 54 patients who were eligible for this study, 36 patients were randomized for SCS plus PT and 18 were randomized for only PT. Of the 36 patients who had trial SCS, 24 (67%) patients had SCS system implantation.</p> <p>At 6-month follow-up,¹⁴ pain intensity in the SCS plus PT group of 24 patients had decreased by a mean of 3.6 cm on the VAS, whereas in the 18 PT-only patients, it had increased by a mean of 0.2 cm ($P < 0.001$). Global perceived effect was much improved in 14 of the 24 (58%) SCS plus PT patients, as compared to 1 of the 18 (6%) PT-only patients ($P < 0.001$). As compared to the PT-only patients, SCS plus PT also resulted in significant improvements in a pain-rating index ($P = 0.02$) and in health-related quality of life both for patients with an affected hand ($P = 0.02$) or foot ($P = 0.008$).</p> <p>During the 12-month follow-up period,¹⁵ quantitative sensory testing was performed on 6 occasions on 24 SCS plus PT patients and 29 non-implanted patients, with one PT-only patient being excluded.¹⁵ SCS had no long-term effect on detection of pain thresholds for pressure, warmth, or cold.</p> <p>At the 2-year follow-up,¹⁶ pain intensity in the SCS plus PT group of 24 patients had decreased by a mean of 3.0 cm on the VAS, whereas in the 11 PT-only patients, it had decreased by a mean of 0 cm ($P < 0.001$). Global perceived effect was much improved in 15 of the 24 (63%) SCS plus PT patients, as compared to 1 of 11 (9%) PT-only patients ($P < 0.001$). As compared to PT-only patients, SCS plus PT also resulted in significant improvements in a pain-rating index ($P = 0.02$), and in health-related quality of life for patients with an affected hand ($P = 0.02$) or foot ($P = 0.008$).</p> <p>Nine of the 24 (38%) patients had 22 complications requiring reoperation during the 2-year period after SCS system implantation.¹⁶ Eight patients had lead repositioning, 7 had revision of the pulse generator pocket, 2 had lead replacement, 3 had system explantation (2 permanently), 1 had system reimplantation and 1 had pulse generator replacement. The frequency of complications decreased markedly after the first year.</p>

Table 1: Studies of the Effectiveness of SCS for CRPS Continued

Author(s)	Description	Results
Harke H, et al., 2005. ¹¹	<p>Prospective study of 29 patients with type I CRPS, in 16 patients in an upper limb, in 10 patients in a lower limb, and in 3 patients in the chest. For all patients, pain medication and physical therapy had been ineffective for ≥ 1 year, and sympathetic block had produced only a temporary, positive response. Exclusion criteria included a current or previous neurological or personality disorder as well as untreatable coagulation disorders.</p> <p>All patients underwent trial SCS for 5 – 7 days.</p> <p>All patients engaged in a standardized PT program of graded exercises, daily for 30 min., at home.</p> <p>Effectiveness of implanted SCS was evaluated every 3 months after SCS implantation. Deep pain intensity was assessed on a 0 – 10 cm VAS, and, allodynia, pain-related disability, drug consumption, functional status of the limbs, and return to work were determined at those times.</p>	<p>All of the 29 (100%) patients who were eligible for this study had SCS system implantation.</p> <p>At 12-month follow-up, deep pain and allodynia on the VAS were reduced, respectively, from a mean of 10 cm to 1.7 cm and from a mean of 10 cm to 0.03 cm ($P < 0.01$). Severe pain-related disability and strong functional limitations in daily living activities of more than 60 – 90% were significantly reduced, as reflected in a $> 50\%$ decrease in disability score ($P < 0.01$).</p> <p>At a mean follow-up period of 35.6 ± 21 months, deep pain was at a median level of 2.0 cm and allodynia had been completely abolished. Seventeen of the 29 (59%) patients did not require analgesic medications, and 16 (55%) patients were on low-dose tricyclic antidepressants to optimize activities of daily living. Twelve of the 16 (75%) patients with impaired hand and finger function had regained almost normal ranges of motion, and grip strength had increased almost 50% of normal ($P < 0.01$). Eight of 10 (80%) patients with an affected leg had resumed walking without crutches. Overall, 70% of the patients had returned to work.</p>
Forouzanfar T, et al., 2004. ¹²	<p>Prospective study of 36 type I CRPS patients who had implanted SCS systems, in 19 patients in the cervical region and in 17 patients in the lumbar region. The CRPS must have been producing impaired function and extension of symptoms outside of the area of trauma, been present ≥ 6 months and been unresponsive to conventional treatment (e.g., sympathetic block, transcutaneous electrical nerve stimulation, analgesic medication). All patients had undergone trial SCS for a period of 7 days, with the criterion for SCS system implantation being $\geq 50\%$ reduction in pain intensity on the VAS during this period.</p> <p>Effectiveness of SCS was evaluated with mailed questionnaires at 6, 12 and 24 months after SCS implantation, with pain intensity being assessed on the VAS, and global perceived effect, and health-related quality of life being assessed at those times.</p>	<p>At all of the follow-up periods of 6, 12 and 24 months, the pain intensity was significantly decreased ($P < 0.001$), although it increased linearly with time ($P = 0.03$). Outcomes for pain intensity between cervical and lumbar SCS were similar.</p> <p>At all follow-up evaluations, at least 50% of the patients with cervical SCS and 40% of the patients with lumbar SCS reported $\geq 50\%$ less pain intensity on the VAS.</p> <p>At all follow-up evaluations, at least 42% of the patients with cervical SCS and 47% of the patients with lumbar SCS reported at least “much improvement” in global perceived effect. Also, health-related quality of life significantly improved ($P < 0.02$) in both groups.</p> <p>Twenty-three of the 36 (64%) patients had complications or adverse effects during or after SCS system implantation. Seven patients had revision of the pulse generator pocket, 6 had lead repositioning, 4 had lead replacement, 4 had system explantation, 2 had pulse generator replacement and 1 had system reimplantation.</p>

Table 1: Studies of the Effectiveness of SCS for CRPS Continued

Author(s)	Description	Results
Bennett DS, et al., 1999. ⁵	<p>Retrospective, multicenter study of 101 CRPS patients who had implanted SCS systems, with 30 patients (Group I) having single-lead quadrapolar systems and 71 patients (Group II) having dual-lead octapolar systems. Patients had been candidates for trial SCS only after failing more conservative therapies including injection therapies, physical therapy including desensitization, and medical management with various classes of medication. Exclusion criteria for SCS had included significant phobias, personality disorders, high levels of dysfunctional disorders, or questions of compliance with the modality.</p> <p>Effectiveness of SCS was evaluated at last follow-up after implantation, with pain relief being assessed with a 0 – 10 cm VAS and patient satisfaction with SCS being determined.</p>	<p>Group I had a mean follow-up of 18.7 ± 4.9 months (range, 11 – 33 months) and Group 2 had a mean follow-up of 23.5 ± 8.7 months (range, 8 – 44 months). The mean improvement of the VAS score of Group II was significantly greater at 6.00 ± 1.59 than the mean improvement of the VAS score of Group I at 3.70 ± 0.79 (P < 0.0001). Overall patient satisfaction scores were 70% in Group I and 91% in Group II (P < 0.05).</p> <p>Four of the 30 (13.3%) Group I patients had spontaneous lead migrations and 5 of the 71 (7%) Group II patients had traumatic lead migrations, with the latter migrations requiring surgical revision. Four of the 30 (13.3%) Group I patients and 2 of the 71 (2.8%) Group II patients had SCS system explantation due to poor or no pain coverage after multiple attempts at reprogramming.</p>
Kemler MA, et al., 1999. ¹³	<p>Retrospective study of 23 consecutive patients with type I CRPS, in 10 patients in an arm and in 13 patients in a leg. All patients had severe pain that had been unresponsive to conventional medical therapies.</p> <p>All patients underwent trial SCS for 1 week, with the criterion for SCS system implantation being 50% pain relief on a 0 – 10 cm VAS during this period.</p> <p>Effectiveness of SCS was evaluated by mail at last follow-up, with pain relief being assessed with the VAS, and global perceived effect being determined.</p>	<p>Of the 23 patients who had trial SCS, 18 (78%) patients had SCS system implantation. At a mean follow-up of 32 months (range, 6 – 79 months), the mean VAS score for 15 of the implanted patients had improved from 7.9 cm to 5.4 cm (P < 0.001). Thirteen of the 15 (87%) patients reported a global perceived effect of much improved or improved, and so SCS was regarded as successful for them.</p> <p>Nine of the 18 (50%) patients had complications requiring reoperation. Four of the patients had SCS system explantation, with 1 of these patients having a new system implanted. Two patients had lead repositioning, 1 patient on 5 occasions and the other patient on 2 occasions.</p>

Table 1 Summary

Of these five studies of SCS for CRPS, one is a prospective, randomized, controlled study,^{14,15,16} two are prospective studies,^{11,12} and two are retrospective studies.^{5,13} In three studies where results of SCS were reported, an SCS system was implanted in 71 of 88 (81%) patients (range, 67% to 100% of the trial SCS patients among these studies).^{11,13,14}

Follow-up of patients implanted with SCS systems was long term in all of these studies with follow-up periods ranging from 19 months to 36 months. At long-term follow-up, these five studies found that an implanted SCS system provided overall significant pain relief.^{5,11,12,13,16}

SCS for CRPS has also been associated with substantial long-term success as measured by global perceived effect.^{12,13,16} One study demonstrated that SCS has led to a reduction in the use of analgesic medications.¹¹ Two studies have shown that SCS led to improvements in function and activities of daily living.^{11,13} One study showed that SCS enabled 70% of patients to return to work.¹¹

The most frequent complication of SCS system implantation and use has been electrode migration.^{5,12,13,16} Various complications have also led to revision of the pulse generator pocket and system explantation.^{12,13,16}

Cost of SCS for CRPS

Table 2 summarizes two economic studies assessing the cost of SCS for FBSS, reported in 2002 and 2006. Although these studies determined costs for SCS using different fee schedules, and reported costs for different years and currencies that do not equate to 2007 U.S. dollars, they illustrate changes in SCS cost over time.

Table 2: Studies of the Cost of SCS for CRPS

Author(s)	Description	Results
Kumar K, et al., 2006. ¹⁷	Calculated healthcare costs in year 2005 Canadian dollars of SCS and its complications in 160 consecutive patients who received SCS system implantation, in Saskatchewan, Canada, from January 1995 to December 2004. The clinical indications for SCS were not given. Trial SCS had been unsuccessful in 25 patients. SCS failed in 25 patients, with 7 systems being explanted. Fifty-one complications occurred in 42 of the 160 patients.	<p>The mean cost of unsuccessful trial stimulation was \$7,859 per patient. The overall mean cost of SCS implantation was \$23,205 per patient, and the mean cost of maintaining an uncomplicated case was \$3,609 per year, including the amortized cost of replacing the implantable pulse generator every 4 years. The mean cost of SCS system explantation was \$1,739 per patient.</p> <p>The mean cost to rectify a complication was \$7,092 (range, \$130 – \$22,406) per patient. Consequently, if a complication occurs in a given year, its cost will add to the maintenance cost, for a total of \$10,701.</p>
Kemler MA, Furnée CA, 2002. ¹⁸	<p>Calculated healthcare costs in year 1998 Euros for 54 CRPS patients in the Netherlands, who were randomized in a 2:1 ratio received SCS plus PT (36 patients) or only PT (18 patients)^{14,15,16} (see above). Costs were not discounted. The factor for conversion of 1998 Euros to 1998 U.S. dollars was 1.04.</p> <p>The first-year cost included the SCS system and its testing and implantation, and actual complication costs. The cost for subsequent years to death was based on a 41-year life expectancy, an annual complication rate of 28%, determined from published data, and an estimated mean battery life of 5.8 years.</p>	<p>The mean first-year cost for the 36 patients who were eligible for SCS plus PT was 9,805€ per patient and for the 18 patients who had only PT was 5,741€ per patient. The mean first-year cost for the 24 patients who had SCS implantation (minus the cost of PT) was 12,721€ per patient.</p> <p>The mean cost from the first year to death for the 36 patients who were eligible for SCS plus PT was 171,153€ per patient and for the 18 patients who had only PT was 229,624€ per patient. The mean first-year cost from the first year to death for the 24 patients who had SCS implantation (minus the cost of PT) was 193,580€ per patient.</p>

Table 2 Summary

The referenced studies showed that the mean first-year cost of SCS, which includes trial SCS and SCS system implantation, became substantially less in the second year. This was also found in three economic studies of SCS specifically for FBSS.^{8,19,20}

One study that used actual cost found that SCS became cost-effective, as compared to conventional management, beyond 2.5 years of its use.⁸ One study that used a cost model found that this time period was less than 2 years,¹⁹ and another study that used a cost model found that this time period was 5.5 years, but could decrease to 2.1 years or less for patients who would respond well to SCS.²⁰

Conclusions

The referenced long-term clinical studies have shown that SCS provides statistically significant pain relief in patients with CRPS.

Economic studies have indicated that as compared to the conventional medical management of patients with CRPS, SCS should become cost-effective after about 2 years of its use.

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- Peripheral causalgia
- Epidural fibrosis
- Arachnoiditis or lumbar adhesive arachnoiditis
- Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or causalgia

Contraindications:

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Warnings: Sources of strong electromagnetic interference (e.g., defibrillation, diathermy, electrocautery, MRI, RF ablation, and therapeutic ultrasound) can interact with the neurostimulation system, resulting in serious patient injury or death. These and other sources of EMI can also result in system damage, operational changes to the neurostimulator or unexpected changes in stimulation. Rupture or piercing of the neurostimulator can result in severe burns. An implanted cardiac device (e.g., pacemaker, defibrillator) may damage a neurostimulator, and the electrical pulses from the neurostimulator may result in an inappropriate response of the cardiac device.

Precautions: The safety and effectiveness of this therapy has not been established for pediatric use (patients under the age of 18), pregnancy, unborn fetus, or delivery. Patients should be detoxified from narcotics prior to lead placement. Clinicians and patients should follow programming guidelines and precautions provided in product manuals. Patients should avoid activities that may put undue stress on the implanted neurostimulation system components. Patients should not scuba dive below 10 meters of water or enter hyperbaric chambers above 2.0 atmosphere absolute (ATA). Electromagnetic interference, postural changes, and other activities may cause shocking or jolting.

Adverse Events: Adverse events may include undesirable change in stimulation described by some patients as uncomfortable, jolting or shocking; hematoma, epidural hemorrhage, paralysis, seroma, CSF leakage, infection, erosion, allergic response, hardware malfunction or migration, pain at implant site, loss of pain relief, chest wall stimulation, and surgical risks.

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