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Spinal Cord Stimulation as Treatment for Complex Regional Pain Syndrome Should Be Considered Earlier Than Last Resort Therapy

Lawrence Poree, MD, MPH, PhD*; Elliot Krames, MD†; Jason Pope, MD‡§; Timothy R. Deer, MD¶; Robert Levy, MD, PhD; Louise Schultz, BS††**

Background: Spinal cord stimulation (SCS), by virtue of its historically described up-front costs and level of invasiveness, has been relegated by several complex regional pain syndrome (CRPS) treatment algorithms to a therapy of last resort. Newer information regarding safety, cost, and efficacy leads us to believe that SCS for the treatment of CRPS should be implemented earlier in a treatment algorithm using a more comprehensive approach.

Methods: We reviewed the literature on pain care algorithmic thinking and applied the safety, appropriateness, fiscal or cost neutrality, and efficacy (S.A.F.E.) principles to establish an appropriate position for SCS in an algorithm of pain care.

Results and Conclusion: Based on literature-contingent considerations of safety, efficacy, cost efficacy, and cost neutrality, we conclude that SCS should not be considered a therapy of last resort for CRPS but rather should be applied earlier (e.g., three months) as soon as more conservative therapies have failed.

Keywords: Cost neutrality, efficacy, fiscal neutrality, pain treatment continuum, S.A.F.E. principles, safety, spinal cord stimulation

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Jason Pope is a paid consultant for St. Jude and Spinal Modulation. Jason Pope is a speaker for Medtronic and Jazz Pharmaceuticals.
Robert Levy is a paid consultant for St. Jude, Medtronic, Spinal Modulation, Nevro, Bioness, and Vertos Medical.
Elliot Krames is a paid consultant for Nevro and Spinal Modulation. Dr. Krames is a Medtronic stockholder.
Timothy R. Deer consults for St. Jude Medical, Spinal Modulation, Bioness Inc., Nevro, Medtronic Neuromodulation, Jazz Pharmaceutical, Flowonix Inc., and Vertos Medical.
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INTRODUCTION

To date, there are no scientifically well-established treatments for complex regional pain syndrome (CRPS) and, further, none are curative (1). Because of ignorance of precise end points for the CRPS, differing studies regarding CRPS probably inadvertently admix different syndromes. Some studies document a greater than 95% spontaneous remission in CRPS I, while others document persistent, disabling symptoms despite aggressive treatment (2). A previous algorithm of care for the treatment of chronic pain syndromes including CRPS based its algorithmic thinking on efficacy, initial costs, and levels of invasiveness (3) (Fig. 1).

Today, the decision as to which treatment should be performed on what patient will be determined by the new realities of evidence-based medicine, the appropriateness of the therapy for a given patient, and the concept of cost neutrality. Based on our review of the most recent literature using the published S.A.F.E. evaluation principles (4,5), this paper is designed to establish a basis for algorithmic medical planning so that spinal cord stimulation (SCS) has priority and is not used as "last resort" therapy for CRPS and failed back surgery syndrome (FBSS) (6). The S.A.F.E. principles, an evaluative set of principles for pain therapies, stand for safety, appropriateness, fiscal or cost neutrality, and efficacy.

CRPS, the Syndrome

CRPS, previously called reflex sympathetic dystrophy (RSD), is a poorly understood constellation of signs, symptoms, and physical findings, thought to be due to inflammation, peripheral sensitization, or central sensitization or a combination of the above (7).

Address correspondence to: Elliot Krames, MD, Pacific Pain Treatment Centers, 2000 Van Ness, Suite 402, San Francisco, CA 94109, USA. Email: krames118@gmail.com

* Department of Anesthesiology, University of California San Francisco, San Francisco, CA, USA;
† Pacific Pain Treatment Centers, San Francisco, CA, USA;
‡ Napa Pain Institute, Napa, CA, USA;
§ Vanderbilt University School of Medicine, Nashville, TN, USA;
¶ The West Virginia University School of Medicine, Charleston, WV, USA;
** Department of Neurosurgery, University of Florida College of Medicine Jacksonville, Jacksonville, FL, USA; Shands Jacksonville Neuroscience Institute, University of Florida College of Medicine Jacksonville, Jacksonville, FL, USA; and
†† Touro Medical School, Vallejo, CA, USA

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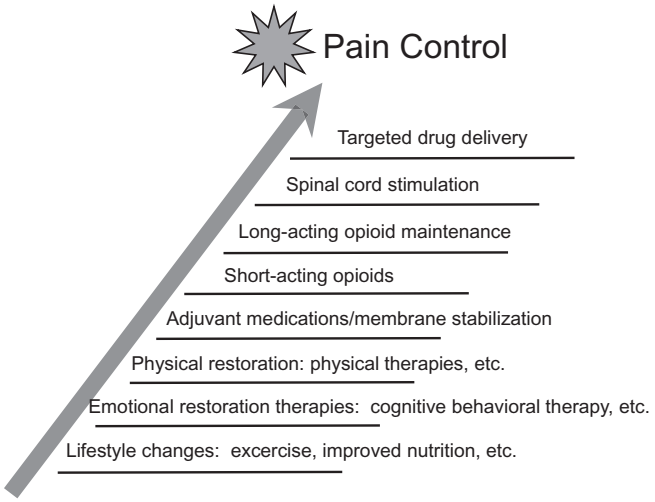

Figure 1. In this algorithm, it was proposed that those therapies proven to be efficacious, less likely to do harm, and are less costly used before therapies proven to be efficacious with greater propensities to do harm and more costly. As each therapy tried failed to provide efficacy for any one patient, that therapy, as the algorithm suggested, would be discarded for a more invasive and more costly therapy (3).

Research is lacking regarding the origin(s) of CRPS and only recently has a consensus been reached as to what constitutes diagnostic criteria for the syndrome. Though fracture is the most common underlying cause of the syndrome, CRPS has the potential to develop from any number of sources that include surgery, sprains, burns, minor peripheral injuries, and/or inflammation, to name a few (8).

The subgrouping of CRPS into two distinct types, CRPS types I and II, has evolved and is primarily recognized by a variety of vasomotor, sensory, sudomotor, and motor/trophic signs and symptoms. CRPS II is similar to CRPS I with one distinct difference; the inciting event in CRPS II is a major nerve lesion (1).

Spontaneous pain, abnormally evoked pains, temperature and color asymmetry, swelling, loss of function, and allodynia are commonly observed in both types of CRPS (9). CRPS also is accompanied by a movement disorder including tremor, muscle weakness, and impairment of voluntary motor control including dystonia. Dystonia occurs in approximately 20% of CRPS patients and is characterized by fixed flexion of the distal extremities including the fingers, wrist, and feet (10,11).

Another consideration regarding CRPS is whether the pain syndrome is maintained by the sympathetic nervous system, e.g., sympathetically maintained pain (SMP), or whether the pain is absent in abnormal sympathetic nervous system involvement, e.g., sympathetically independent pain (12). Recently, Oki et al. demonstrated a deficiency of metallothionein in injured nerves of CRPS type II nerves, further supporting the role of reactive oxygen species in the development of neuropathic pain (13). Common symptoms associated with SMP include burning pain, touch-evoked and cold allodynia, and cold hyperalgesia (14,15).

CRPS, the Diagnostic Criteria

Proper diagnostic criteria have been continuously developed and reexamined since the syndrome was first characterized by Silas Weir Mitchell during the Civil War (16) (Fig. 2).

Figure 2. Silas Weir Mitchell, who became a neurologist, was the first to describe symptoms of nerve injury and the resultant "causalgia" during the American Civil War, which is now called complex regional pain syndrome type II.

In 1994, the International Association for the Study of Pain (IASP) presented the initial criteria for the disorder (17), which has subsequently been modified by others (18–20), more recently modified by Harden et al. in 2007 (the Budapest Criteria [21]), validated in 2010 (22), and approved by the IASP in 2012.

The original IASP definition/criteria were the first time that CRPS was defined as a diagnosable disease or syndrome (17). These diagnostic criteria developed from a consensus conference of experts and suitably encompassed RSD and causalgia, with a major nerve lesion distinguishing the latter from the former. There were four criteria established within the IASP's definition of CRPS in 1994, the first being an inciting event for the syndrome, although it was not a requirement for diagnosis. Disproportionate pain to the said inciting event, allodynia or hyperalgesia, and vasomotor or sudomotor signs or symptoms in the affected area constituted the second and third criteria, respectively. Although, at the time, these diagnostic criteria of the IASP were considered to be authoritative, there was little examination as to their validity.

Not until several years after the establishment of these criteria did Reinders et al. (18), Bruehl et al. (19), and Harden et al. (21,22) explore the validity and efficacy of these criteria. Reinders et al. reported that using the IASP criteria would likely result in the overdiagnosis of CRPS, while Bruehl et al. recommended a refinement of the IASP criteria and proposed their own new diagnostic criteria for research purposes. The proposal by Bruehl et al. (19) itemized signs and symptoms in order to create a diagnosis that was more quantitative in nature and proposed four subgroups of signs and symptoms to make the diagnosis of CRPS. These four subgroups included the sensory, the vasomotor, the sudomotor/edema, and the motor/trophic domains. To qualify as a diagnosis of CRPS for research purposes, one symptom in each of the four subgroups and one sign in two or more subgroups and ongoing pain, not consistent with an injury, had to be present, as well, to make the diagnosis.

The 2007 criteria (the Budapest Criteria) established by consensus by Harden et al. (21) examined the validity of the IASP criteria and they concluded that there was a lack of specificity to the criteria. Harden et al.'s study, an extension of the aforementioned Bruehl et al.'s external validity study, cited the importance of motor dysfunction, range of motion deficiencies, and burning pain in CRPS

and noted the exclusion of these crucial signs and symptoms in the IASP criteria. The study also mentioned defining categorical signs and symptoms as a crucial part of establishing validity in the diagnosis of CRPS. These 2007 criteria had effectively maximized the sensitivity and specificity of the diagnosis of CRPS for the clinical setting. Within this proposal, there were key elements that are maintained from the IASP criteria, namely, the general definition of CRPS and its key components, i.e., disproportionate, regionally located, distal pain that is not accounted for by other pathology. The four subgroups of signs and symptoms are the same as the previously mentioned diagnostic subgroups and include the following:

- *Sensory pathology group* relating to hyperesthesia, allodynia, and hyperalgesia to pinprick
- *Vasomotor pathology—temperature and color asymmetry*
- *Sudomotor/edema* relating to any abnormal sweating changes and/or edema
- *Motor/trophic pathologies*, as previously mentioned, involve motor dysfunction, limited range of motion, and/or abnormal changes in hair, nails, or skin.

According to these diagnostic criteria, in order to qualify for the clinical diagnosis of CRPS, the patient must report one symptom in three of the four categories and one sign during a visit in two or more of the subgroups. The significance of the new criteria lies in the methodology. The proposed Budapest Criteria were validated in 2010 and published by Harden et al. (22). This validation study compared current IASP diagnostic criteria for CRPS with the proposed new diagnostic criteria (the "Budapest Criteria") regarding diagnostic accuracy. Structured evaluations of CRPS-related signs and symptoms were conducted in 113 CRPS I and 47 non-CRPS neuropathic pain patients. Discriminating between diagnostic groups based on the presence of signs or symptoms meeting IASP criteria showed high diagnostic sensitivity (1.00) but poor specificity (0.41), replicating prior work. In comparison, the Budapest clinical criteria retained the exceptional sensitivity of the IASP criteria (0.99) but greatly improved upon the specificity (0.68). As designed, the Budapest research criteria resulted in the highest specificity (0.79), again replicating prior work. Analyses indicated that inclusion of four distinct CRPS components in the Budapest Criteria contributed to enhanced specificity. Overall, results corroborated the validity of the Budapest Criteria and suggested that they improved upon existing IASP diagnostic criteria for CRPS.

Diagnostic Testing

Today, there is no one objective diagnostic test that conclusively proves the existence of CRPS, and therefore diagnosis is based on historical and clinical evaluation. However, a combination of a proper patient evaluation and certain testing to eliminate other pathologies does help in formulating a diagnosis of the syndrome. Observation of clinical signs, such as sudomotor/edema changes, is part of the evaluation of the CRPS patient. Simple pinprick or brush-stroke tests are effective in observing touch allodynia and hyperalgesia. Autonomic changes represented in skin abnormalities can be evaluated via tests such as infrared thermometry and quantitative sudomotor axon reflex test (23–25). An electromyography/nerve conduction study effectively determines if the patient has a nerve lesion and, therefore, distinguishes CRPS I and II (26).

During the early stages of the syndrome, bone scintigraphy can provide insight into vascular bone changes (27). There have been studies reporting varying results in sensitivity and specificity of triple-phase bone scanning and its usefulness in supporting the diagnosis of CRPS. Several studies in the last 20 years have reported sensitivity and specificity of more than 80% (28–30) and some studies suggest that bone scintigraphy can be used as a possible predictor of the potential onset and development of CRPS (31,32). A most recent meta-analysis of the use of scintigraphy for CRPS concluded that "the findings of this meta-analysis support the use of triple-phase bone scan in ruling out CRPS type I, owing to its greater sensitivity and higher negative predictive value than both magnetic resonance imaging and plain film radiography" (33). Despite the results of this meta-analysis, the IASP diagnostic criteria do not include triple-phase bone scan.

Incidence and Prevalence

Exploration of the incidence and prevalence of CRPS reveals limited population-based studies. Of note, the recent Netherlands study by de Mos et al. (9) and the Olmsted County study by Sandroni et al. (34) both reported higher incidence in women, three and four times that of men, respectively. A lack of a "gold standard" for diagnostic criteria limited each study in a similar and unavoidable manner. De Mos et al. used three different diagnostic criteria in her study, which included the criteria of the IASP (17), the criteria of Bruehl et al. (19), and the criteria of Veldman et al. (35), in contrast with Sandroni et al.'s use of the IASP and the stricter Harden et al.'s criteria (20).

The most common inciting event for CRPS in these population-based studies was distal peripheral extremity injury, and of those with CRPS I, 29% after sprain, 24% after surgery, 23% from idiopathic causes, 16% after fractures, and 8% after contusion/crush injuries (36). Upper extremity pathology was observed more than lower extremity pathology, with no favorability for left or right sides (2,34). In examination of the afflicted population in each prevalence studies, CRPS II accounted for less than 10% of the total CRPS population in each study. Average age onset differed for each study. The average age of onset for the studies was 46.9 $\pm$ 16 years for the Olmsted County study (34) and 52.7 $\pm$ 17.31 years for the Netherlands study of de Mos et al. (9). The overall incidence of the disease in the Netherlands study was 26.2 per 100,000 person years and in the Olmsted County study, 5.46 per 100,000 person years (9,34).

Etiology

The exact etiology of CRPS is unknown, although some studies have begun to explore a variety of factors. As stated previously, the present thinking is that the syndrome(s) is (are) related to causative factors, leading to either peripheral or central sensitization. In their review, Janig and Baron state emphatically that CRPS is a disease of the central nervous system (37).

Oki et al. demonstrated a deficiency of metallothionein in injured nerves of CRPS type II nerves, supporting the role of reactive oxygen species in the development of neuropathic pain (13). There is evidence of potential genetic predisposition and genetic links affecting incidence in HLA A3, B7, and DR2 tissue types (38). Oaklander et al. have presented evidence that CRPS is a small-fiber neuropathy and take the position that CRPS is a neuropathic pain process (39). Albrecht et al. studied the enervation of CRPS affected skin and skin not affected by CRPS. In the CRPS affected areas, they found changes of innervation as well as changes to blood vessels. These authors too concluded that CRPS is a neuropathic pain syndrome (40). In an editorial published in *Pain*, *Journal of the International Association for the Study of Pain*, Janig and Baron cautioned readers

on concluding that CRPS is a neuropathic pain process (41). They list a host of factors that lead to this caution.

TREATMENT OPTIONS FOR CRPS

There are a myriad of treatment options touted in the literature regarding CRPS that include noninvasive medical management such as mirror-image feedback (42) and physical and occupational therapies to interventions that include sympathectomies. To date, there is no curative treatment, and CRPS responds poorly to these aforementioned conventional strategies (43). SCS, on the other hand, has been reported to reduce pain and improve function (44). In 2002, a consensus group suggested an updated algorithm of care for patients with CRPS (45) (Fig. 3).

There are a variety of medications that have been used to treat the symptoms of CRPS with some success. These range from nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opioid analgesics and medications used to decrease nerve excitability such as anticonvulsants, tricyclic antidepressants, membrane-stabilizing medications, the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine (46–48), biophosphonates (49,50), and thalidomide (51,52). Salmon calcitonin for CRPS has been well studied (53); however, one randomized controlled trial (RCT) found no more efficacy of the drug when compared with placebo (54). While some of these medication regimes have been shown to provide some relief, none have been accepted as a standard of care for CRPS.

Procedures and therapies for CRPS, as for other chronic pain syndromes, are either noninvasive (physical/occupational therapies, medication management, cognitive and behavioral therapies, acupuncture/acupressure, herbal remedies, complimentary medical practice, etc.) or invasive (continuous epidural analgesia/blockade, sympathetic blockade, sympatholysis, and neuromodulation therapies such as SCS, peripheral nerve stimulation, intrathecal therapies [ITs], deep brain stimulation, and motor cortex stimulation).

Numerous studies have reported anecdotal clinical benefit with the use of sympatholysis for CRPS. These studies have been typically small and uncontrolled case series. In one study, surgical sympathectomy gave permanent relief to patients with RSD, especially when the reported symptoms were less than 12-month duration (55). A study of a large case series of 73 patients with documented SMP who underwent cervical or lumbar sympathectomy for CRPS I reported that one year after surgery 25% of patients had significant pain relief and that an additional 50% reported some reduction of pain (56). However, transient (less than three months) postprocedural sympathalgia developed in 33% of patients who underwent cervical sympathectomy and 20% who underwent lumbar sympathectomy. At three months postprocedure, 10% of

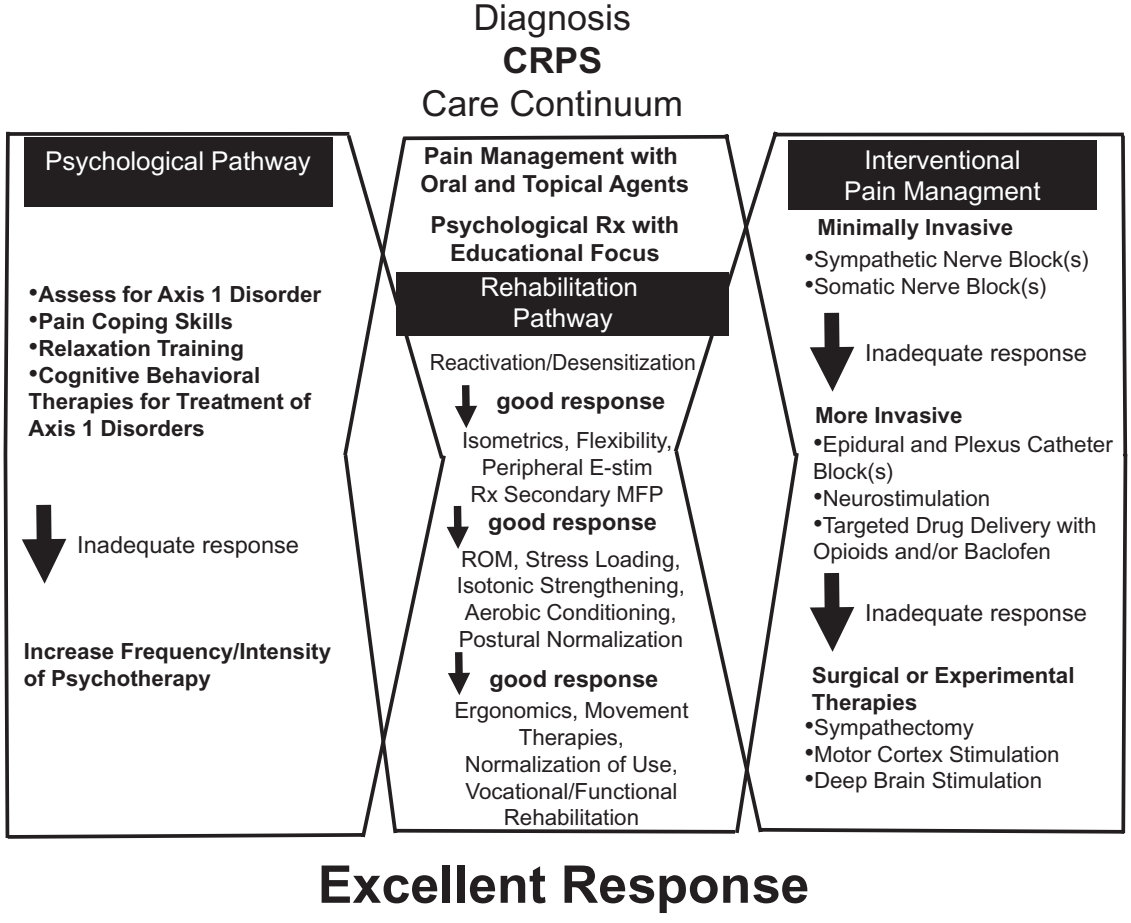

Figure 3. Updated proposed CRPS treatment algorithm of Stanton-Hicks et al. (45). Permission granted from Wiley, Inc. Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, Lubenow TR, Oakley JC, Racz GB, Raj PP, Rauck RL, Rezai AR. An Updated Interdisciplinary Clinical Pathway for CRPS: Report From an Expert Panel. Pain Practice 2002. Vol 2, Number 1, 1–16. (Publisher: Wiley-Blackwell, Inc.) CRPS, complex regional pain syndrome; MFP, myofascial pain; ROM, range of motion.

patients reported no reduction in pain or disability and 7% of patients developed new regional pain or sweating disorders. Tasker, in his review of outcome data of sympathectomy for CRPS I, reported that long-term positive outcomes were poor (57). Also, a meta-analysis of trials and case series that involved 1144 patients showed that the benefit of sympathetic block with local anesthetics was "indistinguishable from that of placebo" (58). One review on the subject concludes that "interrupting the sympathetic nervous system seems futile for obtaining long-term relief of pain in these patients" (59). Studies using regional intravenous (IV) guanethidine to create sympatholysis also show that IV guanethidine is no better than placebo (60).

Intrathecal delivery of medications such as morphine (6), clonidine (61), baclofen (62), and ziconotide (63) also has been used for the treatment of pain of CRPS. Intrathecal delivery allows the use of medications that have prohibitive side-effects if delivered by other routes such as orally and transdermally.

Although there are many therapeutic choices for CRPS, it is important that physicians and other medical care professionals treating patients with the disorder use these therapies in a logical and rational manner (Fig. 3) and in the context of interdisciplinary care. As stated above, with present-day knowledge, this paper will present evidence that SCS, by using the S.A.F.E. evaluation principles (4) (safety, appropriateness, fiscal neutrality, and efficacy), should not be a therapy of last resort for CRPS and should be employed much sooner, probably before initiating long-term opioid maintenance.

Ketamine creams applied to the affected area and ketamine infusions are used for the treatment of CRPS. In 2002, Ushida et al. published on the analgesic effects of ketamine ointment in a group of patients with CRPS (64). Ketamine ointment, between 0.25% and 1.5%, was applied to the affected extremities in five patients with CRPS I and two patients with CRPS II. One to two weeks later, the authors observed improvement of the report of pain intensity and decreased swelling in four patients with acute early dystrophic stage of CRPS I. Finch et al. (65) published a double-blind placebo-controlled crossover trial to determine the effects of topical ketamine, an NMDA receptor antagonist, on the sensory disturbances in 20 patients with CRPS. On two occasions separated by at least one week, sensory tests to light touch, pressure, punctate stimulation, light brushing, and thermal stimuli were performed in the symptomatic and contralateral limb and on each side of the forehead before and 30 min after 10% ketamine cream was applied to the symptomatic or healthy limb. Venous blood for the plasma estimations of ketamine and norketamine was obtained one hour after application of the creams. Ketamine applied to the symptomatic limb inhibited allodynia to light brushing and hyperalgesia to punctate stimulation. Systemic effects of the ketamine are unlikely to account for this as the plasma levels were below detectable limits. As touch thresholds were unchanged, NMDA receptors may contribute to the sensory disturbances in CRPS via actions at cutaneous nociceptors. Allodynia and hyperalgesia were detected in the ipsilateral forehead to a range of stimuli (brushing, pressure, punctate stimulation, cold, heat, and warmth). In several patients, ketamine treatment of the symptomatic limb inhibited allodynia to brushing the ipsilateral forehead, suggesting that the mechanism that mediates allodynia in the symptomatic limb contributed to allodynia at more remote sites. The authors concluded that topical ketamine shows promise for the treatment of CRPS. In 2005, Goldberg et al. published a report on efficacy of multi-low-dose ketamine infusions for CRPS (48). Patients diagnosed with CRPS by a single neurologist were assigned to receive a ten-day outpatient infusion of ketamine. The infusion, monitored by an anesthesiologist, was administered in a short procedure unit after each patient had been instructed on how to complete a pain questionnaire. Monitoring consisted of continuous electrocardiogram, pulse oximetry, and noninvasive blood pressure every 15 min. The authors found a significant reduction in pain intensities from the start of infusions to the tenth day with "nadirs" of pain, the lowest on day 10. The authors concluded that a four-hour ketamine infusion escalated from 4 to 80 mg over a ten-day period can result in significant reduction in pain and increase in function. Schwartzman et al. published an RCT comparing IV ketamine with IV placebo in a group of patients with CRPS I (66). Study subjects were evaluated for at least two weeks prior to treatment and for three months following treatment. All subjects were infused intravenously with normal saline with or without ketamine for four hours (25 mL/hour) daily for ten days. The maximum ketamine infusion rate was 0.35 mg/kg/hour, not to exceed 25 mg/hour over a four-hour period. Subjects in both the ketamine and placebo groups were administered clonidine and midazolam. This study showed that IV ketamine administered in an outpatient setting resulted in statistically significant ($p < 0.05$) reductions in many pain parameters. It also showed that subjects in their placebo group demonstrated no treatment effect in any parameter. In 2012, Azari et al. published a systematic review of the efficacy and safety of ketamine in CRPS (67). The authors searched PubMed and the Cochrane Controlled Trials Register searched using the MeSH terms "ketamine," "complex regional pain syndrome," "analgesia," and "pain" in the English literature. The manuscript bibliographies were then reviewed to identify additional relevant papers. Observational trials were evaluated using the Agency for Healthcare Research and Quality criteria; randomized trials were evaluated using the methodological assessment of randomized clinical trials. The search methodology yielded three randomized, placebo-controlled trials, seven observational studies, and nine case studies/reports. The authors concluded that the data available reveal ketamine as a promising treatment for CRPS and that the optimum dose, route, and timing of administration remained to be determined.

SCS FOR CRPS

SCS is a reversible pain therapy for neuropathic pain syndromes applied with sophisticated techniques that include multi-output implanted pulse generators and a choice of electrodes, some of which can be placed percutaneously and some of which can be placed directly by way of a laminotomy. SCS offers patients an advantage in that its routine screening trial emulates the definitive procedure and a patient can tell whether or not the treatment will be successful and, if not, avoid the cost of an unsuccessful implant.

After the development of the Leyden jar in 1745 by Pieter van Musschenbroek (1692–1761) (68), made it possible for physicians to control electric current, the therapeutic use of electrical stimulation spread throughout the western world. Electrical stimulation became a scientifically based and viable medical therapy after the 1965 publication of Melzack and Wall's gate control theory of pain (69). By 1967, advances in implantable cardiac pacemakers enabled investigators to adapt this technology for direct electrical stimulation of the spinal cord with surgically implanted electrodes and externalized pulsed generators. The first spinal cord stimulator, then called dorsal column stimulation, was implanted into a patient with terminal disease by Shealy et al. in 1967 (70).

SCS delivers low voltage electrical stimulation to the spinal cord or intraspinal nerve roots to block or decrease the sensation of pain. There are a number of putative mechanisms for the pain-relieving

effects of SCS (71). The gate control theory of pain, as developed by Melzack and Wall, proposes that stimulation of large sensory nerve fibers activates inhibitory interneurons, thereby competitively inhibiting the transmission of impulses from small nociceptive nerve fibers (62). Stimulation of the dorsal columns has been demonstrated to increase the release of γ-amino butyric acid and decrease the release of the excitatory amino acid glutamate at the dorsal horn of rats with neuropathic pain (72,73). Other theories for the antinociceptive effects of SCS include direct current blockade in neural tissue (74), activation of supraspinal antinociceptive nuclei in the brain (75), and inhibition of supraspinal and segmental sympathetic outflow (76). The technical goal of SCS is to achieve stimulation-induced paresthesias at a comfortable level, which completely overlap the patient's pain topography (77).

USING THE S.A.F.E. PRINCIPLES WHEN EVALUATING THERAPIES FOR THE PAIN OF CRPS

As previously stated, Krames et al. have introduced the SAFE principles as a way to appropriately ordinate therapies for the treatment of chronic pain (4–6). S.A.F.E. is an acronym standing for safety, appropriateness, time to fiscal neutrality, and efficacy. The remainder of this paper's focus will be on the use of S.A.F.E. principles to determine a more up-to-date and appropriate algorithm for pain care of CRPS, relegating SCS to an earlier position on a continuum of care than its present position on that continuum.

The Principle of Safety

Persistent chronic pain is rarely life threatening and thus treatments for chronic pain of CRPS including invasive and noninvasive therapies should be held to a higher standard of safety than treatments for life-threatening illness such as advanced cardiac life support. As with all invasive pain-relieving procedures, surgery and neuromodulation technologies are inherently associated with biological and surgical risks including infection, bleeding, and injury to neural tissues and long-term pain and disabilities. As such, the positioning of invasive procedures including nerve blocking and neuromodulation technologies in an algorithm to treat persistent chronic pain for CRPS has traditionally come after trials of less invasive treatments such as physical therapies and medication management (3).

While medications are certainly less invasive and may be safer for short-term management of patients with acute pain, their long-term use for chronic pain may be associated with greater biological risk than neuromodulation interventions. Chronic use of NSAIDs is an example of a conservative therapy that has increased risk of injury over time. Chronic use of NSAIDs for pain management is associated with a 17–31% incidence of gastric ulcer formation, leading to 16,500 deaths and more than 100,000 hospitalizations every year in the estimated 20 million patients taking chronic NSAIDs in the United States (78–80). In a ten-year period, this would give rise to one million hospitalizations for NSAID-induced gastritis. Similarly, patients treated with chronic opioids are at risk of a variety of adverse events including endocrinopathy (81–83), bowel obstruction (84), cognitive impairment (85–88), and respiratory depression (89).

In fact, over the last decade, there has been an increase in opioid-related deaths due to poor prescription practices, abuse, or both. Paulozzi et al. (90), using data from the U.S. Drug Enforcement Administration, found that unintentional drug poisoning mortality rates increased on average 5.3% per year from 1979 to 1990 and 18.1% per year from 1990 to 2002. Between the years 1999 and 2002, the number of opioid analgesic poisonings on death certificates increased 91.2%. By 2002, the number of opioid analgesic poisoning was listed as more than death by either heroin or cocaine. The authors concluded that "a national epidemic of drug poisoning deaths began in the 1990s. Prescriptions for opioid analgesics also increased in this time frame and may have inadvertently contributed to the increases in drug poisoning deaths."

Non-neuromodulation procedures used to treat CRPS such as sympathetic blockade/neurolysis of the upper and lower extremity, continuous infusion of local anesthetics, and continuous infusion of ketamine also are associated with risks to the patient. Stanton-Hicks published a review of the complications of sympathetic blockade and stated that "complications of sympathetic blockade vary depending on the sympathetic ganglia blocked, the location, the approach, and the agents used. . . (91)." Some of these complications include damage to the recurrent laryngeal nerve and chronic hoarseness, collapse of a lung, infection of a disk (discitis), injection of local anesthetic into a vertebral artery or carotid artery resulting in blindness, in brain stem or cerebellar infarct, or even death, genitofemoral neuritis and chronic pain, etc.

In comparison with these examples of the risk of noninvasive therapies and non-neuromodulation invasive therapies, the greatest biological risks of SCS for chronic pain occur during the operative and postoperative periods with infection being the most common complication. In a ten-year retrospective study of 160 patients treated with SCS, Kumar et al. reported a total of 7.5% biological adverse events with 4.4% incidence of infection and a 3.1% incidence of seroma, and no neural injury or death (92). In an extensive analysis of the literature, Cameron reviewed the safety and efficacy of SCS over a period of 20 years (93). Complications found included biological and device-related complications. The biologic complications found in this study were, for the most part, minor and treatable and included infection (100 events of 2972 cases or an incidence of 3.4%), hematoma (8 of 2972 patients or an incidence of 0.3%), paralysis (1 event in 2972 patients or 0.03%), cerebrospinal fluid (CSF) leak (8 of 2972 patients or 0.3%), allergic reaction (3 events in 2753 patients or 0.1%), and skin erosion (0.03%). In a recent review and analysis of the literature regarding complications and risks associated with the placement of postlaminotomy paddle leads, Levy et al. (94), using the U.S. Food and Drug Administration Manufacturer and User Facility Device Experience, found an incidence rate of major motor deficit (0.25%), limited motor deficit (0.14%), autonomic changes (0.013%), sensory deficit (0.10%), and CSF leak postdural puncture (0.047%) in a retrospective analysis of 44,587 patients. The total incidence of epidural hematoma with limited motor deficit was 0.036%, with major motor deficit to be 0.12% and the incidence without motor deficit to be 0.034%. The authors concluded that this small incidence of complication could be avoided by the adoption of approaches that improve procedural safety (such as appropriate preoperative imaging to rule out spinal stenosis) and by careful patient follow-up and complication management.

The results of these analyses of complications of SCS, in our estimation, support the hypothesis that the risk of injury from the chronic use of certain medications such as NSAIDs and opioids far outweighs the risks caused by long-term treatment with SCS. Certain non-neuromodulation procedures also are associated with risks and these risks might be greater than the biologic risks of SCS. Thus, when comparing the relative safety of various treatments for

the chronic pain of CRPS, it is essential to assess the risks of each comparator therapy over the same duration of time.

The Principle of Appropriateness

When determining a therapy for a patient, it is most important to secure a diagnosis as well as to confirm the absence of any medical or psychosocial contraindications for the procedure. The pertinent question when choosing therapy should be: *is the given therapy for a given individual or group of individuals appropriate?* The answer to this question is important, not only to the patient receiving the therapy but also to society as well because the appropriate allocation of health-care dollars for appropriate therapies for the appropriate individual is basic to a sound and prudent health-care system.

Everyone would agree that patients with peptic ulcer disease or those with renal failure should not be treated with chronic NSAID therapy or that chronic opioid therapies should be avoided if possible in patients with underlying drug addictions. Likewise, systemic infections and coagulopathies are medical contraindications to certain interventions and that premorbid psychiatric illness such as schizophrenia or conversion disorders are psychiatric barriers to performing elective invasive procedures including neuromodulation therapies. Disregarding these contraindications increases the risk of injury to patients, is the major reason for intervention failure, and may result in additional cost to treat added complications.

Patients with significant psychosocial comorbidities such as active psychosis, unresolved psycho-emotional traumas, certain personality disorders, unresolved pain-related litigation, untreated severe mood disorders, and serious untreated drug addictions, to name a few, may all be at increased risk of treatment failure with implanted technology such as SCS (95,96). When Shealy first described the use of SCS for the treatment of persistent cancer pain, he recommended that appropriate patients be emotionally stable and have limited elevations in the Minnesota Multiphasic Personality Inventory depression scale (61). Since his initial report, numerous investigators have addressed the importance of appropriate psychosocial evaluations and the risk of failure of neuromodulation technology when psychosocial comorbidities are not effectively addressed. Long et al. (97) reported that neuromodulation technology in patients that did not have appropriate psychosocial evaluation prior to treatment had a long-term success rate of only 33%. This percentage increased to 70% in patients that were subjected to psychosocial evaluations and screening. This finding was supported by a later more extensive review in 1993 by De La Porte and Van de Kelfe (98). In their review, they found that, in studies where good psychosocial screening was implemented, the initial SCS success rates were 85% and long-term success rates were 60%. Whereas, in studies where there was no psychosocial screening, initial success rates were 50% and long-term success rates were only 35%. In 1998, The European Federation of IASP Chapters published a consensus document on neuromodulation of pain that included psychosocial exclusion criteria for implanted technologies (99). These included major psychiatric disorders; poor compliance and/or insufficient understanding of the therapy; lack of appropriate social support; substance abuse; and drug-seeking behavior. A later international consensus report added active homicidal or suicidal behavior, hypochondriasis, and psychopathologic somatization to the list of psychosocial exclusion criteria for neuromodulation technology (86).

Yet, identifying psychosocial contraindications for neuromodulation interventions is not the only reason for performing a psychosocial evaluation. In a recent prospective study, Heckler et al. revealed that a presurgical behavioral medicine evaluation stratifying patients offered neuromodulation devices for pain control into different risk groups successfully predicted the long-term trend in emotional, functional, and pain status one year after the initial evaluation (100). While subsequent studies have confirmed these findings, standardization of the psychologic screening tools and consensus of what psychosocial factors are contraindications to neuromodulation treatment remain elusive. Interestingly, Williams et al. (101) in a multicenter analysis of factors that might lead to negative or positive outcomes of SCS found that of a total of 228 patients with psycho-emotional illness, 14 patients with mood disorder and 7 patients with anxiety disorder had negative outcomes of SCS and 30 patients with mood disorder and 17 patients with anxiety disorder had positive outcomes of SCS, hardly exciting information.

Disregarding psychosocial factors also may increase the risk of injury to patients and result in failure of therapeutic interventions and unnecessary cost. According to the National Institutes of Health, it is estimated that more than $100 billion is spent on treatment for persistent pain, which exceeds the combined expenditure for heart disease, cancer, and acquired immune deficiency syndrome (102,103). Thus, it is critical for the future viability of neuromodulation therapies that measures be taken to ensure that only appropriate patients be provided with advanced technologies.

Efficacy and Cost Efficacy: The Principle of Fiscal Neutrality (an Index of Cost Effectiveness)

As mentioned above, health-care costs have steadily increased over the last few decades and are expected to continue to rise (104,105). A recent article published in 2006 claims that the estimated health-care cost to Americans is more than $70 billion per year and is responsible for a half million lost workdays and costs more than $150 billion annually in health-care, disability, and related expenses in the United States (106). Health-care expenditures make up only about 10% of the costs of chronic pain in the United States. Pain medications contribute substantially to health-care costs, with more than 312 million prescriptions for analgesics (137 million for opioids) written each year (Merck Pharmaceutical, personal communication, 2002). As the upper limit of annual costs for medication nears $21,500/year per person ($19,823 in 2002, with the annual inflation rate of 3%), the total could be as high as $62.5 billion annually. Moreover, the costs of medications used to treat pain increased by an average of 27% from fiscal year 2000 through fiscal year 2001.

While the high cost of and demand for medical technology are two of many reasons for the increase in health-care costs, many physicians and policy makers question whether medical technology is being used appropriately (107,108). With shrinking resources and increased demand, health administrators struggle to allocate appropriate resources while maintaining fiscal responsibility. As a result, third-party payers and nonpain management physicians are reluctant to authorize or refer patients for neuromodulation technology as part of a treatment algorithm for persistent pain. Shiroiwa et al. (109) measured the willingness to pay (WTP), defined as the amount of money a society, an individual, a business, a country, etc., would be willing to pay for added value, in this case, the amount that a country would be willing to pay for an additional one quality-adjusted life-year gain (QALY) to determine the threshold of the incremental cost effectiveness. Their study used the Internet to compare WTP for the additional year of survival in a perfect status of health in Japan, the Republic of Korea, Taiwan, Australia, the United Kingdom, and the United States. The authors found that, although

the threshold for cost effectiveness of medical interventions was thought to be between $50,000 and $100,000 in the United States and between £20,000 and £30,000 in the United Kingdom, the WTP values were $62,000 and £23,000 for the United States and United Kingdom, respectively.

Thus, appropriate positioning of neuromodulation technology within a treatment algorithm for persistent pain of CRPS must take into account the financial implications of this treatment (cost effectiveness) with fiscal neutrality being one financial goal for implementation. In this context, fiscal neutrality implies that the cost of implementing a new therapy (e.g., SCS) does not result in greater financial expenditure than the current therapy (e.g., conservative medical management [CMM]).

When compared with CMM for the treatment of chronic pain, SCS has been shown, in some studies, to be cost effective overall. Kumar et al. (110), in their cost-effectiveness analysis of the treatment of chronic pain of FBSS with SCS vs. alternative therapies, found that the actual mean cumulative cost for SCS therapy over a five-year period was $29,123 (Canadian) per patient when compared with $38,029 (Canadian) for patients with conventional pain therapy (CPT). The cost of treatment for the SCS group was greater than that for the CPT group in the first 2.5 years; however, the costs of treating patients with SCS became less than those for CPT after that period and remained so during the rest of the follow-up period. In addition, 15% of SCS-treated FBSS patients were able to return to employment because of superior pain control and lower drug intake. The authors concluded that SCS was cost effective in the long term for patients with FBSS, despite the initial high costs of the implantable devices. In 1997, Bell et al. published an economic model of the cost effectiveness of treating FBSS with SCS vs. a mix of other therapies including surgery and medication management (including a 10% probability of re-operation) (111). For a five-year period, the expected per patient cost of SCS was US$50,540 vs. US$76,180 for chronic maintenance. The authors further found that with a SCS success rate of 56%, the break even for costs would occur at 3.5 years for systems with internal power generators that required battery replacement and 2.5 years for those with external power generators when compared with the "mix of therapies" for FBSS. Willis studied the cost and therapeutic benefit to patients with SCS (112). Sixty patients were retrospectively evaluated and 60/68 patients were evaluated at a mean of 5.8 years postimplant. Therapeutic success was defined as follows: 1) at least 50% reduction in pain while performing usual activities; 2) SCS system providing either good or excellent relief; and 3) the patient would repeat the procedure for same results. Cost-benefit success was defined as a >50% reduction in average medical care use. In this study, the author found that 36 of 55 patients (65.7%) evaluated for therapeutic efficacy met criteria for therapeutic success; 83% reported good-to-excellent pain relief and 94% reported improved daily functioning. Regarding cost, 39 of 50 patients (78.7%) evaluated for cost efficacy met criteria for cost-benefit success. Overall, 25 of 48 (52.1%) patients met criteria for combined success, indicating that therapy was successful and use of health-care resources was significantly reduced.

Taylor et al. published several papers on cost efficacy of SCS for CRPS. To review the clinical and cost effectiveness of SCS for the management of patients with CRPS and to identify the potential predictors of SCS outcome, these authors published a systematic review of the literature and metaregression on the topic (113). The authors, using electronic data bases, searched for controlled and uncontrolled studies and economic evaluations relating to the use of SCS in patients with either CRPS type I or II. One RCT, 25 case series, and one cost-effectiveness study were included. In the RCT in type I CRPS patients, SCS therapy leads to a reduction in pain intensity at 24 months of follow-up (mean change in visual analog scale [VAS] score −2.0), whereas pain was unchanged in the control group (mean change in VAS score 0.0) ($p < 0.001$). In the case series studies, 67% (95% confidence interval [CI] 51%, 84%) of type I and type II CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. No statistically significant predictors of pain relief with SCS were observed in multivariate metaregression analysis across studies. An economic analysis based on the RCT showed a lifetime cost saving of approximately €58,470 (US$76,943 in today's dollars) with SCS plus physical therapy (PT) compared with PT alone. The mean cost per quality-adjusted life year at 12-month follow-up was €22,580 (US$29,714 in today's dollars). The authors concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS type I. Taylor, again in a systematic review of SCS for CRPS and FBSS, published in 2005, found that SCS not only reduces pain, improves quality of life, reduces analgesic consumption, and allows some patients to return to work, with minimal significant adverse events, but also may result in significant cost savings over time (114). Kemler and Furnée evaluated the economic aspects of treatment of chronic RSD (CRPS) with SCS, using outcomes and costs of care before and after the start of treatment (115). Fifty-four patients with chronic RSD were randomized to receive either SCS together with PT (SCS + PT; $N = 36$) or PT alone (PT; $N = 18$). Twenty-four SCS + PT patients responded positively to trial stimulation and underwent SCS implantation. During 12 months of follow-up, costs (routine RSD costs, SCS costs, and out-of-pocket costs) and effects (pain relief by VAS and health-related quality of life [HRQL] improvement by EuroQol-5D [EQ-5D]) were assessed in both groups. Analyses were carried out up to one year and up to the expected time of death. The authors found that SCS was both more effective and less costly than the standard treatment protocol. As a result of high initial costs of SCS, in the first year, the treatment per patient is $4000 more than control therapy. However, in the lifetime analysis, SCS per patient is $60,000 cheaper than control therapy. In addition, at 12 months, SCS resulted in pain relief (SCS + PT [−2.7] vs. PT [0.4] [$p < 0.001$]) and improved HRQL (SCS + PT [0.22] vs. PT [0.03] [$p = 0.004$]).

In the realm of chronic pain management, it is not acceptable to only account for up-front costs when comparing therapies. It is the long-term cost that must be accounted for. For example, Bedder et al. first reported that implanting an initially more expensive intrathecal pump for opioid delivery as compared with delivery with an external pump for cancer pain management was cost neutral at three months and resulted in a cost savings thereafter (116). Similarly, when compared with CMM strategies for chronic pain, some authors found that implanted intrathecal opioid delivery was cost neutral at 22–28 months after implant and generated a cost savings thereafter (117–120).

Fiscal neutrality may even be achieved on day 1 of the implant when compared with re-operations as observed by North et al. in their study of SCS vs. conventional repeat spine surgery (re-operation) for treatment of FBSS (121) and Andrell et al.'s study of SCS vs. coronary artery bypass surgery for intractable angina (122). In fact, in the North et al.'s study and the Andrell et al.'s study, implementing SCS was actually a cost savings as compared with repeat spine surgery or cardiovascular surgery. Taylor and Taylor estimated that when compared with CMM, SCS also was more effective and

less costly when treating FBSS over the lifetime of a patient (123). In a literature review, Taylor et al. reported that the time to fiscal neutrality, when using SCS, was one to three years in a variety of pain conditions including CRPS (124).

The time to fiscal neutrality is influenced not only by the initial cost of implanting neuromodulation technology and the cost of comparator therapies including costs of complications but also by the long-term cost of the technology including end of life battery replacement, mechanical and biological complications, lead migration, and lead and catheter fracture. In addition to the biologic risks associated with neuromodulation technologies discussed above, there also are "hardware" complications of implanted devices that include system failure and system breakdown. When occurring, these hardware complications add to the cost of the therapy and must be accounted for when evaluating the fiscal implications of implementing a given therapy and certainly do add to the time of fiscal neutrality. In her literature review of efficacy and safety of SCS, Cameron found a 13.2% incidence of lead migration and a 9.1% incidence of lead breakage following analysis of 2972 patients from 51 papers (95). In an analysis of 289 patients with SCS systems, Rosenow et al. found a 32% failure rate when using percutaneous-type leads placed in the thoracic spine and attached to a pulse generator placed in the gluteal region for the treatment of lower extremity pain (125). Turner et al., in a systematic review of the SCS literature for FBSS and CRPS, found 22 articles out of 583 that addressed complication rates (126). They found that a mean of 10.2% of patients had some type of equipment failure, with 23.1% of patients undergoing revision of the stimulator for reasons other than battery change and 11.0% of patients undergoing removal of the stimulator for any reason. Reducing these complications and thus the long-term cost associated with implementation of neuromodulation technology by improving surgical techniques, improving electrode design, and programmability helps to further reduce the time to fiscal neutrality (127–129).

Simpson et al. published a Health Technology Assessment (HTA) in 2009 analyzing RCTs published on SCS for neuropathic and ischemic origins (130). This paper reviewed prospective RCTs from the US, European, Canadian, and Australian literature, reviewing three prospective RCTs relating to SCS for neuropathic pain (two FBSS and one CRPS) and ischemia. An economic analysis also was performed. The authors reviewed all relevant RCTs up to September of 2007 and limited their reviews to English. Reviewed were studies trialing SCS in adults for neuropathic pain who had an inadequate response to pain from medical, physical, or surgical treatment. Comparison groups included conventional medical management, PT, and re-operation. Excluded from this health technology analysis was neurostimulation for other parts of the body. Outcome measures were based on the three RCTs and included pain, quality of life, physical and functional abilities, medication use, complications, and adverse events. The authors found and reviewed three RCTS for FBSS (North et al. and PROCESS) and one for CRPS I (Kemler). The characteristics of the three RCTs precluded a meta-analysis. This HTA concluded that SCS was more effective than re-operation or conventional medical management in reducing the chronic neuropathic pain of FBSS and CRPS I in carefully selected patients. The cost analysis suggests that SCS for FBSS when compared CMM or re-operation is a cost-effective intervention and less than £20,000 per QALY. The cost of effectiveness of SCS for CRPS I was less convincing and in some cases above £30,000 per QALY. Furthermore, the CMM used in the Kemler study was different from that used by the National Health Service and further research was called for to establish clinical effectiveness.

Using rechargeable batteries to reduce costs over time actually may increase the time to fiscal neutrality because of their up-front increased costs, but over time, this advance in technology decreases the costs of SCS systems significantly. Hornberger et al. (131), using a generalized state-transition probability framework to model costs, found that a rechargeable SCS system is projected to require from 2.6 to 4.2 fewer battery generator replacements for battery depletion when compared with a nonrechargeable SCS system. The total lifetime savings of a rechargeable system ranged from $104,000 to $168,833. In all of the one-way sensitivity analyses conducted, a rechargeable system saved money. The authors concluded that a rechargeable SCS system is projected to save up to $100,000 over a patient's lifetime.

SCS for CRPS: The Principle of Efficacy

Since the first SCS device was placed by Shealy, Mortimer, and Reswick in 1967 (70), there has been much written regarding efficacy of SCS in the relevant literature, but there has been, according to present-day rules of evidence (132), very little in regards to accepted proof that SCS in fact works for chronic pain and the chronic pain of CRPS (Table 1). Be that as it may, *a lack of evidence is not evidence that SCS does not work*.

There have been several reviews and systematic reviews of the literature on the subject. Taylor et al. (113), using electronic data bases, searched for controlled and uncontrolled studies and economic evaluations relating to the use of SCS in patients with either CRPS type I or II. One RCT, 25 case series, and one cost-effectiveness study were included. In the RCT in type I CRPS patients, SCS therapy leads to a reduction in pain intensity at 24 months of follow-up (mean change in VAS score −2.0), whereas pain was unchanged in the control group (mean change in VAS score 0.0) ($p < 0.001$). In the case series studies, 67% (95% CI 51%, 84%) of type I and type II CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. No statistically significant predictors of pain relief with SCS were observed in multivariate metaregression analysis across studies. The authors concluded that "SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). . . ." Mailis-Gagnon et al. published a systematic review on SCS for chronic pain in 2004 (133). The authors searched MEDLINE and EMBASE through September 2003; the Cochrane Central Register of Controlled Trials (Issue 3, 2003); and textbooks and reference lists in retrieved articles. They also contacted experts in the field of pain and the main manufacturer of the stimulators and included trials with a control group, either RCTs or nonrandomized controlled clinical trials, which assessed SCS for chronic pain. Two independent reviewers selected the studies, assessed study quality, and extracted the data. One of the assessors of methodological quality was blinded to authors, dates, and journals. The data were analyzed using qualitative methods (best evidence synthesis). The authors found that two RCTs (81 patients in total) met their inclusion criteria. One was judged as being of high quality (score of 3 on Jadad scale [134]) and the other of low quality (score of 1 on Jadad scale). One trial included patients with CRPS type I and the other patients with FBSS. The follow-up periods varied from 6 to 12 months. Both studies reported that SCS was effective; however, meta-analysis was not undertaken because of the small number of patients and the heterogeneity of the study population. The authors of this systematic review concluded that, although there is limited evidence in favor of SCS for FBSS and CRPS type I, more trials are needed to confirm whether SCS is an effective treatment for certain types of

Table 1. Efficacy of spinal cord stimulation (SCS) for complex regional pain syndrome (CRPS)

Author/title Design	Methods	Results	Conclusions
Kumar K, Nath RK, Toth C (140) *SCS is effective in the management of reflex sympathetic dystrophy.* Neurosurgery 1997;40:503–509. Retrospective analysis	• An analysis of our records revealed 12 consecutive patients diagnosed as having reflex sympathetic dystrophy (RSD) before undergoing SCS. • Eight of the 12 patients had undergone previous ablative sympathectomy. • The mean age of the nine men and three women was 38.2 years. • All suffered extremity injuries from a variety of causes. • The level of pain present preoperatively and postoperatively was determined by administering a modified McGill Pain.	• All 12 patients experienced relief of pain after trial stimulation and had their systems permanently implanted. • At an average of 41-month follow-up, all patients were using their stimulators regularly and only two were receiving adjunctive minor pain medication. • Eight patients reported excellent pain relief, and four patients described good results. Five minor complications occurred.	• SCS is an effective treatment for the pain of RSD, including recurrent pain after ablative sympathectomy. • The low morbidity of this procedure and its efficacy in patients with refractory pain related to RSD suggest that SCS is superior to ablative sympathectomy in the management of RSD.
Calvillo O, Racz G, Didie J, Smith K (141) *Neuroaugmentation in the treatment of CRPS of the upper extremity.* Acta Orthop Belg 1998;64:57–61. Retrospective analysis	Chart review	• Thirty-six patients with advanced CRPS Rx with either SCS or peripheral nerve stimulation (PNS) or both. • Thirty-six months later, pain decreased by 53%, which was statistically significant. • Analgesics decreased by 50%.	Neuroaugmentation with either SCS/PNS or both results in significant relief of pain of CRPS of the upper extremity.
Bennett D, Alo K, Oakley J, Feler C (142) *SCS for CRPS I [RSD]: a retrospective multicenter experience from 1995 to 1998 of 101 patients.* Neuromodulation 2002;2:202–210. Retrospective multicenter series	• Visual analog scales (VASs) for pain and patient satisfaction data on $N = 101$ patients. • Patients were divided into two groups: group I had single-lead quadripolar systems, group II had dual-lead octapolar systems.	• Mean pain scores decreased in both groups with a significantly greater decrease in group II ($p < 0.0001$). • 74.6% of group II patients preferred multiple programming arrays with 15.5% requiring frequencies > 250 Hz. • Overall satisfaction scores were 70% in group I and 91% in group II ($p < 0.05$).	• SCS is an effective treatment of pain in CRPS I. • Frequencies > 250 Hz were necessary in some patients to maintain or reestablish pain control. • Bilateral multielectrode leads appear superior with application of multiple arrays, permitting paresthesia steering without need for surgical revision.
Kemler MA, Barendse G, van Kleef M et al. (135) *Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy.* N Engl J Med 2000;343:618–624. Prospective randomized controlled trial (RCT)	• Patients CRPS for at least six months. • Thirty-six patients were assigned to receive treatment with SCS plus physical therapy (PT) and 18 were assigned to receive PT alone. • The spinal cord stimulator was implanted only if a test stimulation was successful. • We assessed the intensity of pain (on a VAS from 0 cm [no pain] to 10 cm [very severe pain]), the global perceived effect (on a scale from 1 [worst ever] to 7 [best ever]), functional status, and the health-related quality of life.	• The test stimulation of the spinal cord was successful in 24 patients; the other 12 patients did not receive implanted stimulators. • In an intention-to-treat analysis, the group assigned to receive SCS plus PT had a mean reduction of 2.4 cm in the intensity of pain at six months, as compared with an increase of 0.2 cm in the group assigned to receive PT alone ($p < 0.001$ for the comparison between the two groups).	In carefully selected patients with chronic RSD, electrical stimulation of the spinal cord can reduce pain and improve health-related quality of life.
Van Buyten JP, VanZundert J, Vueghs P, Vanduffel L (143) *Efficacy of SCS: 10 years of experience in a pain centre in Belgium.* Eur J Pain 2001;5:299–307. • Retrospective chart analysis • Independent third party interview	• Over a ten-year period in a single centre, 254 patients were subjected to a trial period of SCS with an externalized pulse generator. • Two hundred seventeen of the patients showed satisfactory results justifying permanent implantation of a SCS system. • In 1998, an independent physician invited 153 patients (155 pain cases), who still had the system in place and who could be contacted for an interview.	• Sixty-eight percent of the patients rated the result of the treatment as excellent to good after an average follow-up of almost four years. • The resumption of work by 31% of patients who had been working before the onset of pain supports these positive findings.	SCS is effective with a significant return to work.
Harke H, Gretenkort P, Ladleif HU et al. (138) *The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study.* Anesth Analg 2001;92:488–495. Randomized, placebo, controlled trial	• Forty-three patients with peripheral neuropathic pain, exclusively pain reduced by SCS (SCS), were switched into a painful state after SCS inactivation. • This mode was used to assess the pain-relieving effect of carbamazepine (CMZ) and opioids in a double-blinded, placebo-controlled trial. • In phase 1, the patients were randomly allocated to receive either CMZ (600 mg/day) or placebo during an SCS-free period of eight days. • In phase 2, after a CMZ elimination interval of seven days, 38 patients received either sustained-release morphine (90 mg/day) or placebo for eight days. • In cases of intolerable pain, the patients were authorized to reactivate their SCS. • The pain intensity was rated on a numeric analog scale.	• In 38 patients who completed phase 1, significant delay in pain increase was observed in the CMZ group as compared with placebo ($p = 0.038$). • In phase 2, the trend observed with morphine was insignificant ($p = 0.41$). • Two CMZ patients and one morphine patient showed complete pain relief and preferred to continue the medication. • *Thirty-five patients returned to SCS.*	• We conclude that CMZ is effective in peripheral neuropathic pain. • Morphine obviously requires larger individually titrated dosages than those used in this study for results to be adequately interpreted. • Although the authors made no conclusion regarding the efficacy of SCS, 35/38 patients elected to return to SCS.
Oakley JC, Weiner RL (144) *SCS for CRPS: a prospective study of 19 patients at two centers.* Neuromodulation 2002;2:47–50. Prospective case series	• Nineteen patients with CRPS are reported as a subgroup enrolled at two centers participating in a multicenter study of efficacy/outcomes of SCS. • Specific preimplant and postimplant tests to measure outcome were administered.	• Statistically significant improvement in the Sickness Impact Profile physical and psychosocial subscales is documented. • The McGill Pain Rating Index words chosen and sensory subscale also improved significantly as did VAS scores. • The BDI trended toward significant improvement.	Patients with CRPS benefit significantly from the use of SCS, based on average follow-up of 7.9 months.
Kemler MA, De Vet HCW, Barendse GAM et al. (136) *The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial.* Ann Neurol 2003;55:13–18. RCT with two-year follow-up to original 2000 study published in *The New England Journal of Medicine* (*NEJM*)	• Thirty-six patients were treated with SCS and PT (SCS + PT) and 18 patients received solely PT. • Twenty-four SCS + PT patients were implanted; the remaining 12 patients were not. • We assessed pain intensity, global perceived effect, functional status, and health-related quality of life. • Patients were examined before randomization, before implantation, and also at 1, 3, 6, 12, and 24 months thereafter.	• At two years, three patients were excluded from the analysis. • The intention-to-treat analysis showed improvements in the SCS + PT group concerning pain intensity (–2.1 vs. 0.0 cm; $p < 0.001$) and global perceived effect (43% vs. 6% much improved; $p = 0.001$). • There was no clinically important improvement of functional status. • Health-related quality of life improved only in the group receiving SCS.	After careful selection and successful test stimulation, SCS results in a long-term pain reduction and health-related quality of life improvement in chronic RSD.

Table 1. *Continued*

Author/title Design	Methods	Results	Conclusions
Turner JA, Loeser JD, Deyo RA, Sanders SB (126) *Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications.* Pain 2004;108:137–147. Systematic review	• Systematic review of the literature on the effectiveness of SCS in relieving pain and improving functioning for patients with failed back surgery syndrome (FBSS) and CRPS. • Review of SCS complications. • Two authors independently extracted data from each article and then resolved discrepancies by discussion.	• Literature searches yielded 583 articles, of which seven met the inclusion criteria for the review of SCS effectiveness and 15 others met the criteria only for the review of SCS complications. • One randomized trial, which found that PT plus SCS, compared with PT alone, had a statistically significant but clinically modest effect at 6 and 12 months in relieving pain among patients with CRPS. • Six studies of much lower methodological quality suggest mild to moderate improvement in pain with SCS. • Pain relief with SCS appears to decrease over time. • The one randomized trial suggested no benefits of SCS in improving patient functioning. • Although life-threatening complications with SCS are rare, other adverse events are frequent. On average, 34% of patients who received a stimulator had an adverse occurrence.	
Cameron T (93) *Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20 years review.* J Neurosurg (Spine 3) 2004;100:254–267. Literature review	• Identified 68 studies that fulfilled the efficacy inclusion/exclusion criteria, grouped on the basis of pain indication, with an overall population of 3679 patients. • Fifty-one studies fulfilled all safety inclusion/exclusion criteria.		
Farouzanfar T, Kemler MA, Weber WEJ, Kessels AGH, van Kleef M (145). *SCS in CRPS: cervical and lumbar devices are comparably effective.* Br J Anaesth 2004;92:348–353. Prospective series	• Thirty-six patients with a definitive implant were included in this study. • A pain diary was obtained from all patients before treatment and six months and one and two years after implantation. • All patients were asked to complete a seven-point Global Perceived Effect (GPE) scale and the EuroQol-5D (EQ-5D) at each postimplant assessment point.	• Pain intensity was reduced at six months, one year, and two years after implantation ($p < 0.05$). • Repeated measures analysis of variance showed a statistically significant, linear increase in the VAS score ($p = 0.03$). • According to the GPE, at least 42% of the cervical SCS patients and 47% of the lumbar SCS patients reported at least "much improvement." • The health status of the patients, as measured on the EQ-5D, was improved after treatment ($p < 0.05$). This improvement was noted both from the social and from the patients' perspective. • Complications and adverse effects occurred in 64% of the patients and consisted mainly of technical defects.	• SCS reduced the pain intensity and improves health status in the majority of the CRPS I patients in this study. • There were no differences between cervical and lumbar groups with regard to outcome measures.
Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R (133) *SCS for chronic pain.* Cochrane Database Syst Rev. 2004;(3). Systematic review	• Searched MEDLINE and EMBASE to September 2003; the Cochrane Central Register of Controlled Trials (Issue 3, 2003); and textbooks and reference lists in retrieved articles. • We also contacted experts in the field of pain and the main manufacturer of the stimulators. • *Selection Criteria*: We included trials with a control group, either RCTs or nonrandomized controlled clinical trials, which assessed SCS for chronic pain. • *Data Collection and Analysis*: Two independent reviewers selected the studies, assessed study quality, and extracted the data. One of the assessors of methodological quality was blinded to authors, dates, and journals. The data were analyzed using qualitative methods (best evidence synthesis).	• Two RCTs (81 patients in total) met our inclusion criteria. One was judged as being of high quality (score of 3 on Jadad scale) and the other of low quality (score of 1 on Jadad scale). • One trial included patients with CRPS type I (RSD) and the other patients with FBSS. • The follow-up periods varied from 6 to 12 months. • Both studies reported that SCS was effective; however, meta-analysis was not undertaken because of the small number of patients and the heterogeneity of the study population.	Although there is limited evidence in favor of SCS for FBSS and CRPS type I, more trials are needed to confirm whether SCS is an effective treatment for certain types of chronic pain. In addition, there needs to be a debate about trial designs that will provide the best evidence for assessing this type of intervention.
Harke H, Gretenkort P, Ladleif HU, Rahman S (146) *SCS in sympathetically maintained CRPS type I with severe disability. A prospective clinical study.* Eur J Pain 2005;9:363. Prospective series	A prerequisite for eligibility to SCS treatment was the responsiveness of patients to sympathetic nerve block. In 29 patients with chronic sympathetically maintained CRPS I, the efficacy of SCS on deep pain, allodynia, and functional disability was determined. Pain intensity was estimated during SCS-free intervals of 45 min (inactivation test) every three months and compared with that under SCS treatment.	• On SCS treatment, both deep pain and allodynia could be permanently reduced from 10 to 0–2 on a 10-cm VAS ($p < 0.01$). • During the inactivation tests, reoccurrence of pain up to eight VAS (quartiles 6–8) was measured. • Considerable impairments in daily living activities, objectified by the pain disability index, were also restored ($p < 0.01$). • After a follow-up period of 35.6 ± 21 months, 12 of 16 patients with affected upper limb showed significant increase of the fist grip strength from 0 to 0.35 (quartiles 0.1–0.5) kg compared with 0.9 (quartiles 0.7–1.1) kg on the unaffected side ($p < 0.01$). • Eight of ten patients with lower limb disability resumed walking without crutches. • Previous pain medication could be significantly reduced ($p < 0.01$).	As a result of permanent pain relief under long-term SCS combined with physiotherapy, the functional status and the quality of life could be significantly improved in sympathetically maintained CRPS I.

Table 1. *Continued*

Author/title Design	Methods	Results	Conclusions
Taylor R, Van Buyten J, Buchser E et al. (113) *Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors.* Eur J Pain 2006;10:91–101. Systematic review	• The authors, using electronic data bases, searched for controlled and uncontrolled studies and economic evaluations relating to the use of SCS in patients with either CRPS type I or II. • One randomized controlled trial, 25 case series, and one cost-effectiveness study were included.	• In the randomized controlled trial in type I CRPS patients, SCS therapy lead to a reduction in pain intensity at 24 months of follow-up (mean change in VAS score −2.0), whereas pain was unchanged in the control group (mean change in VAS score 0.0) ($p < 0.001$). • In the case series studies, 67% (95% confidence interval 51%, 84%) of type I and type II CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. • No statistically significant predictors of pain relief with SCS were observed in multivariate metaregression analysis across studies. • An economic analysis based on the randomized controlled trial showed a lifetime cost saving of approximately €58,470 (US$60,800) with SCS plus PT compared with PT alone. The mean cost per quality-adjusted life year at 12-month follow-up was €22,580 (US$23,480).	• The authors concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). • Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS type I.
Taylor RS (114) *Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis.* J Pain Symptom Manage 2006;31:S13–S19. Systematic review	A systematic review and meta-analysis was performed to review the efficacy, safety, and cost effectiveness of SCS in CRPS and refractory neuropathic back and leg pain/FBSS.		The results support the use of SCS in patients with refractory neuropathic back and leg pain/FBSS (grade B evidence) and CRPS type I (grade A evidence)/type II (grade D evidence). SCS not only reduces pain, improves quality of life, reduces analgesic consumption, and allows some patients to return to work, with minimal significant adverse events, but also may result in significant cost savings over time.
Kemler et al. (137) *Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial.* J Neurosurg. 2008;108:292–298. RCT with five years follow-up to original 2000 study published in *NEJM*	• Thirty-six patients were treated with SCS and PT (SCS + PT), and 18 patients received solely PT. • Twenty-four SCS + PT patients were implanted; the remaining 12 patients were not • We assessed pain intensity (VAS and McGill Pain Questionnaire; global perceived effect, functional status, and health-related quality of life; Nottingham Health Profile, Sickness Impact Profile-68, the EQ-5D, and the Self-Rating Depression Scale. • Patients were examined before randomization, before implantation, and also at 1, 3, 6, 12, 24, 36, 48, and 60 months thereafter. • Thirty-one patients were followed for five years in the PT + SCS group vs. 13 patients in the PT group.	• Mean pain intensity was 1.7 with SCS and PT vs. 1.0 with PT alone. • SCS did not influence health-related scores. • 18/20 patients with implant indicated that they had positive treatment, 95% said they would have the treatment again. • Complication rate 42% in implanted patients. • Battery life approximately four years.	• Long-term follow-up demonstrates that SCS benefits for CRPS diminish over time, and no linger significant after three years of follow-up, although 95% of patients with implants would undergo the therapy again.
Kumar K, Rizvi S, Bnurs SB (44) *Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction.* Neurosurgery 2011;69:566–580. Retrospective analysis	• Twenty-five patients with complete medical records implanted with SCS for CRPS type I of at least six months, failure of conservative medical management and undergone psychiatric evaluation. • Outcome measures that were recorded include VAS, Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), EQ-5D, Short Form 36 (SF-36), pain localization drawings, and medication usage data at implant (baseline), three months, 12 months, and last follow-up (mean 88 months). • Analyzed impact of age, sex, disease stage, delay of diagnosis to treatment with SCS, and upper vs. lower limb pain on outcomes.	• Twelve males and 13 females, mean age 51.2 years, followed mean 88 months, median 62.96 months. • Ten had upper and 15 lower extremity pain. • At 88 months, ODI declined to 50.25% from 70.18, EQ-5D rose from 0.31 to 0.57, BDI to 19.08 from 27.57, SF-36 increased 24.16 to 39.61, and VAS 5.58 from 8.42 cm. • Magnetic resonance angiogram revealed moderate to strong correlations with increased pain intensity, depression, and reduced functional and health status when SCS treatment was delayed greater than 12 months after diagnosis of CRPS I. • Drug consumption decreased at least 25% after SCS was initiated.	• SCS is a safe, cost effective, reversible, and minimally invasive intervention that provides long-term relief to patients with CRPS and should be employed earlier in treatment algorithm.
Sears NC, Machado AG, Nagel SJ, et al. (139) *Long-term outcomes of spinal cord stimulation with paddle leads in the treatment of complex regional pain syndrome and failed back surgery syndrome.* Neuromodulation 2011;14:312–18. Retrospective analysis	• Medical records reviewed from 1997 to 2008, with surgical paddle stimulator for least six months. • Demographic information acquired, along with National Reporting System and questionnaire.	• Eighteen patients with CRPS identified, with mean number of years of pain prior to surgery 9.6 with VAS scale 9.2. • Six months postsurgical VAS 4.7, percentage reduction 49.6%; 55.6% had >50% pain reduction, 77.8% would undergo the procedure again for the same outcome. • 50.0% reported greater than 50% relief at equal to or greater than four-year follow-up.	• Patients with CRPS have high degree of satisfaction, willingness to undergo the same procedure again for the same outcome at a mean follow-up approximately four years.

chronic pain. In addition, there needs to be a debate about trial designs that will provide the best evidence for assessing this type of intervention.

The RCT for CRPS that these authors were referencing was the article by Kemler et al. published in 2000 (135). The authors performed an RCT involving patients who have had CRPS I for at least six months. Thirty-six patients were assigned to receive treatment with SCS plus PT and 18 were assigned to receive PT alone. SCS was implanted in only those who had a successful trial. They assessed the intensity of pain using a VAS score, the global perceived effect, the functional status, and the HRQL. These authors found that the test stimulation of the spinal cord was successful in 24/36 patients. In an intention-to-treat analysis, the group assigned to receive SCS plus PT had a mean reduction of 2.4 cm in the intensity of pain at six months when compared with an increase of 0.2 cm in the group assigned to receive PT alone ($p < 0.001$). In addition, the proportion of patients with a score of 6 ("much improved") for the global perceived effect was much higher in the SCS group than in the control group (39% vs. 6%, $p = 0.01$). There was no clinically important improvement in functional status. The HRQL improved only in the 24 patients who actually underwent implantation of SCS. Six of the 24 patients had complications that required additional procedures, including removal of the device in one patient. The authors concluded that in carefully selected patients with chronic CRPS I, SCS can reduce pain and improve HRQL. In a two-year follow-up study (136), the authors found that in an intention-to-treat analysis, the SCS + PT group showed improvements concerning pain intensity ($p < 0.001$) and global perceived effect (43% vs. 6% much improved; $p = 0.001$) when compared with the PT group alone. There was no clinically important improvement of functional status. HRQL improved only in the group who actually received SCS. They concluded that after careful selection and successful test stimulation, SCS results in a long-term pain reduction and HRQL improvement in chronic RSD (CRPS I). Although the authors found, at five years, no difference between the PT-alone group and SCS-PT group, 95% of their remaining patients with SCS would not give up their devices (137). Harke et al. in an interesting RCT, not studying the effects of SCS in a population of patients with SCS implants for neuropathic pain, studied the effects of carbamazapine and morphine vs. placebo in the group (138). Of interest to this discussion is that 35/43 patients elected to return to the use of their SCS systems in spite of the fact that carbamazapine reduced their SCS-off neuropathic pain significantly when compared with placebo or morphine. Table 1 showed a literature review on efficacy of SCS for CRPS.

Sears et al. in 2011 retrospectively reviewed satisfaction and efficacy for SCS paddle lead implants, at a mean of four years, for treatment of FBSS. The authors reported on 18 patients with mean follow-up of four years. Despite a slight loss in efficacy, 14/18 patients would undergo the same procedure again for the same outcome, while 10/12 with the implant for four years or greater would undergo the same procedure again (139).

In contrast to Kemler's five-year follow-up, Kumar et al. (44) recently published a retrospective review of 25 patients who had CRPS for at least six months and followed these patients for 88 months. These authors followed changes in VAS, Oswestry Disability Index, Beck Depression Inventory, EQ-5D, and Short Form 36. All measures demonstrated a statistically significant improvement that was maintained when compared with the baseline measurements. Interestingly, their data suggested moderate to strong correlations with increased depression, decreased functional and health status, and worse pain when SCS treatment was delayed in excess of 12 months after the diagnosis. The authors concluded that SCS has long-term efficacy for treatment of CRPS.

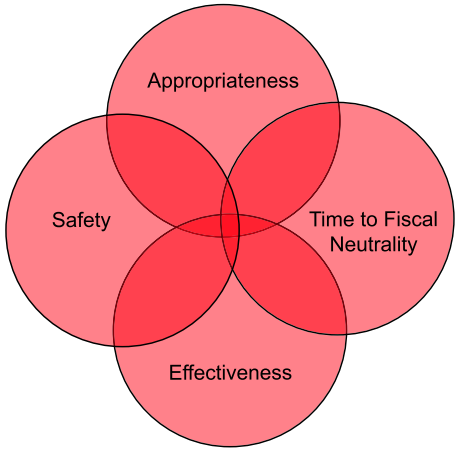

Figure 4. S.A.F.E. analysis analyzes safety, appropriateness, time to fiscal neutrality, and efficacy individually for each therapy and put together as a Venn diagram.

An Algorithm of Care for the Treatment of Pain From CRPS Based on the S.A.F.E. Principles

Because there is extensive evidence that SCS therapy is effective for the treatment of pain from CRPS and, when compared with medication management, is more cost effective, safer, and cost neutral over time, it is clear to us from this SAFE analysis and evidence that SCS should be used before embarking on long-term opioid/medication management for the disease/syndrome and should be used in conjunction with and as a facilitator therapy to therapies that restore physical and emotional well-being (Figs. 3–5). It is also clear from the literature that SCS may not be needed to cure the syndrome and that less invasive therapies such as physical and emotional restorative therapies, as well as well-timed interventions such as sympathetic blockade, may, in fact, cure some of the syndrome.

CONCLUSIONS

Patients with chronic pain secondary to CRPS who respond to SCS therapy can and do achieve significant clinical benefit and cost savings when compared with a control group treated "conservatively" with long-term opioid therapies and CMM. Pain care treatments can be expensive and a treatment algorithm of care based on sound scientific and evidenced-based knowledge is a key to appropriate utilization of health-care resources. Previously, algorithms of care for patients with chronic pain syndromes had been based on up-front costs and levels of invasiveness (1). Krames et al. (4,5) have given us a new set of evaluative tools for therapeutic choice when deciding on an appropriate pain therapy for patients with chronic pain, the S.A.F.E. principles. Based on the evidence presented in this paper, it is clear that SCS for the treatment of chronic pain of CRPS is more safe, appropriate, more cost effective with a relatively low time to fiscal neutrality, and as effective or even more effective when compared with chronic opioid maintenance or CMM in some instances. In his early recommendations, Krames placed SCS as last resort therapy along with ITs (Fig. 1). As seen in Figure 5, SCS/dorsal

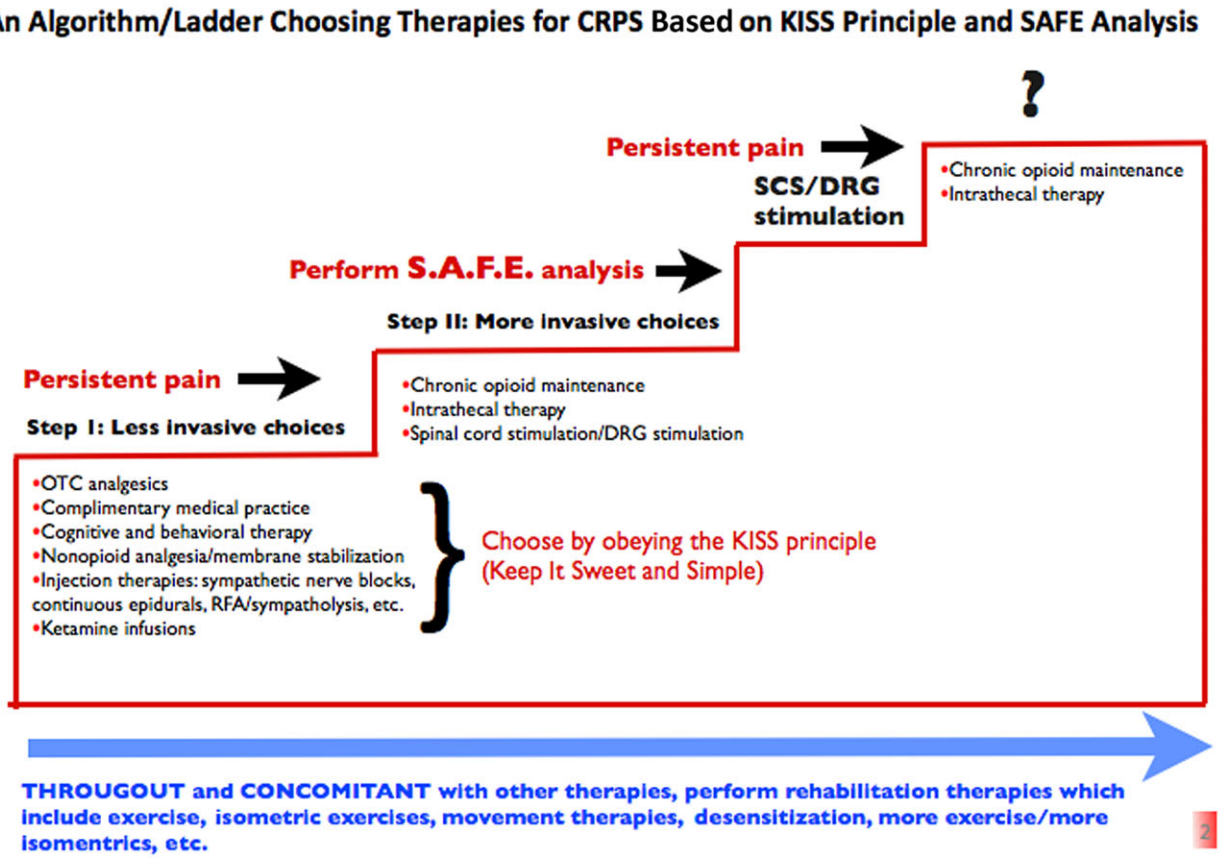

Figure 5. Presented in this figure is a proposed algorithm or ladder approach to choosing multiple therapies for the relief of pain/cure for CRPS utilizing S.A.F.E. analysis for more invasive CRPS treatments. Rehabilitation modalities should be used throughout as therapies from less invasive to more invasive within the ladder are tried and discarded either because of failure to relieve pain or the development of intolerable side-effects. Because not much is written on efficacy, appropriateness, and cost efficacy of less invasive therapies, the logical use of these therapies should obey the KISS principle (keep it sweet and simple). If pain persists after use of these less invasive therapies, the use of more invasive therapies is appropriate and the choice of more invasive therapies should be based on S.A.F.E. analysis. Based on our S.A.F.E. analysis, spinal cord stimulation should be used before chronic opioid maintenance or intrathecal therapies. CRPS, complex regional pain syndrome; DRG, dorsal root ganglion; OTC, over the counter; RFA, radio frequency ablation; S.A.F.E., safety, appropriateness, fiscal or cost neutrality, and efficacy; SCS, spinal cord stimulation.

root ganglion stimulation should now, based on our S.A.F.E. analysis, be placed on a ladder of care before chronic opioid maintenance and certainly before ITs. Because a S.A.F.E. analysis was not performed comparing systemic vs. intrathecal administration of opioids, we have not suggested which therapy should come first. It is also important to remember, as seen in the algorithm, that functional improvement and rehabilitation remains the key to reversing the pain and functional disabilities of CRPS and SCS should be used only as a facilitator to and in conjunction with these therapies in an interdisciplinary care setting.

Lastly, this paper is only an analysis of the literature on CRPS. It would be prudent and most illuminating to actually prospectively corroborate these findings with an RCT randomizing patients with CRPS to either a group of patients receiving CMM (physiotherapies, emotional restoration, and medication management) alone or a group of patients receiving SCS plus CMM.

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REFERENCES

1. Yong CO, Bruehl SP. Complex regional pain syndrome. *Curr Treat Options Neurol* 2003;5:499–511.
2. Inhofe PD, Garcia-Moral CA. Reflex sympathetic dystrophy: a review of the literature and a long-term outcome study. *Orthop Rev* 1994;23:921–924.
3. Krames E. Interventional pain management appropriate when less invasive therapies fail to provide adequate analgesia. *Med Clin North Am* 1999;83:787–808.
4. Krames E, Poree L, Deer T, Levy R. Rethinking algorithms of pain care: the use of the S.A.F.E. principles. *Pain Med* 2009;10:1–5.
5. Krames E, Poree L, Levy R, Deer T. Implementing the S.A.F.E. principles for the development of pain medicine therapeutic algorithms that include neuromodulation techniques. *Neuromodulation* 2009;12:104–113.

6. Krames E, Monis S, Poree L, Levy R, Deer T. Using the SAFE principles for patients with failed back surgery syndrome. *Neuromodulation* 2011;14:299–311.
7. Ribbers GM, Geurts AC, Stam HJ, Mulder T. Pharmacologic treatment of complex regional pain syndrome I: a conceptual framework. *Arch Phys Med Rehabil* 2003;84:141–146.
8. Sieweke N, Birklein F, Riedl B et al. Patterns of hyperalgesia in complex regional pain syndrome. *Pain* 1999;80:171–177.
9. de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker BHCh, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007;129:12–20.
10. Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. *Neurology* 1990;40:57–61.
11. van Hilten JJ, van de Beek WJ, Vein AA, van Dijk JG, Middelkoop HA. Clinical aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. *Neurology* 2001;56:1762–1765.
12. Taken from the internet. http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=4117&nbr=3162.
13. Oki G, Wada T, Kosuke I, Hikono A, Kouichi S et al. Metallothionein deficiency in the injured peripheral nerves of complex regional pain syndrome as revealed by proteomics. *Pain* 2012;153(3):532–539.
14. Pappagallo M, Rosenberg AD. Epidemiology, pathophysiology, and management of complex regional pain syndrome. *Pain Pract* 2001;1:11–20.
15. Bennet DS, Brookoff D. Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia) and spinal cord stimulation. *Pain Med* 2006;7:S64–S96. doi: 10.1111/j.1526-4637.2006.00124.x.
16. Silas Weir Mitchell MD. The physician who discovered causalgia. *J Hand Surg [Am]* 2004;29:181–187.
17. Merskey H, Bogduk N. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. Seattle, WA: IASP Press, 1994.
18. Reinders MF, Geertzen JHB, Dijkstra PU. Complex regional pain syndrome type I: use of the International Association for the Study of Pain diagnostic criteria defined in 1994. *Clin J Pain* 2002;18:207–215.
19. Bruehl S, Harden RN, Galer BS et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. *Pain* 1999;81:147–154.
20. Harden RN, Bruehl S, Galer BS et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 1999;83:211–219.
21. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med* 2007;8:326–331.
22. Harden RN, Bruehl S, Perez Roberto SGM et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. *Pain* 2010;150:268–274.
23. Wasner G, Schattschneider J, Binder A, Baron R. Complex regional pain syndrome—diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord* 2003;41:61–75.
24. Birklein F, Riedl B, Claus D, Neundorfer B. Pattern of autonomic dysfunction in time course of complex regional pain syndrome. *Clin Auton Res* 1998;8:79–85.
25. Sandroni P, Low PA, Ferrer T et al. Complex regional pain syndrome I (CRPS I): prospective study and laboratory evaluation. *Clin J Pain* 1998;14:282–289.
26. Bruehl S, Harden RN, Galer BS et al. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? *Pain* 2002;95:119–124.
27. Kozin F, Soin JS, Ryan LM, Carrera GF, Wortmann RL. Bone scintigraphy in the reflex sympathetic dystrophy syndrome. *Radiology* 1981;138:437–443.
28. Werner R, Davidoff G, Jackson MD, Cremer S, Ventocilla C, Wolf L. Factors affecting the sensitivity and specificity of the three-phase technetium bone scan in the diagnosis of reflex sympathetic dystrophy syndrome in the upper extremity. *J Hand Surg [Am]* 1989;14:520–523.
29. Zyluk A. The usefulness of quantitative evaluation of three-phase scintigraphy in the diagnosis of post-traumatic reflex sympathetic dystrophy. *J Hand Surg Br* 1999;24:16–21.
30. Wuppenhorst N, Maier C, Frettloh J, Pennekamp W, Nicolas V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. *Clin J Pain* 2010;26:182–189.
31. Weiss L, Alfano A, Bardfeld P, Weiss J, Friedmann LW. Prognostic value of triple phase bone scanning for reflex sympathetic dystrophy in hemiplegia. *Arch Phys Med Rehabil* 1993;74:716–719.
32. Demangeat JL, Constantinesco A, Brunot B, Foucher G, Farcot JM. Three-phase bone scanning in reflex sympathetic dystrophy of the hand. *J Nucl Med* 1988;29:26–32.
33. Cappello ZJ, Kasdan ML, Louis DS. Meta-analysis of imaging techniques for the diagnosis of complex regional pain syndrome type I. *J Hand Surg [Am]* 2012;37:288–296.
34. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted County, a population-based study. *Pain* 2003;103:199–207.
35. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993;342:1012–1016.
36. Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. *Pain* 1999;80:539–544.
37. Janig W, Baron R. Complex regional pain syndrome is a disease of the central nervous system. *Clin Auton Res* 2002;12:150–164.
38. Van de Beek WJT, Roep BO, van der Slik AR, Giphart MJ, van Hilten BJ. Susceptibility loci for complex regional pain syndrome. *Pain* 2003;103:93–97.
39. Oaklander AL, Rissmiller JG, Gelman LB et al. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *Pain* 2006;120:235–243.
40. Albrecht PJ, Hines S, Eisenberg E et al. Pathological alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. *Pain* 2006;120:244–266.
41. Janig W, Baron R. Is CRPS a neuropathic pain syndrome? *Pain* 2006;120:227–229.
42. McCabe CS, Haigh RC, Ring EFJ et al. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology (Oxford)* 2003;42:97–101.
43. Complex regional pain syndrome: a review of evidence-supported treatment options. *Curr Pain Headache Rep* 2003;7:188–196.
44. Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. *Neurosurgery* 2011;69:566–580.
45. Stanton-Hicks MD, Burton AW, Bruehl SP et al. An updated interdisciplinary clinical pathway for CRPS: report from an expert panel. *Pain Pract* 2002;2:1–16.
46. Harbut RE, Graeme E, Correll BE. Successful treatment of a nine-year case of complex regional pain syndrome type-I (reflex sympathetic dystrophy) with intravenous ketamine-infusion therapy in a warfarin-anticoagulated adult female patient. *Pain Med* 2002;3:147–155.
47. Kiefer RT, Rohr P, Ploppa A et al. A pilot open-label study of the efficacy of subanesthetic isomeric S(+)-ketamine in refractory CRPS patients. *Pain Med* 2008;9:44–54.
48. Goldberg ME, Domsky R, Scaringe D et al. Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. *Pain Physician* 2005;8:175–179.
49. Yanow J, Pappagallo M, Pillai L. Complex regional pain syndrome (CRPS/RSD) and neuropathic pain: role of intravenous bisphosphonates as analgesics. *Scientific World Journal* 2008;8:229–236.
50. Breure B, Pappagallo M, Ongseng F, Chen CI, Goldfarb R. An open-label pilot trial of ibandronate for complex regional pain syndrome. *Clin J Pain* 2008;24:265–289.
51. Ching DWT, McClintock A, Beswick F. Successful treatment with low-dose thalidomide in a patient with both Behcet's disease and complex regional pain syndrome type I: case report. *J Clin Rheumatol* 2003;9:96–98.
52. Rowbotham MC. Pharmacologic management of complex regional pain syndrome. *Clin J Pain* 2006;22:425–429.
53. Harden RN. Complex regional pain syndrome. *Br J Anaesth* 2001;87:99–106.
54. Sahin F, Yilmaz F, Kotevoglu N, Kuran B. Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin Rheumatol* 2005;25:143–148.
55. Schwartzman RJ, Liu JE, Smulles SN, Hyslop T, Tahmoush AJ. Long term outcome following sympathectomy for complex regional syndrome type 1 (RSD). *J Neurol Sci* 1997;150:149–152.
56. Bandyk DF, Johnson BL, Kirkpatrick AF et al. Surgical sympathectomy for reflex sympathetic dystrophy syndromes. *J Vasc Surg* 2002;35:269–277.
57. Tasker R. Reflex sympathetic dystrophy—neurosurgical approaches. In: Stanton -Hicks M, Janig W, Boas R, eds. *Reflex sympathetic dystrophy*. Boston, MA: Kluwer Academic Publishers, 1990: 124–134.
58. Carr DB, Cepeda MS, Lau J. What is the evidence that for the therapeutic role of local anesthetic sympathetic blockade in RSD or causalgia? An attempted meta-analysis (abstract). In: *Eighth world congress on pain*. Seattle, WA: IASP, 1996: 406.
59. Schott GD. Visceral afferents: their contribution to "sympathetic dependent" pain. *Brain* 1994;117:397–413.
60. Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in sympathetic dystrophy: a systematic review and a randomized double-blind crossover study. *J Pain Symptom Manage* 1995;10:13–20.
61. Ackerman L, Follett K, Rosenquist R. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symptom Manage* 2003;26:668–677.
62. Zuniga RE, Perra S, Abram SE. Interthecal baclofen: a useful agent in the treatment of well established complex regional pain syndrome. *Reg Anesth Pain Med* 2002;27:90–93.
63. Stanton-Hicks M, Kapural L. An effective treatment of severe complex regional pain syndrome type 1 in a child using high doses of intrathecal ziconotide. *J Pain Symptom Manage* 2006;32:509–511.
64. Ushida T, Toshikazu T, Tetsuya K et al. Analgesic effects of ketamine ointment in patients with complex regional pain syndrome type 1. *Reg Anesth Pain Med* 2002;27:524–528.
65. Finch PM, Knudsed L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain* 2009;146:18–25.
66. Schwartzman RJ, Alexander GM, Grothusen JR et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 2009;147:107–115.
67. Azari P, Lindsay DR, Briones D et al. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. *CNS Drugs* 2012;26:215–228.
68. Taken from the internet, October 30, 2008. Wikipedia. http://en.wikipedia.org/wiki/Leyden_jar
69. Melzack K, Wall PD. Pam mechanism®: a new theory. *Science* 1965;150:971–979.
70. Shealy CM, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns. *Anesth Analg* 1967;46:489–491.
71. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation* 2002;2:150–164.
72. Cui JG, Meyerson BA, Sollevi A, Linderoth B. Effects of spinal cord stimulation on tactile hypersensitivity in mononeuropathic rats is potentiated by GABA-B and adenosine receptor activation. *Neurosci Lett* 1998;247:183–186.

73. Meyerson BA, Cui J-G, Yakhnitsa V et al. Modulation of spinal pain mechanisms by spinal cord stimulation and the potential role of adjuvant pharmacotherapy. *Stereotact Funct Neurosurg* 1997;68:129–140.
74. Larson SJ, Sances A Jr, Riegel DH et al. Neurophysiological effects of dorsal column stimulation in man and monkey. *J Neurosurg* 1974;41:217–223.
75. Saade NE, Tabet MS, Soueidan SA, Bitar M, Atweh SF, Jabbur SJ. Supraspinal modulation of nociception in awake rats by stimulation of the dorsal column nuclei. *Brain Res* 1986;369:307–310.
76. Linderoth B, Fedorcsak I, Meyerson BA. Is vasodilatation following dorsal column stimulation mediated by antidromic activation of small diameter fibers? *Acta Neurochir Suppl* 1989;46:99–101.
77. Krames E. Spinal cord stimulation: indications, mechanism of action, and efficacy. *Curr Pain Headache Rep* 1999;3:419–426.
78. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105:31S–38S.
79. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888–1899.
80. Fennerty MB. NSAID-related gastrointestinal injury: evidence-based approach to a preventable complication. *Postgrad Med* 2001;110:87–89.
81. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain* 2008;9:28–36.
82. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain* 2002;3:377–384.
83. Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioid-evidence for opioid-induced inhibition of adrenal androgen production. *J Pain* 2006;7:901–907.
84. Panchal SJ, Muller-Schweffe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 2007;61:1181–1187.
85. Banning A, Sjogren P. Cerebral effects of long-term oral opioids in cancer patients measured by continuous reaction time. *Clin J Pain* 1990;6:91–95.
86. Bowen JD, Larson EB. Drug-induced cognitive impairment. Defining the problem and finding solutions. *Drugs Aging* 1993;3:349–357.
87. Chapman S. The effects of opioids on driving ability in patients with chronic pain. *Am Pain Soc Bull* 2001;11:1–5.
88. Galski T, Williams JB, Ehle HT. Effects of opioids on driving ability. *J Pain Symptom Manage* 2000;19:200–208.
89. McCrimmon DR, Alheid GF. On the opiate trail of respiratory depression. *Am J Physiol Regul Integr Comp Physiol* 2003;285:R1274–R1275.
90. Paulozzi LJ, Budnitz DS, Yongli X. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf* 2006;15:618–627.
91. Stanton-Hicks M. Complications of sympathetic blocks for extremity pain. *Tech Reg Anesth Pain Manag* 2007;11:148–151.
92. Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of SCS, suggestions to improve outcome, and financial impact. *J Neurosurg* 2006;5:191–203.
93. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20 years review. *J Neurosurg (Spine 3)* 2004;100:254–267.
94. Levy R, Henderson J, Slavin K et al. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. *Neuromodulation* 2011;14:412–422.
95. North RB, Kidd DH, Zahurak M, James CS, Long DM. Spinal cord stimulation for chronic intractable pain: experience over two decades. *Neurosurgery* 1993;32:384–395.
96. Beltrutti D, Lamberto A, Barolat G et al. The psychological assessment of candidates for spinal cord stimulation for chronic pain management. *Pain Pract* 2004;4:204–221.
97. Long D, Erickson D, Campbell J, North R. Electrical stimulation of the spinal cord and peripheral nerves for pain control. *Appl Neurophysiol* 1981;44:207–217.
98. De La Porte C, Van de Kelfe E. SCS in failed back surgery syndrome. *Pain* 1993;52:55–61.
99. Gybels J, Erdine S, Maeyaert J et al. Neuromodulation of pain. A consensus statement prepared by a task force of the European Federation of IASP Chapters (EFIC). *Eur J Pain* 1998;2:203–209.
100. Heckler DR, Gatchel RJ, Lou L, Whitwork T, Bernstein D, Stowell AW. Presurgical behavioral medicine evaluation (PBME) for implantable devices for pain management: a 1-year prospective study. *Pain Pract* 2007;7:110–122.
101. Williams KA, Gonzalez-Fernandez M, Hamzehzadeh S et al. A multi-center analysis evaluating factors associated with spinal cord stimulation outcome in chronic pain patients. *Pain Med* 2011;12:1142–1153.
102. Cousins MJ. Foreword. In: Fordyce WE, ed. *Back pain in the workplace: management of disability in nonspecific conditions task force report*. Seattle, WA: International Association for the Study of Pain Press, 1995.
103. Turk DC, Burwinkle TM. Clinical outcomes, cost-effectiveness, and the role of psychology in treatments for chronic pain sufferers. *Prof Psychol Res Pr* 2005;36:602–610.
104. Catlin A, Cowan C, Heffler S et al. National health spending in 2005. *Health Aff (Millwood)* 2006;26:142–153.
105. Borger C, Smith S, Truffer C et al. Health spending projections through 2015: changes on the horizon. *Health Aff (Millwood)* 2006;25:W61–W73.
106. Gatchel RJ, Okifuji A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *J Pain* 2006;7:779–793.
107. Iglehart JK. Opinion polls on health care. *N Engl J Med* 1984;310:1616–1620.
108. Blendon RJ, Altman DE. Public attitudes about health-care costs; a lesson in national schizophrenia. *N Engl J Med* 1984;311:613–616.
109. Shiroiwa T, Sung YK, Fukuda T et al. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ* 2010;19:422–437.
110. Kumar K, Malik S, Denny D. Treatment of chronic pain with SCS versus alternative therapies: cost-effectiveness analysis. *Neurosurgery* 2002;51:106–116.
111. Bell G, Kidd D, North R. Cost-effectiveness analysis of spinal cord stimulation in treatment of failed back surgery syndrome. *J Pain Symptom Manage* 1997;13:286–295.
112. Willis KD. A simple approach to outcomes assessment of the therapeutic and cost-benefit success rates for spinal cord stimulation therapy. *Anesthesiol Clin North America* 2003;21:817–823.
113. Taylor R, Van Buyten J, Buchser E et al. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain* 2006;10:91–101.
114. Taylor R. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. *J Pain Symptom Manage* 2006;31:S13–S19.
115. Kemler MA, Furnée CA. Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy. *Neurology* 2002;59:1203–1209.
116. Bedder MD, Burchiel K, Larson A. Cost analysis of two implantable narcotic deliver systems. *J Pain Symptom Manage* 1991;6:368–373.
117. Mueller-Schweffe G, Hassenbusch SJ, Reig E. Cost effectiveness of intrathecal therapy for pain neuromodulation. *Neuromodulation* 1999;2:77–87.
118. Hassenbusch SJ, Paice JA, Patt RB, Bedder MD, Bell GK. Cost effectiveness of intrathecal therapy. *J Pain Symptom Manage* 1997;14 (Suppl):S36–S48.
119. Lissovoy G, Brown RE, Halpern M, Hassenbusch SJ, Ross E. Cost-effectiveness of long-term intrathecal morphine therapy for pain associated with failed back surgery syndrome. *Clin Ther* 1997;19:96–112.
120. Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. *J Neurosurg* 2002;97:803–810.
121. North RB, Kidd D, Shipley J, Taylor R. SCS versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized controlled trial. Clinical studies. *Neurosurgery* 2007;61:361–369.
122. Andrell P, Ekre O, Eliasson T et al. Cost-effectiveness of SCS versus coronary artery bypass grafting in patients with severe angina pectoris—long-term results from the ESBY study. *Cardiology* 2003;99:20–24.
123. Taylor RJ, Taylor RS. SCS for failed back surgery syndrome: a decision-analytic model and cost-effectiveness analysis. *Int J Technol Assess Health Care* 2005;21:351–358.
124. Taylor RS, Taylor RJ, Van Buyten JP, Buschser E, North R, Bayliss S. The cost effectiveness of SCS in the treatment of pain: a systemic review of the literature. *J Pain Symptom Manage* 2004;27:370–378.
125. Rosenow JM, Stanton-Hicks M, Rezai AR, Henderson JM. Failure modes of spinal cord stimulation hardware. *J Neurosurg Spine* 2006;5:183–190.
126. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain* 2004;108:137–147.
127. Henderson JM, Schade CM, Sasaki J, Caraway DL, Oakley JC. Prevention of mechanical failures in implanted SCS systems. *Neuromodulation* 2006;9:183–191.
128. North RB, Kidd DH, Petrucci L, Dorsi MJ. SCS electrode design: a prospective, randomized, controlled trial comparing percutaneous with laminectomy electrodes: part II—clinical outcomes. *Neurosurgery* 2005;57:990–996.
129. Follett KA, Boortz-Marx R, Drako JM et al. Prevention and management of intrathecal drug delivery and SCS system infections. *Anesthesiology* 2004;100:1582–1594.
130. Simpson E, Duenas A, Holmes M, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1–179.
131. Hornberger J, Kumar K, Verhulst E, Clark MA, Hernandez J. Rechargeable SCS versus nonrechargeable system for patients with failed back surgery syndrome: a cost-consequences analysis. *Clin J Pain* 2008;24:244–252.
132. Greenhalgh T. How to read a paper. Taken from the internet http://books.google.com/books?hl=en&lr=&id=_5a0UyIOx_MC&oi=fnd&pg=PR9&dq=rules+of+evidence+based+medicine&ots=D5oSFrIGUC&sig=g4gINiB-H1hFtSq8U_8zOSfEdgc#PPP1,M1.
133. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. SCS for chronic pain. *Cochrane Database Syst Rev* 2004;(3):CD003783.
134. Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials: current issues and future directions. *Int J Technol Assess Health Care* 1996;12:195–208.
135. Kemler MA, Barendse G, van Kleer M et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343:618–624.
136. Kemler MA, De Vet HCW, Barendse GAM et al. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2003;55:13–18.
137. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M et al. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year follow-up. *N Engl J Med* 2006;354:2394–2396.
138. Harke H, Gretenkort P, Ladleif HU et al. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. *Anesth Analg* 2001;92:488–495.
139. Sears NC, Machado AG, Nagel SJ et al. Long-term outcomes of spinal cord stimulation with paddle leads in the treatment of complex regional pain syndrome and failed back surgery syndrome. *Neuromodulation* 2011;14:312–318.

140. Kumar K, Nath RK, Toth C. SCS is effective in the management of reflex sympathetic dystrophy. *Neurosurgery* 1997;40:503–509.
141. Calvillo O, Racz G, Didie J, Smith K. Neuroaugmentation in the treatment of CRPS of the upper extremity. *Acta Orthop Belg* 1998;64:57–61.
142. Bennett D, Alo K, Oakley J, Feler C. SCS for CRPS I [RSD]: a retrospective multicenter experience from 1995 to 1998 of 101 patients. *Neuromodulation* 2002;2:202–210.
143. Van Buyten JP, VanZundert J, Vueghs P, Vanduffel L. Efficacy of SCS: 10 years of experience in a pain centre in Belgium. *Eur J Pain* 2001;5:299–307.
144. Oakley JC, Weiner RL. SCS for CRPS: a prospective study of 19 patients at two centers. *Neuromodulation* 2002;2:47–50.
145. Farouzanfar T, Kemler MA, Weber WEJ. Kessels AGH, van Kleef M. SCS in CRPS: cervical and lumbar devices are comparably effective. *Br J Anaesth* 2004;92:348–353.
146. Harke H, Gretenkort P, Ladleif HU, Rahman S. SCS in sympathetically maintained CRPS type I with severe disability. A prospective clinical study. *Eur J Pain* 2005; 9:363.

COMMENTS

Treatment of an acute inflammatory process requires an immediate response and if the pathology is known, introduction of appropriate measures. Treatment of chronic pain at least if its source is understood, is directed at the pathophysiology and achieving symptomatic relief that will promote the earliest return of function as possible. Resolution of all types of chronic pain is not always that easy. Shortcomings are a lack of knowledge concerning the pathophysiology, limitations of pharmacotherapy, the impact of chronic disease and pain on the individual, and the progressive loss of function.

Complex regional pain syndrome (CRPS) is one such condition. In recent years, much has been learned about its pathophysiology, and there is agreement that this condition has widespread neuropathic and inflammatory components. The order in which and when treatment for these processes should be introduced requires an algorithmic approach. Certainly the restoration of function which is one characteristic that is rapidly lost during the course of this syndrome requires a physiotherapeutic approach to arrest further loss of function or at best, return function to normal if possible.

The paper by Poree et. al. attempts to put these thought processes into focus by at first addressing the nature of the syndrome as far as it is now understood. It then goes on to look at the various treatments that have been historically applied, as well as the more recent purpose-directed treatments that are evolving due to some chinks of light in the armor of this syndrome are shed. Excessive pain which is the single most prominent symptom of CRPS has resulted in the incremental use of opioids and other pharmacological adjuncts are perceived as a more cost effective management for severe pain.

Although large evidence-based studies are wanting, the authors eloquently assemble a very convincing argument in support of the use of neurostimulation, in particular spinal cord stimulation (SCS) to manage the syndrome. Certainly from analgesic effect alone, SCS is instrumental in modifying pain by at least 50% thereby allowing patients to participate in exercise therapies. While a previous algorithm did suggest that SCS should be used when progress in the physiotherapeutic algorithm ceases or regresses, until recently there has been a paucity of good data to support the earlier introduction of this modality in the treatment of CRPS.

Now there is an increasing body of evidence in favor of early introduction of SCS in the treatment algorithm. These studies have shown that SCS can materially improve the outcome of CRPS treatment, although larger prospective studies will help to validate this premise. In fact, this paper sets the stage for future studies. While not addressed, but implied by this paper, is the prevention of further reorganization in the pain matrix centrally and improvement of microcirculatory aspects and as a consequence, better tissue nutrition. In the current climate of cost containment, limited resources and the contemporary hysteria regarding opioid administration, the authors of this paper make a compelling argument in favor of SCS in CRPS management.

Michael Stanton-Hicks, MD
Cleveland, OH, USA

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Complex regional pain syndrome (CRPS) by its nature is complicated and difficult to treat. Those not well familiar with the syndrome find it difficult to comprehend appropriate timely therapy. In this paper, Krames, et al provide a thorough perspective on CRPS and its treatment including the fiscal considerations of therapy. Despite the fact that the literature on spinal cord stimulation (SCS) for CRPS is not robust, the authors present the data in a logical fashion to make the argument that SCS should not be reserved as a treatment of last resort for CRPS but instead should be moved up to much earlier in the treatment algorithm when appropriate. Those who use SCS as one treatment modality for CRPS have their experience validated by the authors' conclusions.

One caveat must be underscored: the use of SCS as a monotherapy for CRPS is poorly advised. SCS should only be used as one component of a comprehensive interdisciplinary functional rehabilitation program for the treatment of CRPS. The dictum "use it or lose it" provides the rationale for early implementation of SCS in the CRPS treatment algorithm in this context because in order to proceed in physical therapy it is essential to have a method of pain control that in many cases SCS provides best.

Joshua P. Prager, MD, MS
Los Angeles, CA, USA

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

