CASE CONFERENCE

Management of Chronic Limb Pain with Spinal Cord Stimulation

Guy R. Fogel MD*; Stephen I. Esses, MD‡; Octavio Calvillo, MD, Phd†,‡

**Spine Fellow, †Department of Anesthesiology, and ‡Professor of Orthopedics, Brodsky Chair of Spinal Surgery, Baylor College of Medicine, Houston, Texas*

■ **Abstract:**

Background: Spinal Cord Stimulation (SCS) is a treatment option for chronic pain patients. The most common indication for SCS is the failed back syndrome with leg pain. In the last decade, advances in our understanding of appropriate stimulation programming, lead placement and the physiology of SCS, have led to changes in multi-site stimulation, and stimulation with differing programs. In the past, low back, axial neuropathic type pain was not responsive to SCS. With dual electrode arrays, and dual stimulation with alternating programs of stimulation, steering of stimulation paresthesia, and versatile programmable stimulation parameters, SCS has become a more versatile form of analgesia.

Purpose: To describe the current treatment rational for SCS and the results of that treatment.

Results: The SCS is most efficient in patients with neuropathic pain of the extremities and less efficacious in patients with axial pain.

Conclusion: SCS is the most effective treatment for limb pain not amenable to surgical decompression. The success of SCS in this chronic pain group is 80% successful in treatment of leg pain, and much less effective in treatment of axial pain. ■

INTRODUCTION

The rational use of implantable technologies for pain control should be founded on the knowledge of the neurobiology of pain, and the clinical presentations of pain syndromes. The treatment modalities of the pain management practitioner include all of the modalities and therapies, conservative, pharmacologic, and invasive, used to treat chronic pain syndromes. The purpose of this paper is to describe the basis for the rational use of 1 implantable modality, Spinal Cord Stimulation (SCS).

Electrical stimulation was first considered for treatment of intractable pain based on the publication of the gate control theory of pain by Melzack and Wall in 1965.[1] Shealy et al, in 1967, first introduced electrical stimulation of the spinal cord and peripheral nerves for chronic limb pain.[2] In the decade following the studies, several thousand stimulators were implanted. The initial enthusiasm was dampened by reports of high complication and failure rates. At issue, were increased breakage and displacement of electrical leads, and failure of the implanted receiver, the high cost of the implant, and difficulty defining the patient population, which could respond with a reasonable pain relief percentage.[3–5]

SCS has been applied to a variety of diagnoses, including tumors, brachial plexus injuries, spinal cord injury, multiple sclerosis, peripheral vascular disease and ischemic limb pain, ischemic cardiac angina, arachnoiditis, and pain after failed back surgery.[3] However, even among those with intractable lower extremity pain, the outcome results have shown wide variability.[6–10] In the last decade, advances in our understanding of appropriate stimulation programming, lead placement and the physiology of SCS, have led to changes of multisite stimulation, and stimulation with differing programs. In the past, low back, axial neuropathic type pain was not treatable, but with dual electrode arrays, and dual stimulation with alternating programs of stim-

Address correspondence and reprint requests to: Stephen I. Esses, MD, Professor of Orthopedics, Brodsky Chair of Spinal Surgery, Baylor College of Medicine, 6560 Fannin Suite 1900, Houston Texas 77030. Tel: (713) 986-5740; Fax: (713) 986-5741; E-mail: sesses@mysurgeon.com.

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ulation, steering of stimulation paresthesia, and versatile programmable stimulation parameters, SCS has become a more versatile form of analgesia. However, based on results, the SCS is most efficient in patients with neuropathic pain of the extremities and less efficacious in patients with axial pain.[11,12]

CHARACTERISTICS OF CHRONIC PAIN

Chronic physical pain may be divided into 2 types: nociceptive and neuropathic pain. The differences are important in predicting the efficacy of SCS to treat the chronic pain. Nociceptors are the nerves which sense and respond to injury of the body. They signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain. The pain is typically well localized, constant, and often with an aching or throbbing quality. This is normal pain in response to injury of the body.

Neuropathic pain is the result of an injury or malfunction in the peripheral or central nervous system. Neuropathic pain is not caused by nociceptors; however, the pain is often triggered by an injury. The pain frequently has burning, lancinating, or electric shock qualities. Hyperpathia and allodynia are symptoms of neuropathic pain. Hyperpathia is an increased pain from a stimulus which would be painful normally. Allodynia is pain from stimuli, which are not normally painful, or pain that occurs other than in the area stimulated. Persistent allodynia is also a common characteristic of neuropathic pain. The pain may persist for months or years beyond the apparent healing of any damaged tissues. Examples include post herpetic neuralgia, reflex sympathetic dystrophy, causalgia, components of cancer pain, phantom limb pain, entrapment neuropathy, and peripheral neuropathy. Neuropathic pain is frequently chronic, and tends to have a less robust response to treatment with opioids.

In some conditions the pain appears to be caused by a complex mixture of nociceptive and neuropathic factors. An initial nervous system dysfunction or injury may trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation. For example, Failed back syndrome probably represent a mixture of neuropathic and nociceptive pain. A second example, myofascial pain is probably secondary to nociceptive input from the muscles, but the abnormal muscle activity may be the result of neuropathic factors.

Spinal Cord Stimulation is indicated for patients suffering from chronic intractable pain of the trunk or limbs. In terms of pain type, SCS is most effective for treating *peripheral neuropathic* pain which results from actual damage to the peripheral nerves. Causalgia is an example of peripheral neuropathic pain. SCS is generally *not* effective for treating 2 other types of pain: (1) *nociceptive* pain, which results from nerve irritation (not damage) caused by noxious stimuli such as heat, pressure, or chemicals (burn pain, muscle injury pain, and cancer pain are examples of nociceptive pain and (2) *central* pain which is caused by Central Nervous System (CNS) damage from a stroke or spinal cord injury.

HISTORICAL REVIEW

Application of electrical current through the skin began in the mid 1790 and by the early 20th century, different types of electrical devices were available. However, with the increased availability of different types of analgesic drugs and ablative pain relieving procedures such as rhizotomy, cordotomy, and thalamotomy, the electrical devices had little use and were abandoned. Modern pain control with electricity started with the report of Melsack and Wall who proposed the gate theory of pain.[1] Within the year, Wall and Sweat demonstrated peripheral nerve stimulation could bring pain relief.[13] Shealy devised an implantable type of stimulator for the spinal cord known as a dorsal column stimulator.[2] In the seventies, Long and Sweat independently reported implantable peripheral nerve stimulators.[3,4] Soon afterward, an implantable deep brain stimulator was reported by Hosobuchi and Adams.[14] The initial theory of the function of the stimulator was to inhibit the C-fibers by stimulating the larger myelinated fibers.[2] Even today, the mechanism of pain relief is poorly understood.

Initially, stimulation was difficult to promote widely for several reasons. There was the general lack of experience with treatment of this difficult group of pain patients. Also a lack of understanding of the comorbidities of the patient's chronic pain syndrome, and inappropriate patient selection, all lead to poor widespread acceptance. With the advent of electrodes implanted through a needle under local anesthesia and a decrease in complications such as breakage and migration of leads, and the infection rate, the usage of the spinal cord stimulators has risen again.

INDICATIONS

The patient with intractable pain who is most likely to be helped by a spinal cord stimulator would have leg

pain of greater intensity than back pain, chronic pain of more than 6 months duration that failed to respond to conservative measures, or was not a candidate for conventional surgical treatment. Many have had multiple back surgeries. Some had reflex sympathetic dystrophy. In addition to the long history of back and leg complaints, many patients have additional health problems, including diabetes, hypertension, arthritis, renal and cardiac disease, multiple nonspinal operations, history of Hodgkin's lymphoma, other cancers, gastrointestinal maladies and Paget's disease. These patients are of any age 20–85 years. They have all been treated with narcotic medications for pain relief before the spinal cord stimulator. The patient is found to be refractory to conservative modalities of pain relief. All patients should have a benign form of intractable pain with an organic basis. The pain may be radicular or nonspecific but should be worse in the extremities, usually legs. Some axial pain is acceptable. There should not be a major psychiatric condition. Testing may include visual analog scales to assess leg and back pain intensity. Pain Drawings identify the extent of the painful areas of the back and extremities.

SCS has been most effective in treating neurogenic pain of peripheral origin. The SCS will relieve pain only if paresthesias are induced in the area of the patient's pain, and some say, if the pain returns after the stimulation is stopped, although there is no scientific substantiation.

The most common diagnosis treated by SCS, is failed back syndrome. Failed back syndrome (FBS) may be defined as chronic pain associated with degenerative spondylosis usually lumbar, associated with a history of previous surgery and absence of current surgical indications. The FBS patients have lower extremity pain and dysthesias associated with axial back pain. The limb pain may be in a particular dermatome, however many FBS will not have an anatomic radiculopathy. Most series do not differentiate in the types of diagnosis or leg pain.[10,11,15] Many authors report less satisfactory outcome in treatment of axial pain. This may be related to the presence of less receptive nociceptive pain or during the trial setting, that paresthesias may not be reproduced in the axial locations of the pain.[11,12,16–20]

Relief of cancer pain is also reported as poor.[21,22] Usually SCS is not effective in central pain such as stroke or spinal cord injury. However, SCS may be effective, if paresthias are reproduced in the patient's painful area. SCS has been effective in angina and claudication of peripheral vascular disease.[23–25]

THE STIMULATOR

The stimulator is commercially available. The basic principles have remained the same, since the early pioneering work of Shealy. The electrode is designed to fit the field of stimulation, spinal cord, peripheral nerve, or deep brain. The electrode may be monopolar or quadripolar. A bipolar lead was evaluated and discarded. There is no particular difference in the electrode performance. However, the need for subsequent revision of the electrode is 24.5% in the quadripolar versus 68.4% in the monopolar. There is less "lead migration," breakage, and a lower infection rate. One factor in the difference of revision rates between the 2 electrode types may be that the monopolar is always used in trial stimulation and may be incorporated in the permanent placement of an implant. The quadripolar is only used in permanent implant group.

The electrode is connected to a passive receiver, or a battery powered stimulator. The battery powered units are self powered and activated by external control. The passive receivers are activated by a radio signal transmitted by antennae. The patient has complete control of the duration and strength of stimulation. Incorporation of the trial stimulation period had improved the selection of long term implant patients.[7,8,9,10]

THE TRIAL PROCEDURE

There should be a separate trial stimulation procedure and a permanent implantation in those patients who have a favorable pain relief response with paresthesias produced in the area of the patient's pain. The implantation of trial electrodes may be done with a local anesthetic in a day surgery, or as an over-night hospital stay. Most trial and permanent electrodes are inserted through an epidural Tuohy needle. Sometimes a laminectomy is required in the lower thoracic spine to place the electrode in the epidural space under direct vision. The laminotomy is usually required in the presence of previous surgery, technical difficulty, or epidural scarring. After implantation, the electrode is connected to a handheld programmer that allows various levels of stimulation to be tested during the trial period. Patients are encouraged to increase their activities to near normal during the trial. This should give some indication of the extent to which the permanent stimulator could be expected to control pain levels. After demonstrating greater than 50% reduction of pain, the patient will undergo the permanent implantation of the stimulating system. The pulse generator is implanted in a sur-

gically prepared pocket on the abdomen. An extension wire is tunneled to the lead for the SCS system. Further parameter adjustment may be undertaken as an outpatient. The versatility of the current programming means there are literally thousands of combinations of stimulation parameters to test. Computerized testing systems have been developed to maximize the patient's response.

Some of the patients fail the trial. The failure of the trial in cord central pain situations may be from several sources. One is difficulty accessing the epidural space secondary to trauma or surgery. Second is difficulty producing paresthesias over a large enough area of the patient's pain. Third, is the die-back of dorsal column above a severe cord lesion seen in spinal cord injury patient. Risks are low and neurologic injury is virtually zero. However, a canal stenosis at the proposed implantation site may cause increased risk to the underlying spinal cord. Pre-operative evaluation of the canal space at the proposed implantation site is important. Infections may occur in 5%. Also mechanical and electrical failures become more common with the passage of time. There remains a fairly constant revision rate for nonfunctioning components.

CHARACTERISTICS OF THERAPEUTIC STIMULATION

Recently, some insight has been gained in the physiologic mechanisms underlying the pain relief of SCS. Initially, SCS evolved as a direct clinical application of the well known gate-control theory of Melzack and Wall. However their gate theory would imply all acute and chronic nociceptive pain could be suppressed. This has not turned out to be accurate. The SCS is almost exclusively beneficial for neuropathic pain and not helpful for nociceptive pain. In the patients with ischemia of angina and peripheral vascular disease, which would be described as nociceptive pain, the SCS may actually have its beneficial effect because of improved ischemia rather than any nociceptive pain relief. In addition to the electrophysiologic mechanism of Melzack and Wall, neurochemical mediators may mediate the SCS induced analgesia. There is no evidence that endogenous opiod release is caused by SCS. No increase in opiod peptides have been demonstrated.[26] The effects of SCS are unchanged by Naloxone, an opiod antagonist.[27,28] Various aminoacid neurotransmitters have been shown to participate in nociception. Inhibitory transmitters like taurine and glycine have been studied in relation to SCS-induced analgesia, using microdyalisis has demonstrated SCS increases the concentration of glycine in spinal cord tissue, and proposes glycine as a reasonable candidate to explain SCS-induced analgesia.[29,30] Another neuro-transmitter, gama-amino butyric acid(GABA), is increased with SCS.[31,32] Linderoth demonstrated SCS is capable of inducing significant increases of GABA in the dorsal horn of the rat.[33] Further investigations by Linderoth demonstrated increases of serotonin with SCS in decerebrate cats. Serotonin is an important mediator of analgesia at the spinal level;[34] therefore, it is possible that serotonin could be a mediator in SCS-induced analgesia. Catecholamines in SCS induced analgesia may be increased. Noradrenergic mechanisms may modulate the nociception at the spinal level.[26]

SCS is applied with low intensity and generally in the 50–70 Hz and pulse width of 0.2–0.5 msec. Stimulation paresthesiae must cover the entire painful area. SCS must be applied continuously for periods of at least 20–30 minutes. Effective pain relief with SCS is most likely to occur in cases with neuropathic pain. There is little evidence that purely nociceptive forms of pain, whether acute or chronic, will respond.[28,33,35] SCS is most effective for on-going spontaneous pain and less for pain evoked by load and posture.

RESULTS

Some patients (20% to 40%) will fail the trial stimulation. There are several reasons reported. There may be a failure to get paresthesias in the area of pain. There may be no response to less than 50% relief of pain to stimulation. Patients who receive 50% relief are usually implanted with permanent stimulator. Kim et al noted 20% immediate failures after permanent implantation.[8] Kim et al noted the electrode was the same for the trial and permanent, allowing some placebo effect. An additional 25% to 40% may work well long term and then lose pain control, usually for technical reasons. Most of the technical late failures will improve with revision of the stimulator or electrodes. However, there is a small group that may lose efficiency and not regain it with revision. These are termed "late failures" and current thought is that this may be a manifestation of "tolerance" to the stimulator.[36] Tolerance is described as the gradual loss of pain relief while stimulated, without mechanical problems. This tolerance has been reported with deep brain stimulation also.[9] Kumar notes Amytriptylline and L-Tryptophan have no benefit in tolerance cases.

See Table 1 for a summary of results from the literature of the last 10 years.

Table 1. A Decade of SCS Clinical Series

Reference	Study Design	Size	Type Pain	Follow-up	Results
Devulder J et al 1990[47]	Retrospective	45	Mixed: failed back	5 yr	77% Very good pain relief
Kumar K 1991[15]	Retrospective	121	Mixed: most failed back	6 mo to 10 yr ave 40 mo	40% Pain control by SCS
North RB 1991[12]	Retrospective	50	Failed back	2.2 yr (5 yr max)	53% > 50% pain relief; 5.0 yr: 47% > 50% pain relief
Simpson BA 1991[48]	Retrospective	60	Mixed trauma and failed back	2–9 yr (ave 20 mo)	Modest 23.3%; significant 46.7%
Spiegelmann R 1991[49]	Retrospective	43	Mixed, RSD, Failed surgery	3–33 mo (ave 13 mo)	63% Pain relief
Tasker RR 1992[50]	Retrospective	35	Mixed, Iatrogenic, inflammation, vascular	30 yr experience	50% success. 25 pts had >than 50% pain relief at 1 yr.
De La Porte C 1993[51]	Retrospective	64	Failed back surgery	1–7 yr (ave 4 yr)	55% had >50% pain relief
North RB 1993[52]	Retrospective	205	Mixed	2–20 yr (ave 7.1 yr)	52% HAD >50% relief pain.
LeDoux 1993[11]	Retrospective	32	Failed back syndrome	2 yr	76% Good at 1 yr, 37% 5 yr.
Ohnmeiss 1996[10]	Prospective	40	Failed back syndrome	1–2 yr	53% at 6 wks, 26% at 1–2 yr
Burchiel 1996[7]	Prospective	219	Failed back and leg pain	1 yr	55% success in 70 pts at 1 yr.
Kumar et al 98[8]	Retrospective			66 mo ave	
Kim 2001[8]	Retrospective	122	Mixed Non-specific limb pain evoked pain	3.9 yr (0.3–9 yr)	60.7% received implant 79% success.

Pain, narcotic usage, return to work, and activities of daily living are deemed measures of success at last follow-up. Pain criteria for success of the SCS have been difficult to decide. Most authors consider SCS successful if there continues to be greater than 50% relief of the index pain level at 1 year after implantation. Narcotic usage is a highly variable follow-up parameter. Some series report reduction in drug usage, and changes to less potent analgesics. Other studies find no reduction. Many authors avoid treating patients who use narcotics excessively. Improved return to work data again is equivocal. Some authors report a higher incidence of return to work. However, a high percentage of the patients are disabled, or retired, skewing the data.[7,8,10,37]

RESULTS IN DIFFERENT DIAGNOSES

Non-specific limb pain may be treated as effectively as neuropathic pain if a peripheral nerve is the root cause of the pain. Central pain is amenable if paresthesias are obtained in area of pain.[8] SCS is the most important pain technique available for treatment of intractable pain of benign origin. SCS may be most valuable in failed back syndrome (FBS).[6,11,18–20,37,38,39] SCS has clearly been more effective in relieving intractable leg pain, than in treating axial back pain. SCS is at least as good if not better than re-operation in patients with FBS. For those who have failed surgery, it may be the only pain relief available. In a systematic literature review of patients treated for FBS with SCS, Turner and associates found an average of 50% to 60% of patients with FBS report >50% pain relief with the use of the SCS at follow-up.[20]

SCS has been very effective in treating Reflex Sympathetic Dystrophy (RSD), in well-defined indications including a history of limb trauma; pain of more than 1 peripheral nerve distribution; physical findings of dystrophy; and a positive response to a sympathetic blockade.[40–44] Kemler and associates conducted a randomized, controlled trial of SCS for reflex sympathetic dystrophy.[40] The results show that SCS reduces the intensity of pain caused by this disorder in patients in whom all conventional treatments have failed. The success rate was 56% at 6 months in permanently implanted SCS. Kumar etal, reported 12/12 patients with RSD experienced pain relief with trial stimulation and had permanent stimulators implanted.[9] At follow-up, 8 patients reported excellent and 4 good results. Kumar concluded SCS is an effective treatment for the pain of RSD and that SCS is superior to ablative sympathectomy in the management of RSD.

SCS with peripheral neuropathy of diabetes and causalgia may have up to 75% success rate.[6,7,8,9] Kumar reported only moderate success with peripheral neuropathy. Cases showing the best results were causalgia (100%) and diabetic neuropathy (75%). Kumar

reported less responsiveness in post-herpetic neuralgia, other inter-costal neuralgias, spinal cord injury with dysthesias and pain.[9,45]

SCS is less effective in treating amputation stump and phantom limb pain, cauda equina syndrome, and bone and joint pain syndrome. These cases responded initially with early pain relief, but all subsequently lost pain relief. In a small number of cases of amputation stump and phantom limb pain, none were internalized.[9,45]

Multiple Sclerosis showed high early pain relief producing a 92% internalization rate. However, perhaps due to the development of tolerance, there have been good short term then progressive worsening of pain relief in multiple sclerosis.[7,8]

More recently, excellent results have been obtained in vascular claudication, Kumar reported 69% success.[23,28,37,45] There is an interesting side effect in the vascular patient, with the blockade of sympathetic control of the vessels there is a relative increase in perfusion.

In spinal cord injury, cases of complete paraplegia did not respond. All cases with satisfactory responses had incomplete paralysis, with the majority of their pain below the level of the spinal cord lesion. Cauda equina syndrome had early success with erosion to poor pain control.[6,7,8,10,46]

Average short-term success is 66% to 75% while long-term success is about 50%. North points out in 1993 that the late success rate is better if one excludes the implants needing revision of electrode or receiver.[36] These equipment failures should have pain relief restored once the implant is re-activated.

SUMMARY

Chronic pain remains one of the most debilitating of all medical disorders. Chronic pain may lead to loss of employment, destruction of interpersonal relationships and drug addiction. Reasonable long-term success with SCS may be achieved by adhering to these principles.

1. Modest selection criteria. All patients should have exhausted all conservative treatments. Narcotic usage alone should not be a non-exclusionary finding. Many patients will decrease drug usage after stimulator.
2. State of the art SCS equipment should be used.
3. A trial period should be undertaken in all cases. Some patients (15% to 55%) will be excluded from the expense and possible risk of permanent implantation, by failing a trial period.

In conclusion, SCS is an effective and safe therapy that improves the quality of life and activities of daily living, in patients disabled by their chronic pain. The mode of action of SCS is not completely known, but is better defined now, and may be related to controlling neurotransmitters, such as glycine and GABA. With dual stimulation further inroads in the treatment of FBS are made. SCS continues to be most effective for neuropathic pain and less effective for nociceptive mediated pain.

REFERENCES

1. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(699):971–979.
2. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg*. 1967;46(4):489–491.
3. Long DM, Erickson DE. Stimulation of the posterior columns of the spinal cord for relief of intractable pain. *Surg Neurol*. 1975;4(1):134–141.
4. Sweet WH. Control of pain by direct electrical stimulation of peripheral nerves. *Clin Neurosurg*. 1976;23: 103–111.
5. Shealy CN. Dorsal column stimulation. *Surg Neurol*. 1977;7(4):192.
6. Burchiel KJ, et al. Prognostic factors of spinal cord stimulation for chronic back and leg pain. *Neurosurgery*. 1995;36(6):1101–1110, discussion 1110–1111.
7. Burchiel KJ, et al. Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain. *Spine*. 1996;21(23):2786–2794.
8. Kim SH, Tasker RR, Oh MY. Spinal cord stimulation for nonspecific limb pain versus neuropathic pain and spontaneous versus evoked pain. *Neurosurgery*. 2001;48(5): 1056–1064, discussion 1064–1065.
9. Kumar K, et al. Epidural spinal cord stimulation for treatment of chronic pain—some predictors of success. A 15-year experience. Surg Neurol. 1998;50(2):110–120, discussion 120–121.
10. Ohnmeiss DD, Rashbaum RF, Bogdanffy GM. Prospective outcome evaluation of spinal cord stimulation in patients with intractable leg pain. *Spine*. 1996;21(11): 1344–1250, discussion 1351.
11. LeDoux MS, Langford KH. Spinal cord stimulation for the failed back syndrome. *Spine*. 1993;18(2):191–194.
12. North RB, et al. Failed back surgery syndrome: 5-year follow-up after spinal cord stimulator implantation. *Neurosurgery*. 1991;28(5):692–699.
13. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science*. 1967;155(758):108–109.
14. Hosobuchi Y, Adams JE, Rutkin B. Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch Neurol*. 1973;29(3):158–161.

15. Kumar K, Nath R, Wyant GM. Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. *J Neurosurg*. 1991;75(3):402–407.

16. North RB, et al. Failed back surgery syndrome: 5-year follow-up in 102 patients undergoing repeated operation. *Neurosurgery*. 1991;28(5):685–690, discussion 690–691.

17. North RB, et al. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. *Pain*. 1991;44(2):119–130.

18. North RB, et al. A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: initial results. *Stereotact Funct Neurosurg*. 1994;62(1–4):267–272.

19. North RB, Kidd DH, Piantadosi S. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a prospective, randomized study design. *Acta Neurochir Suppl (Wien)*. 1995;64:106–108.

20. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. *Neurosurgery.* 1995;37(6):1088–1095, discussion 1095–1096.

21. Long DM. Fifteen years of transcutaneous electrical stimulation for pain control. Stereotact Funct *Neurosurgery*. 1991;56(1):2–19.

22. Long DM. Conquering pain. *Neurosurgery*. 2000;46(2):257–259.

23. Augustinsson LE, et al. Spinal cord stimulation in cardiovascular disease. *Neurosurg Clin N Am*. 1995;6(1): 157–165.

24. Grill WM, et al. Emerging clinical applications of electrical stimulation: opportunities for restoration of function. *J Rehabil Res Dev*. 2001;38(6):641–653.

25. Moore R, Chester M. Neuromodulation for chronic refractory angina. *Br Med Bull*. 2001;59:269–278.

26. Linderoth B, et al. Release of neurotransmitters in the CNS by spinal cord stimulation: survey of present state of knowledge and recent experimental studies. *Stereotact Funct Neurosurg*. 1993;61(4):157–170.

27. Meyerson BA, Brodin E, Linderoth B. Possible neurohumoral mechanisms in CNS stimulation for pain suppression. *Appl Neurophysiol*. 1985;48(1–6):175–180.

28. Meyerson BA, Linderoth B. Mechanisms of spinal cord stimulation in neuropathic pain. *Neurol Res*. 2000;22(3): 285–292.

29. Simpson RK, Robertson CS, Goodman JC. Segmental recovery of amino acid neurotransmitters during posterior epidural stimulation after spinal cord injury. *J Am Paraplegia Soc*. 1993;16(1):34–41.

30. Simpson RK Jr., Robertson CS, Goodman JC. Release of segmental amino acid neurotransmitters in response to peripheral afferent and motor cortex stimulation: a pilot study. *Life Sci*. 1991;49(17):PL113–PL118.

31. Duggan AW. Release of neuropeptides in the spinal cord. *Prog Brain Res*. 1995;104:197–223.

32. Duggan AW, Foong FW. Bicuculline and spinal inhibition produced by dorsal column stimulation in the cat. *Pain*. 1985;22(3):249–259.

33. Linderoth B, et al. Dorsal column stimulation induces release of serotonin and substance P in the cat dorsal horn. *Neurosurgery*. 1992;31(2):289–296, discussion 296–297.

34. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci*. 1984;7:309–338.

35. Meyerson BA, et al. An experimental animal model of spinal cord stimulation for pain. *Stereotact Funct Neurosurg*, 1994;62(1–4):256–262.

36. North RB, et al. Spinal cord stimulation for chronic, intractable pain: experience over two decades. *Neurosurgery*, 1993;32(3):384–394, discussion 394–395.

37. Lang P. The treatment of chronic pain by epidural spinal cord stimulation—a 15 year follow up; present status. *Axone*. 1997;18(4):71–73.

38. Long DM. The current status of electrical stimulation of the nervous system for the relief of chronic pain. *Surg Neurol*. 1998;49(2):142–144.

39. Bell GK, Kidd D, North RB. Cost-effectiveness analysis of spinal cord stimulation in treatment of failed back surgery syndrome. *J Pain Symptom Manage*. 1997;13(5):286–295.

40. Kemler MA, et al. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. *J Neurosurg*. 1999;90(1 Suppl):79–83.

41. Kemler MA, de Vet HC. Health-related quality of life in chronic refractory reflex sympathetic dystrophy (complex regional pain syndrome type I). *J Pain Symptom Manage*. 2000;20(1):68–76.

42. Kemler MA, et al. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. *Anesthesiology*. 2001;95(1):72–80.

43. Rho RH, et al. Complex regional pain syndrome. *Mayo Clin Proc*. 2002;77(2):174–180.

44. van De Beek WJ, et al. Neurophysiologic aspects of patients with generalized or multifocal tonic dystonia of reflex sympathetic dystrophy. *J Clin Neurophysiol*. 2002;19(1):77–83.

45. Kumar K, et al. Improvement of limb circulation in peripheral vascular disease using epidural spinal cord stimulation: a prospective study. *J Neurosurg*. 1997;86(4):662–669.

46. Alo KM, Holsheimer J. New trends in neuromodulation for the management of neuropathic pain. *Neurosurgery*. 2002;50(4):690–704.

47. Devulder J, et al. Spinal cord stimulation: a valuable treatment for chronic failed back surgery patients. *J Pain Symptom Manage*. 1997;13(5):296–301.

48. Simpson BA. Spinal cord stimulation in 60 cases of intractable pain. *J Neurol Neurosurg Psychiatry*. 1991;54(3): 196–199.

49. Spiegelmann R, Friedman WA. Spinal cord stimulation: a contemporary series. *Neurosurgery*. 1991;28(1):65–70, discussion 70–71.

50. Tasker RR, DeCarvalho GT, Dolan EJ. Intractable pain of spinal cord origin: clinical features and implications for surgery. *J Neurosurg*. 1992;77(3):373–378.

51. De La Porte C, Van de Kelft E. Spinal cord stimulation in failed back surgery syndrome. *Pain*. 1993;52(1): 55–61.

52. North RB. Spinal cord stimulation for chronic, intractable pain. *Adv Neurol*. 1993;63:289–301.