

FROM THE EDITOR-IN-CHIEF

Evidence-Based Review of Neuromodulation for Complex Regional Pain Syndrome: A Conflict Between Faith and Science?



While it was more than 20 years ago, I remember well the face of a 19-year-old woman who presented to me with what was then called reflex sympathetic dystrophy (RSD). Having sustained an innocuous injury during gymnastics practice four years earlier, Susan developed discoloration, swelling, and severe burning pain in her foot and leg. Aggressive rehabilitation therapy, pharmacotherapy, and even sympathectomy had failed to improve her symptoms. A trial of spinal cord stimulation (SCS) was highly successful and a permanent system was implanted with complete relief of her pain and resolution of her symptoms. Most memorable to me was that she returned seven years later, symptom free, requesting that her stimulator be removed prior to her planned pregnancy. The smile on her face as she held her newborn child was the only testament that I needed to convince myself of the efficacy of SCS for RSD.

Since that time, I have had many successes and more than a few failures of SCS for what is now known as complex regional pain syndrome (CRPS). We have developed new stimulation techniques, including high-frequency and intraspinal nerve root stimulation, to rescue the therapy in patients who were no longer obtaining relief. Nonetheless, I remained a strong believer in the value of SCS for CRPS, both due to my personal anecdotal experience and the support of at least one randomized, controlled clinical trial (1).

CRPS is characterized by continuous, intense pain out of proportion to the severity of an injury, if any has been identified, which tends to get worse over time. Typical features include changes in color and temperature of the affected limb(s) accompanied by intense burning pain, skin sensitivity, sweating, and swelling (2). CRPS type I occurs in the setting of a soft tissue injury, while CRPS type II develops following nerve injury. Of particular note is that neuromodulation therapies are widely considered to be valuable therapies for medically refractory CRPS. In fact, the website of the National Institute of Neurologic Diseases and Stroke states that "Spinal cord stimulation... appears to help many patients with their pain" and that "Intrathecal drug pump... decreases side effects and increases drug effectiveness" (Figs. 1 and 2) (2).

It was with this mindset that I approached a recent satellite conference of the International Association of the Study of Pain (IASP) Meeting in Milan, Italy. Organized by Drs. Joshua Prager, Michael Stanton-Hicks, and Candy McCabe, "A Comprehensive Analysis of CRPS Treatment: The New, The Old, What Works and What Doesn't—Updating the Treatment Algorithm" was an IASP Pain and Sympa-

thetic Nervous System Special Interest Group symposium and CRPS guidelines update meeting (Figs. 3–5).

With the participation of such august clinicians and neuroscientists as Ralf Baron, Frank Huygen, Srinivasa Raja, and J.J. Van Hilten, to name a few, this conference promised to be critically important for the direction of CRPS research and therapy for many years to come. I was honored to have been invited to critically review and present the data supporting neuromodulation therapies for CRPS. In performing a formal, evidence-based review of the literature, I expected that an objective and impartial evaluation would fully support my strongly held personal beliefs of the efficacy of neuromodulation therapies for CRPS. Suffice it to say that my faith was seriously challenged.



Figure 1. Frontal (a) and side (b) views of a patient with unilateral complex regional pain syndrome of the foot. (Courtesy of Frank Huygen, MD.)

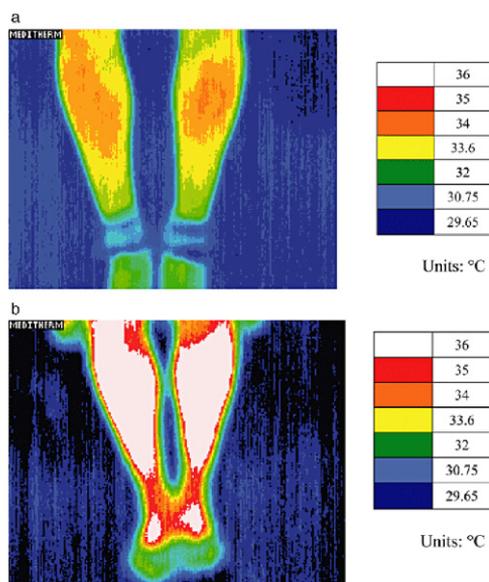


Figure 2. Thermographic image demonstrating the temperature increase immediately after spinal cord stimulation (SCS) in a patient with complex regional pain syndrome (a). Thermography ten days after SCS (b). (Courtesy of Huh et al., 2010)

I approached my daunting task by performing both PubMed and Google-Scholar searches using MeSH terms for each of the major neuromodulation modalities plus RSD or CRPS. I identified notable articles for the following modalities: peripheral nerve stimulation (PNS) ($N = 5$) (3–7), SCS ($N = 34$) (1,8–39), motor cortex stimulation (MCS) ($N = 2$) (40,41), deep brain stimulation (DBS) ($N = 7$) (42–48), and intraspinal drug administration ($N = 21$) (49–69). As dispassionately as possible, I present my analysis of these articles below.



Figure 3. Joshua Prager, MD, Director of the Center for Rehabilitation of Pain Syndromes at the University of California, Los Angeles and Chair, International Association for the Study of Pain Special Interest Group for Pain and the Sympathetic Nervous System.

PERIPHERAL NERVE FIELD STIMULATION (PNFS)

There was no evaluable literature on PNFS for the treatment of CRPS. No evidence-based recommendations can be made.

PERIPHERAL NERVE STIMULATION (PNS)

The literature on PNS for CRPS is dated but valuable. Hassenbusch and coworkers reported a prospective, consecutive series of CRPS patients with symptoms in the distribution of one major peripheral nerve treated with paddle-type PNS leads (6). After a two- to four-day trial, with success defined as 50% or more pain reduction and an objective improvement in physical changes, permanent systems were implanted. Follow-up ranging from two to four years was performed by a disinterested third party. Thirty of the 32 patients had a successful trial (94%), 19 of the 30 (63%) implanted patients had fair or good pain relief at long-term follow-up, and six of the 30 (20%)

returned to work. In successful patients, allodynic and spontaneous pain fell from a visual analog pain score (visual analog scale [VAS]) of 8.3 ± 0.3 to 3.5 ± 0.4 ($p < 0.001$). As might be expected, involvement of more than one peripheral nerve correlated with poor outcome ($p < 0.01$).

Buschmann and Oppel reported on 52 CRPS-type II patients; 47 of these had successful trial stimulation with “marked reduction of pain” and 43 had “lasting, excellent to good success.” At the time of long-term follow-up, pain-related disability fell to 10% (7).

More recent papers on PNS for CRPS have been limited. Monti published a case report of a percutaneous lead implant for CRPS type II (70), while Mirone et al. published a similar case using a paddle-type lead (3). Unfortunately, there are no contemporary studies using contemporary PNS techniques for CRPS. The evidence-based medicine is limited to one prospective consecutive series and one large single center retrospective study, providing only a low level of evidence to suggest PNS for CRPS.

SPINAL COLUMN STIMULATION (SCS)

While I have included an additional eight citations for historical interest alone, there have been 27 papers published since 2000 with particular relevance to SCS for CRPS. This number includes three reports arising from a randomized controlled trial (RCT), 11 meta-analyses and evidence-based medicine reviews, and several prospective and retrospective studies (1,8–39). As demonstrated by this body of literature, it is remarkable to me how objective analysis using evidence-based medicine criteria of the same studies can result in markedly different conclusions.

Grabow and coworkers (2003), for example, considered one RCT, two prospective observational, and 12 retrospective observational studies (69). They highlighted that all but the RCT suffered from significant methodologic weaknesses. They concluded that there was grade B/C evidence for SCS for CRPS (69). The next year, Mailis-Gagnon et al. performed a systematic review highlighting the high quality of the one RCT of SCS for CRPS, giving it a score of three on the Jadad scale. They concluded that “. . .there is limited evidence in favor of SCS for. . .CRPS, Type I, more trials are needed to confirm whether SCS is an effective treatment. . .” (19).

By contrast, Taylor and coworkers performed a systematic review and meta-analysis and concluded that the results support the use of SCS in patients with. . .CRPS type I (grade A evidence)/type II (grade D evidence). They stated that “SCS. . .reduces pain, improves quality



Figure 4. Michael Stanton-Hicks, MD, Pain Consultant, Pain Management and Center for Neurological Restoration, Cleveland Clinic Foundation and Past Chair, International Association for the Study of Pain Special Interest Group for Pain and the Sympathetic Nervous System.



Figure 5. Candy McCabe, RGN, MSc, PhD, Chair, CRPS UK Clinical Research Network and Chair Elect, International Association for the Study of Pain Special Interest Group for Pain and the Sympathetic Nervous System.

of life, reduces analgesic consumption, and allows some patients to return to work, with minimal significant adverse effects, but may also result in significant cost savings over time" (15,16).

Most recently, Perez and coworkers created evidence-based guidelines for CRPS type I. They considered the one RCT and two retrospective cohort studies and concluded that "Spinal cord stimulation administered to CRPS-I patients who are carefully selected and undergo successful trial stimulation causes long term pain reduction and improves quality of life, but does not improve function (level 3)" (31).

The RCT that these evidence-based medicine reviews refer to, of course, is that study reported by Kemler and colleagues in which CRPS patients were randomized to physical therapy alone ($N=18$) or physical therapy plus SCS ($N=36$) and followed for six months (1). Trial stimulation was successful in 24 of the 36 patients. Mean VAS decreased by 2.4 points in the SCS + physical therapy (PT) group, while VAS increased by 0.2 points in the PT alone group ($p < 0.001$). The authors concluded that "carefully selected patients with chronic RSD, spinal cord stimulation can reduce pain and improve quality of life" (1). Two-year follow-up of these patients was reported by Kemler et al. (20). Three patients were excluded from the initial study, but the findings were similar. The SCS + PT group VAS scores decreased by 2.1 points vs. 0.0 in the PT alone group ($p < 0.001$). Analysis of the global perceived effect also favored SCS (43% vs. 6%; $p = 0.001$). Despite the improvements in pain and quality of life, there was no improvement in patients' functional status (1).

Five-year follow-up data on these same patients were presented by Kemler and coworkers in 2006 (21). Without a critical analysis of this paper, one might conclude that there is no longer a benefit of SCS for CRPS at five years, and certainly the paper is plagued by significant methodologic issues (21). Careful analysis reveals, however, that the failure of benefit of SCS + PT vs. PT alone is demonstrated when all patients randomized to the SCS group five years ago are analyzed, including those that had a failed SCS trial and did not undergo permanent implantation. If only patients implanted with SCS devices are considered, there was a mean decrease in VAS of 2.5 points vs. a drop of 1.0 point in the PT alone group ($p = 0.06$). Of interest is that the decrease in VAS in the SCS + PT group is stable over time (2.4 at one year, 2.1 at two years, and 2.5 at five years). Global perceived effect significantly favored SCS ($p = 0.02$). Interestingly, the mean VAS in the SCS + PT group dropped from approximately 6.7 to 4.2, a decrease of about one-third (20). In light of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for chronic pain clinical trial design (71), which establish a decrease in pain of 30% rather than 50%, as being clinically relevant, the impact of SCS on CRPS in the Kemler study should be considered clinically significant. "Much" pain relief was experienced by 35% of SCS + PT patients and only 15% of PT only patients ($p = 0.02$). Ninety percent of SCS patients felt that they had benefited from the therapy and 95% of the SCS patients would undergo the same procedure for the same effect (20).

Harke et al. performed an RCT of carbamazepine, sustained-release morphine, and placebo in patients treated with SCS for CRPS-I (22). While the SCS effect itself was not the subject of the RCT, the authors noted that carbamazepine alone was effective in delaying the increase in CRPS-related pain after SCS was turned off, but that 35 of the 38 patients in the study elected to reactivate their SCS for pain control (22).

Three potentially valuable studies of SCS for CRPS have been published after the aforementioned evidence-based medicine reviews, meta-analyses, and guidelines were published. In an exhaustively documented but retrospective analysis, Kumar et al.

reported 25 patients with complete medical records, CRPS type I of at least six months, failure of conventional medical management, and having completed psychological evaluation treated with SCS. Multiple measures were assessed at baseline, three months, 12 months, and at last follow-up (mean = 88 months; median = 63 months). At this long-term follow-up, ODI scores fell from a baseline of 70.2–50.3%, EQ-5D scores rose from 0.31 to 0.57, BDI scores fell from 27.6 to 19.1, SF-36 scores increased from 24.1 to 39.6, VAS decreased from 8.4 to 5.6, and drug consumption decreased by at least 25%. These findings thus support the long-term effectiveness of SCS for CRPS type I (10).

Also in a retrospective study, Sears and coworkers reported 18 patients treated with surgical paddle-type SCS leads for CRPS; outcome data were collected at six months and again at last follow-up. At six months, VAS had fallen from 9.2 to 4.7, 56% of patients had greater than 50% pain reduction, and 78% would undergo the procedure again for the same effect. At more than four-year follow-up, 50% reported greater than 50% pain relief (23).

Finally, van Eijs et al. published in this journal a study of 74 patients with CRPS-I with a mean disease duration of 17 weeks treated with comprehensive standard therapy. They selected six refractory patients for early SCS treatment. Overall mean pain relief at one year was 35%; while the mental component of the SF-36 improved, there was no effect on its physical component and no clear improvement in functional outcome. The authors conclude that "...the feasibility of performing a RCT on early SCS therapy in CRPS-I is low because of the good disease improvement with standard therapy in the first year after onset." They further conclude that "This study raises questions about the need to use SCS early in the course of CRPS-I because of the probable lack of additional benefit compared with SCS in chronic CRPS-I" (35).

Using SCS for CRPS, we have greater evidence-based medicine support. There is one RCT and many prospective observational and retrospective observational studies supporting the use of SCS for pain control in CRPS. I believe that this level reaches grade A for CRPS type 1 but is low grade at best for CRPS type 2.

DEEP BRAIN STIMULATION (DBS)

While there is an extensive literature on DBS for chronic pain, much of it dates back to the 1980s and 1990s and none of that older literature is more than a retrospective analysis. After nearly 1000 DBS implants worldwide, the Food and Drug Administration disapproved DBS for pain in the United States in 1986. Even after DBS was approved for the treatment of movement disorders and marketed in the United States in 1997, DBS for pain control remained an "off label" and often nonreimbursed therapy. As such, research in DBS for pain control dropped precipitously and most has been performed outside the United States.

Leading the charge has been Tipu Aziz and his group at Oxford. Bittar et al. published a meta-analysis of the DBS literature. The authors identified five sufficiently well-reported cases of causalgia treated with DBS. Five of the five patients had a successful stimulation screening trial and four of the five (80%) reported long-term success (42).

No RCTs of DBS for CRPS exist. Multiple, large, retrospective series appeared in the literature in the last century, but there were very specifically identified, well-described CRPS patients. While there is a suggestion of efficacy in the contemporary literature, there are insufficient data upon which to base any recommendation (Fig. 6).

MOTOR CORTEX STIMULATION (MCS)

MCS has been extensively evaluated over the past 20 years, most notably as a treatment for central poststroke pain and trigeminal neuropathic pain. Velasco and coworkers performed a prospective trial of MCS for CRPS with an embedded randomized double-blind period of “off” stimulation (40). Patients underwent monthly follow-up for one year and then extended follow-up ranging from three to six years. VAS, McGill Pain Questionnaire (MPQ), and measures of sympathetic function (temperature, perspiration, color, and swelling) were measured at each visit. Four of the five patients had a successful stimulation trial and underwent permanent implantation; two patients each had CRPS-1 and CRPS-2. At last follow-up, the authors noted a mean VAS decrease of 75% with associated decreases in hyperalgesia, allodynia, and sympathetic dysfunction (40). VAS, MPQ, and Bourhis scales all decreased during periods when MCS was “on”; the scores tended to return to baseline during blinded “off” periods. The failure to completely return to baseline levels might well be ascribed to a washout effect of MCS, that is to say persistent pain relief lasting longer than the period of stimulation (Fig. 7).

For MCS, as a treatment for the pain and sympathetic dysfunction associated with CRPS, there is a single RCT, involving a small number of patients, plagued with significant methodologic issues. While there is a strong suggestion of efficacy, I wonder whether there are sufficient data upon which to make any recommendations.

INTRATHECAL DRUG DELIVERY (ITDD)

ITDD is often overlooked by those primarily invested in neurostimulation therapies as a potential neuromodulation therapy for CRPS. In fact, some of the best data for neuromodulation therapies for CRPS exist for targeted drug delivery. Using the same search paradigm as noted above, seven reports of IT baclofen (ITB) therapy for CRPS-related dystonia, three reports of IT analgesics for CRPS-related pain, six reports of ITDD for chronic pain patients including those with CRPS, three reports of alternate IT agents for CRPS-related pain, one review paper, and one survey of CRPS treatment practices were identified (49–69).

In their evidence-based guidelines for the treatment of CRPS type 1, Perez and coworkers (31) reviewed the studies by van Hilten et al. (54) and Zuniga et al. (52). They concluded that “There is insufficient evidence that intrathecal baclofen (ITB) is effective in treating dystonia in CRPS-1 patients (level 3)” (31). That same year, Tran et al. performed a meta-analysis and stated that “Improvement has been reported with...intrathecal baclofen... but further trials are required” (68).



Figure 6. Tipu Aziz, FRCS (SN), D. Med. Sci. Professor of Neurological Surgery, Oxford Functional Neurosurgery, Nuffield Department of Surgical Sciences, Oxford University, UK.



Figure 7. Francisco Velasco, MD. Unit for Stereotactic, Functional Neurosurgery and Radiosurgery, Mexico General Hospital, Mexico City, Mexico.

An analysis of their source data demonstrates the difficulty that both groups had with the existing literature. Zuniga et al. presented two cases of patients treated with ITB for CRPS-related dystonia (52). In the *New England Journal of Medicine*, van Hilten et al. reported seven women with CRPS and dystonia who underwent a double-blind placebo controlled randomized crossover trial of three doses of ITB vs. placebo (54). Six of the seven patients had a positive trial and a pump and catheter were implanted. At long-term follow-up, the authors noted some degree of improvement in all six patients, which ranged from complete normalization of function to a decrease in pain and violent jerks without any change in dystonia. They concluded that “In some patients, the dystonia associated with reflex sympathetic dystrophy responds markedly to intrathecal baclofen” (54). Certainly, it is difficult to make evidence-based recommendations based upon such conclusions (Fig. 8).

More recently, van Rijn and coworkers presented the results of a single-blind placebo-run-in, dose-escalation study to evaluate ITB for CRPS-related dystonia with 12-month follow-up (51). Of 42 patients with CRPS who underwent ITB screening, 38 had a successful trial and 36 patients were implanted with a pump and IT catheter. In 31 of the 36 patients, a dose effect of ITB on dystonia was documented in doses of up to 450 µg/day. One patient had no response to ITB and three patients dropped out of the study. An intention-to-treat analysis demonstrated substantial improvement in dystonia scores, pain, disability, and quality of life at 12 months. As with other ITDD applications, the authors noted high device-related complication rates (51).

Case reports of ITDD for CRPS-related pain using IT or epidural morphine, bupivacaine, ropivacaine, clonidine, baclofen, and ziconotide, either alone or in combination, have appeared. In the largest of these reports, Kapural and coworkers reported seven patients with CRPS-related pain treated with IT ziconotide (57). RCTs have failed to demonstrate the effectiveness of IT glycine, given more than four weeks, or IT methylprednisolone, given in a single IT bolus, for either the pain or the dystonia associated with CRPS (65–67).

Thus, while we in the field routinely consider ITB for spasticity a nearly universally effective therapy, the literature supporting ITB for CRPS-related spasticity is poor and that supporting ITDD for CRPS-related pain is even worse. While the literature is full of case reports and small series, there are only two high-quality studies supporting the use of ITB for CRPS-related dystonia, resulting in a low level of evidence for recommendation of this therapy. There is a similarly low level of evidence, at best, for the use of IT ziconotide for CRPS-related pain.

NON-NEUROMODULATION THERAPIES FOR CRPS

This is not to say that I was alone in my recognition of the gaps between widely accepted approaches to CRPS therapy and the



Figure 8. Prof. Dr. Jacobus Bohannes Van Hilten. Professor of Movement Disorder Neurology at the Leiden University Medical Center, the Netherlands and Associate Professor of Man-Machine Systems and Control Group of the Technical University of Delft.

quality of the literature supporting their use. In fact, if there was a single theme that I took from this IASP satellite symposium, it was the paucity and inconsistency of evidence supporting most of the treatments we use for CRPS. In fact, the data supporting SCS for CRPS are quite good when compared with some other therapies. In his evaluation of adrenergic agents, Srinivasa Raja, for example, cited four reports of the efficacy of phenoxybenzamine (all poor level IV evidence), two reports of the efficacy of intravenous phentolamine (both level IV), one report of epidural clonidine (level IV), one report of topical clonidine (level IV), and one RCT that failed to document efficacy of clonidine (72). Raja further cited recent UK guidelines that state that intravenous guanethidine blocks should not be routinely used for CRPS as four RCTs have failed to demonstrate benefit (level IIA evidence for a lack of effect). Similar negative results have been reported with intravenous reserpine (Fig. 9) (72).

In his review of opioids and nonsteroidal anti-inflammatory agents, Professor Ralf Baron faced an equal challenge (73). He identified one double-blind placebo controlled trial demonstrating efficacy of morphine for the pain of CRPS and a second that failed to demonstrate efficacy of sustained-release morphine. An RCT demonstrated the superiority of prednisolone to piroxicam for decreasing the pain of CRPS, while a retrospective study demonstrated no significant effect of diclofenac (Fig. 10) (73).

Non-neuromodulation procedural therapies fared no better. Michael Stanton-Hicks presented evidence on somatosensory and sympatholytic nerve blocks and concluded that as facilitators of diagnosis, prognosis, and rehabilitation, these procedures were of value but the days of their use as stand-alone therapies are over (74). Angela Mailis-Gagnon presented her rigorous systematic reviews of the literature on sympathectomy and concluded that one-quarter of all patients undergoing sympathectomy for neuropathic pain developed new neuropathic pain and that there were many other associated potentially serious side-effects (75). Chemical sympathectomy was only temporarily effective in half of CRPS patients and even then only for cutaneous allodynia; 20–30%



Figure 9. Srinivasa Raja, MD. Professor of Anesthesiology/Critical Care Medicine, Professor of Neurology, and Director of Pain Research and the Division of Pain Medicine at the Johns Hopkins University School of Medicine, USA.



Figure 10. Ralf Baron, MD. Head of the Division of Neurological Pain Research and Therapy and Vice Chair of the Department of Neurology, Christian-Albrechts-Universität Kiel, Germany.



Figure 11. Angela Mailis-Gagnon, MD, PhD. Director of the Comprehensive Pain Program of the Toronto Western Hospital, University Health Network, Canada.

of patients so treated developed neuralgia as a result of the procedure when performed with phenol (Fig. 11) (75).

CONCLUSIONS

I come back to the subtitle of this article: a conflict between faith and science. I have great personal faith that in carefully selected patients, neurostimulation and ITDD can be effective treatments for the pain and spasticity related to CRPS. To be completely honest, I also have great faith that in some patients, neuromodulation helps neither of these CRPS symptoms. However, we are left with a gap between our faith and our science. I routinely recommend that we assess our therapies with the same critical eye as those who do not believe in the effectiveness of neuromodulation therapies. Those of us immersed in the field of neuromodulation often look askance at the literature supporting sympathectomy for CRPS; however, we have seen that the literature support for both interventions is seriously flawed.

While a lack of evidence is not a lack of effectiveness, it remains a lack of evidence. When our patients, our society, and our reimbursement systems all demand evidence-based support of our clinical practice, we cannot ignore the fact that there is inadequate evidence to highly recommend most neuromodulation therapies for CRPS. Some issues cannot be scientifically proven, and in those cases we must rely upon our faith for guidance. The efficacy of neuromodulation therapies for CRPS is, however, something that can be proven or disproven. We have come a long way toward this goal over the past decade, but we have much more to do. External funding agencies, including the National Institutes of Health, have expressed a renewed interest in supporting comparative outcomes and cost-effectiveness research. By taking advantage of these opportunities and supporting properly designed, carefully executed studies, we can finally answer these questions and improve the effectiveness of chronic pain therapy.

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