Pain Physician 2014; 17:235-246 • ISSN 1533-3159

Narrative Review

Present and Potential Use of Spinal Cord Stimulation to Control Chronic Pain

Jason J. Song, MD, PhD, Adrian Popescu, MD, and Russell L. Bell, MD

From: Hospital of the University of Pennsylvania, Philadelphia, PA

Dr. Popescu is with the Department of Physical Medicine & Rehabilitation, Hospital of the University of Pennsylvania, Philadelphia, PA. Dr. Bell is with the Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, Philadelphia, PA.

Address Correspondence:
Jason J. Song, MD, PhD
Hospital of the University of Pennsylvania
Philadelphia, PA
E-mail:
jason.song1@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-25-2013
Revised manuscript received: 12-09-2013
Accepted for publication: 12-27-2013

Free full manuscript: www.painphysicianjournal.com

Background: Spinal cord stimulation is an intervention that has become increasingly popular due to the growing body of literature showing its effectiveness in treating pain and the reversible nature of the treatment with implant removal. It is currently approved by the FDA for chronic pain of the trunk and limbs, intractable low back pain, leg pain, and pain from failed back surgery syndrome. In Europe, it has additional approval for refractory angina pectoris and peripheral limb ischemia.

Objective: This narrative review presents the current evidence supporting the use of spinal cord stimulation for the approved indications and also discusses some emerging neuromodulation technologies that may potentially address pain conditions that traditional spinal cord stimulation has difficulty addressing.

Study Design: Narrative review.

Results: Spinal cord stimulation has been reported to be superior to conservative medical management and reoperation when dealing with pain from failed back surgery syndrome. It has also demonstrated clinical benefit in complex regional pain syndrome, critical limb ischemia, and refractory angina pectoris. Furthermore, several cost analysis studies have demonstrated that spinal cord stimulation is cost effective for these approved conditions. Despite the lack of a comprehensive mechanism, the technology and the complexity in which spinal cord stimulation is being utilized is growing. Newer devices are targeting axial low back pain and foot pain, areas that have been reported to be more difficult to treat with traditional spinal cord stimulation. Percutaneous hybrid paddle leads, peripheral nerve field stimulation, nerve root stimulation, dorsal root ganglion, and high frequency stimulation are actively being refined to address axial low back pain and foot pain. High frequency stimulation is unique in that it provides paresthesia free analgesia by stimulating beyond the physiologic frequency range. The preliminary results have been mixed and a large randomized control trial is underway to evaluate the future of this technology. Other emerging technologies, including dorsal root ganglion stimulation and hybrid leads, also show some promising preliminary results in non-randomized observational trials.

Limitation: This review is a primer and not an exhaustive review for the current evidence supporting the use of spinal cord stimulation and precursory discussion of emerging neuromodulation technologies. This review does not address peripheral nerve stimulation and focuses mainly on spinal cord stimulation and touches on peripheral nerve field stimulation.

Conclusions: Spinal cord stimulation has demonstrated clinical efficacy in randomized control trials for the approved indications. In addition, several open label observational studies on peripheral nerve field stimulation, hybrid leads, dorsal root ganglion stimulation, and high frequency stimulation show some promising results. However, large randomized control trials demonstrating clear clinical benefit are needed to gain evidence based support for their use.

Key words: Spinal cord stimulation, chronic pain; low back pain, high frequency stimulation, peripheral nerve field stimulation, dorsal root ganglion stimulation, failed back surgery syndrome, complex regional pain syndrome, critical limb ischemia, refractory angina pectoris

Pain Physician 2014; 17:235-246

A heightened awareness of the prescription opioid drug problem in the United States has led some pain physicians to explore non-narcotic medications and interventional approaches to address chronic pain. Spinal cord stimulation (SCS) is one of those interventions that have become increasingly popular due to the growing body of literature showing its effectiveness in treating pain and the reversible nature of the treatment with implant removal. The SCS procedure involves placement of electrical leads into the midline epidural space to send pulsed electricity to stimulate the dorsal columns of the spinal cord to replace a painful sensation with a better tolerated tingling sensation called paresthesia.

The gate control theory, although incomplete, is credited for providing a possible mechanism for the efficacy of SCS in pain relief. In 1965, Melzack and Wall (1) published their theory of pain transmission called the gate control theory, proposing that stimulation of the small fibers (pain nerves) in the periphery opens the gate in the dorsal column of the spinal cord to transmit pain sensation to the brain. Whereas, stimulation of the large fibers (responsible for touch and vibration) closes the gate on the small fibers and blocks transmission of pain to the brain (1). A real life example would be a person rubbing an area of skin stung by a bee to relieve the pain. The assumption of SCS technology is that electrical stimulation to the spinal cord would preferentially stimulate the large fibers and lead to "closure of the gate" on the smaller fibers, thus blocking pain transmission to the brain. However, the gate control theory does not explain why neuropathic pain is selectively targeted and nociceptive pain is largely spared. In addition, for some patients, pain does not return immediately after the stimulation is turned off (2).

SCS also appears to affect the sympathetic system, both by addressing sympathetic mediated pain as in complex regional pain syndrome (CRPS) and also to improve blood flow in peripheral ischemia and cardiac ischemia (3). Practical application of the gate control theory was performed in 1967 by the use of SCS and peripheral nerve stimulation on patients with cancer pain by Shealy and Wall, respectively (4,5).

Spinal Cord Stimulation

The SCS device consists of electrode leads, an extension cable, a pulse generator, and a programmer. The leads can be percutaneous, paddle, or hybrid (percutaneous paddle) leads. Percutaneous leads have 4 to 16 electrodes and are introduced into the epidural space via a Tuohy needle, while paddle leads have 4 to 16 electrodes and are generally placed by open procedure that would involve laminotomy or laminectomy (Fig. 1). The percutaneous approach is less invasive and less expensive, but paddle leads are more stable and less prone to migrate (6). A recent cohort study reported higher postoperative complications with paddle leads, but lower reoperation rates (7).

With the percutaneous approach, the leads are introduced into the epidural space at 4 to 6 levels below the target level and advanced to the desired level under fluoroscopic guidance. SCS leads are generally placed at the midline in the epidural space to stimulate the dorsal column tracts of the spinal cord and avoid stimulation of the dorsal root nerves that are entering the dorsal horn. Stimulation of the dorsal root nerves may lead to unpleasant motor responses or dysesthesia (8). However, in certain instances lateral stimulation is intentionally done to cover dermatomes that are difficult to cover with traditional lead placement (2).

For coverage of specific areas of the body, the following are guidelines for lead placement. For coverage of the legs, the leads are usually placed at midline or just lateral to midline. For axial back pain, one lead is placed at midline and another lead is placed on either side of midline. As will be discussed later, there are other methods to attempt to cover axial back pain. To cover the posterior occipital region, leads can be placed around C2. For upper extremity pain, the leads are placed between C2 to C5 (Fig. 2A). Leads placed at C5, C6 will cover the hand. For chest wall pain and angina, the leads are placed between T1 to T4 (one placed at midline and the other lead more laterally). For coverage of thigh and knee pain, the leads are placed between T9 to T10 (Fig. 2B) and for the lower leg and ankle they are placed between T10 to T12. For coverage of the foot, the leads are placed between T11 and L1. Coverage for the sole of the foot can be difficult, and may require stimulation of the L5 or S1 nerve root (9,10). The final positions of the leads are adjusted from these suggested starting points based on patient feedback.

The electrodes are connected to a power source, either an implanted pulse generator (IPG) or a radiofrequency unit (RF). There are 2 types of IPG, a non-rechargeable and a rechargeable unit. The life span for a non-rechargeable IPG is 4 years, while a rechargeable IPG has a 9-year life span (11). An RF has an external power source. The benefit of the rechargeable IPG is the extended battery life. This relieves some pressure of rationing power usage and allows for varied stimula-

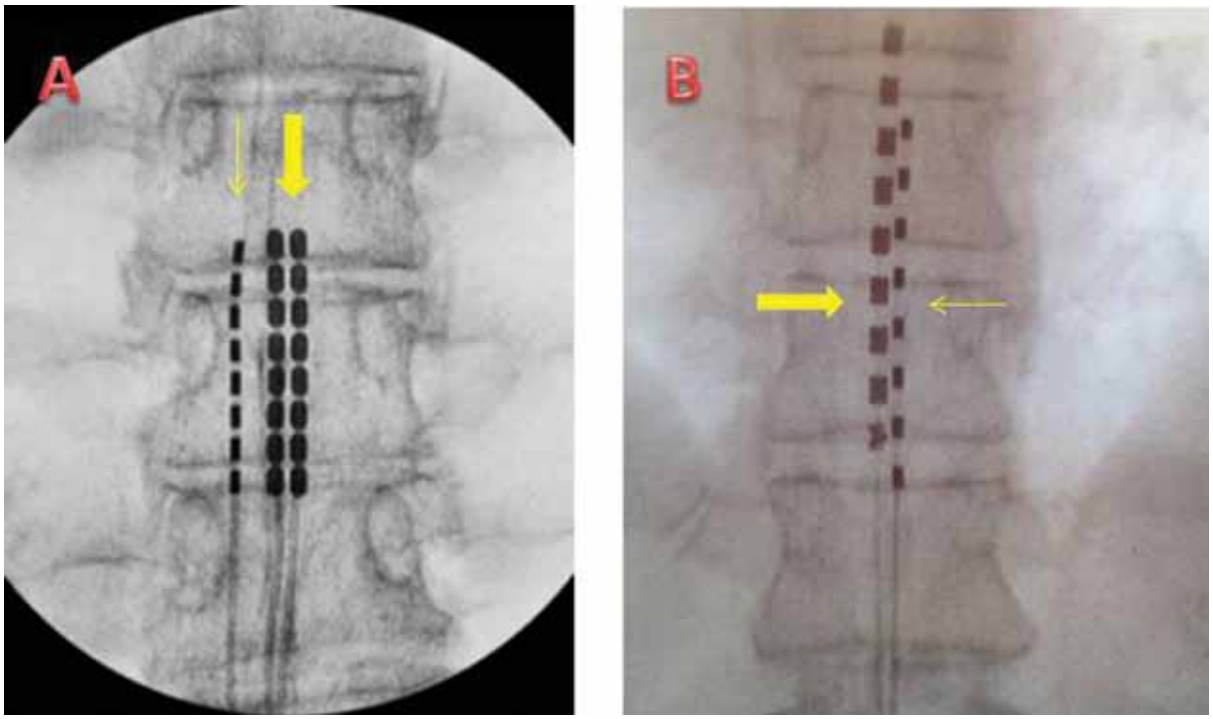

Fig. 1. *Anterior-posterior fluoroscopic images of percutaneous lead, paddle lead, and hybrid (percutaneous introduced paddle) lead implanted into the thoracic epidural space. A. Paddle lead (large arrow) and percutaneous lead (small arrow). (Image courtesy of Boston Scientific). B. Hybrid lead (large arrow) and percutaneous lead (small arrow). (Image courtesy of St. Jude Medical).*

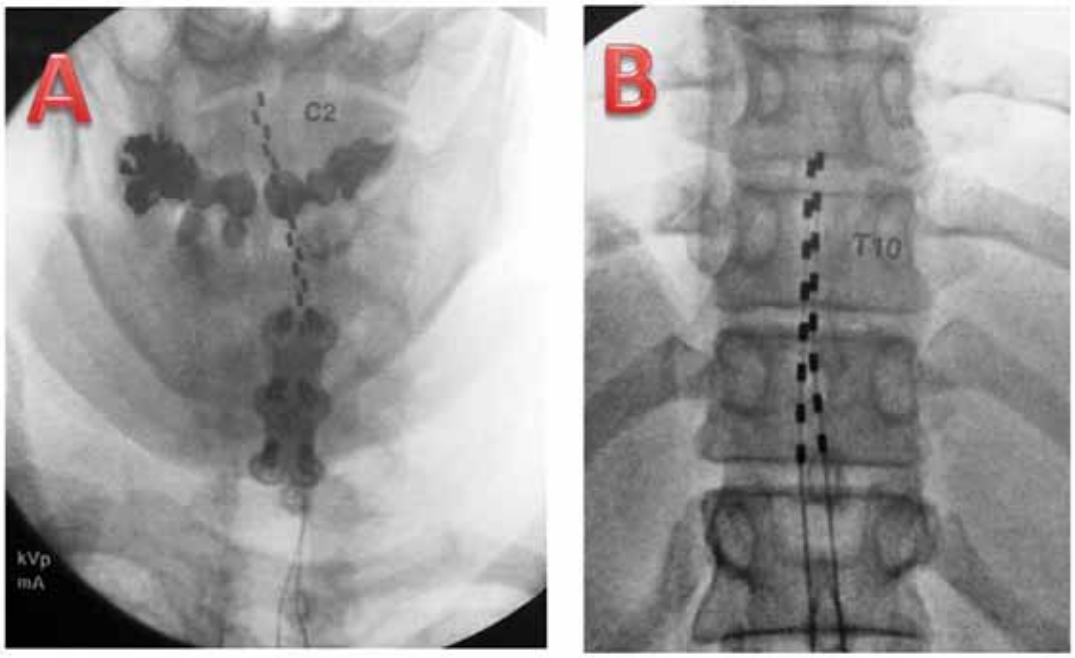

Fig. 2. *Anterior-posterior fluoroscopic images of percutaneous lead placement. A. Percutaneous leads implanted into the midline cervical epidural space. C2 vertebrae is labeled. B. Percutaneous leads implanted into the midline thoracic epidural space. T10 vertrbae is labeled. (Images courtesy of Medtronic)*

tion settings, including high frequency stimulation that is more taxing on battery life.

For the SCS programmer, 3 parameters can be adjusted to maximize pain relief. The 3 parameters include frequency, amplitude, and width. The frequency, measured in hertz (Hz), generally ranges from 40 Hz to 125 Hz, with 50 Hz being the most common (12). The frequency changes the quality of the paresthesias. As will be discussed later, frequencies beyond the physiologic levels, ranging from 1 kHz to 10 kHz, called high frequency stimulation, reportedly provides analgesia without evoking paresthesia. The width affects the size of the area of paresthesia and the amplitude affects the intensity of the electrical stimulation. Both the width and amplitude affect the overall strength of the stimulation. In rats, both the amplitude and frequency of stimulation was found to affect analgesia (13).

SCS is generally reserved for patients who have already failed conservative management. Psychological clearance is generally recommended. Prior to permanent placement, the patient undergoes implantation of a trial stimulation. Pain relief of 50% or greater is generally accepted in order to progress to permanent implantation. Trial period usually lasts between 5 and 7 days and permanent spinal cord stimulators are placed several weeks to one month after a successful trial. SCS is currently approved by the FDA for chronic pain of the trunk and limbs, intractable low back pain, leg pain, and pain from failed back surgery syndrome (FBSS). In Europe, SCS has additional approval for refractory angina pectoris and peripheral limb ischemia.

Failed Back Surgery

FBSS is a condition where the patient continues to have persistent pain despite attempted back surgery to address the condition. It is the most common indication for SCS placement. There can be both axial back pain and radicular leg pain associated with FBSS. In 2005, North and colleagues (14) reported a prospective, randomized control trial (RCT) of 50 patients assigned to SCS or reoperation. At a mean follow-up of 3 years, 47% of patients with SCS reported 50% or greater pain control versus 12% of patients who underwent reoperation. In addition, the SCS group used fewer narcotics versus the reoperation group. The return to work status and activities of daily living did not differ between the SCS group and the reoperation group.

The PROCESS trial, a prospective multicenter RCT (n = 100) comparing SCS + conservative medical management (CMM) versus CMM alone reported that 48% of patients in SCS + CMM group versus 9% in the CMM alone group reported 50% or greater pain relief of leg pain at the 6 months follow-up. By 12 months, 48% of patients in SCS + CMM group versus 18% in the CMM group reported 50% or greater pain relief of leg pain (15). By 24 months, 37% of SCS + CMM group versus 2% of CMM group reported 50% or greater pain relief (16).

In a cost analysis of SCS versus reoperation for FBSS, North and colleagues (17) reported that SCS was less expensive and more effective than reoperation for selected FBSS patients. The mean per patient cost for SCS was US$ 31,530 versus US$ 38,160 for reoperation (intention to treat), US$ 48,357 for SCS versus US$ 105,928 for reoperation (treated as intended), and US$ 34,371 for SCS versus US$ 36,341 for reoperation (final treatment) by the mean follow-up of 3.1 years (17). Kumar and colleagues (18) published a report of FBSS patients where the annual cost of SCS was $29,000 versus $38,000 in the control. Furthermore, 15% of SCS patients returned to work where 0% of the control returned (18). Kumar and colleagues (19), in a separate cost analysis study over a 20 year period, reported that SCS has an incremental cost-effectiveness ratio (ICER) of CAN$ 9,293 per quality-adjusted life years (QALY) gained, indicating that it is cost effective compared to CMM alone for FBSS. However, despite the cost effectiveness of SCS, the overall cost for SCS + CMM was higher (CAN$ 166,439) versus CMM alone (CAN$ 153, 522) (19).

Although SCS can be very effective for pain that radiates down the legs, SCS appears to have more difficulty addressing axial low back pain (20). Various approaches have been tried including single or double percutaneous lead and single or double paddle leads to address the axial low back pain (21-23). Barolat and colleagues (22) reported a prospective, multi-center observational study on a single paddle lead and reported that 88.2% of the patients reported fair to excellent relief in the legs and 68.8% of the patients reported fair to excellent relief in the low back at the one year follow-up. Duyvendak (21) reported an observational study (n = 28) where patients reported 70% relief of back and leg pain with dual paddle leads. North and colleagues (23) compared single versus double percutaneous leads and stated that a single lead at midline was superior to double leads in addressing low back pain. As will be discussed later, peripheral nerve field stimulation (PNfS), nerve root stimulation, and high frequency stimulation have also been utilized to cover axial low back.

Complex Regional Pain Syndrome

CRPS is a multifactorial chronic disease characterized by disabling pain, swelling, and changes of the skin. The cause or mechanism for CRPS is unknown, but sympathetic dysregulation, inflammation, tissue hypoxia, small fiber damage, central sensitization, and cortical reorganization are all implicated with this condition (24). It is speculated that SCS not only controls the neuropathic pain of CRPS, but may also modulate the sympathetically mediated pain. The latter was supported by animal studies where SCS was found to suppress the sympathetic system (25).

Kemler and colleagues (26) reported a randomized trial where 54 patients with CRPS were placed into either SCS with physical therapy (PT) or PT alone. At the 6 months follow-up, the treatment group had a decrease of 2.4 on the visual analog scale (VAS) compared to decrease of 0.2 for the control group. Global perceived effect improved as well (39% for SCS + PT versus 6% for PT alone) (26). At 2 years follow-up, the improvement in VAS and global perceived effect were sustained in the SCS group (VAS -2.1) over the control group (VAS 0.0) (27). However, the pain relieving effects of SCS decreased over time and no significant difference occurred after the 3 year follow-up. However, at the 5 year follow-up, over 95% of the patients implanted with a spinal cord stimulator reported that they would undergo the treatment again (28). Kemler and colleagues (29) published a cost analysis study over a 15 year period and reported ICER of SCS compared to CMM was £3562 per QALY, indicating that SCS is cost effective compared to CMM. However, the overall cost for SCS was higher with £86,770 versus £79,775 for CMM alone (29). Kumar and colleagues, in their cost analysis study over a 20 year period reported that SCS has an ICER of CAN$ 11,216 per QALY gained, indicating that it is cost effective compared to CMM alone for CRPS. However, despite the cost effectiveness of SCS, the overall cost for SCS + CMM was higher (CAN$ 172,577) versus CMM alone (CAN$ 148,799) (19).

Peripheral Ischemic Limb Pain and Refractory Angina Pectoris

Critical limb ischemia and refractory angina pectoris are approved indications for SCS in Europe, but not currently in the United States. In these 2 conditions, it is hypothesized that SCS causes vasodilation and improves blood flow. Critical limb ischemia is a condition caused by vascular compromise causing pain and threat of limb loss. For patients who have critical limb ischemia and are nonsurgical candidates, SCS may be a therapeutic option. Pain relief reported by RCTs was mixed. The Jivegard et al (30) trial showed pain relief for the SCS group at the 18 months follow-up. However, the ESES trial found no difference in pain relief between the SCS and the CMM groups (31). Several individual RCTs reported no significant difference in limb salvage rates between the SCS or the control groups (30,32-34). However, a meta-analysis pooled from the RCTs demonstrated significant limb salvage benefit for SCS, suggesting the individual RCTs were underpowered (35). The benefits of SCS come at a higher cost than conservative management and more complications that come from SCS placement (35). In a cost analysis study of the ESES trial, Klomp and colleagues (36) reported the cost of SCS was higher (EURO 36,600) versus CMM (EURO 28,700). Kumar and colleagues, in their cost analysis study over a 20 year period, reported that SCS has an ICER of CAN$ 9,319 per QALY gained, indicating that it is cost effective compared to CMM alone for peripheral arterial disease. However, despite the cost effectiveness of SCS, the overall cost for SCS + CMM was higher (CAN$ 178,288) versus CMM alone (CAN$ 162,725) (19).

Patients with coronary artery disease and angina who are ineligible for either percutaneous coronary intervention or coronary artery bypass graft (CABG) may be considered for SCS. In RCTs, SCS was found to have fewer angina attacks and less nitrate requirement than CMM (37-39). However, CABG was found to have even less nitrate requirement then SCS, but equivocal reduction in angina. (39). Exercise duration was increased in SCS versus CMM (37,38).). Kumar and colleagues, in their cost analysis study over a 20 year period, reported that SCS has an ICER of CAN$ 9,984 per QALY gained, indicating that it is cost effective compared to CMM alone for refractory angina pectoris. However, despite the cost effectiveness of SCS, the overall cost for SCS + CMM was higher (CAN$ 182,366) versus CMM alone (CAN$ 160,302) (19).

Complications

SCS is a relatively safe procedure and reversible with implant removal. Adverse events were reported between 34% and 38% (27,40). The most common complication for SCS is lead migration and/or breakage, ranging from 10% to 30% depending on the study (15,41,42). Rate of infection ranged from 3% to 5% and persistent pain ranged from 5% to 6% (9,40). The mobility of the spine and spinal cord in relation to the elec-

trode during changes in position of the body, especially during sit to stand transition, may lead to different levels of paresthesias and sometimes uncomfortable stimulation. Some patients even turn off stimulation at night to prevent being woken up by uncomfortable stimulation when shifting in bed (43).

Hybrid Leads

Both single and double paddle leads have been reported in observational trials to have favorable results on low back pain (21,22). However, the paddle lead implantation is more invasive than percutaneous leads and involves laminotomy or laminectomy. Hybrid leads were developed to offer the benefits of paddle leads, but allow for percutaneous introduction into the epidural space (Fig. 1B). De Vos and colleagues (44) reported an open label, observational study of percutaneously introduced paddle lead in patients with FBSS with both back and leg pain (n = 42). In their study, a single hybrid paddle lead was percutaneously introduced into the midline epidural space overlying the spinal cord. At the 6 month follow-up, VAS pain scores improved from 8.0 to 3.2 and 7.5 to 3.5, for leg pain and low back pain, respectively. At the one year follow-up, 51% of patients reported low back pain relief and 71% reported leg pain relief (44). Baseline VAS score was used as an internal control for this study. The lack of a separate comparator did not adequately address the placebo effect as a confounding variable.

Peripheral Nerve Field Stimulation

PNfS is another approach to address low back pain in FBSS patients. PNfS involves subcutaneous placement of leads in the area of pain to provide paresthesia over that area. It is analogous to "carpet bombing" an area of the body versus a precision "missile strike" of a specific nerve that is employed by peripheral nerve stimulation. The larger area of analgesia provided by PNfS may be due to "cross talk" or inter-lead stimulation between 2 separate subcutaneous leads. Falco and colleagues (45) demonstrated in cadavers that subcutaneous inter-lead stimulation can occur over a great distance.

Mironer and colleagues (46) reported a prospective, open label, observational study (n = 20) where the patients were implanted with both SCS and PNfS. The patients were trialed with SCS stimulation alone, PNfS stimulation alone, or a combination to address axial low back pain. In their study, 79% of patient selected the SCS/PNfS combination over either SCS or PNfS alone to address their axial low back pain. Furthermore, the study reported that communication between SCS and PNfS provided a wider coverage of axial low back pain then either alone (46). This supported findings of inter-lead stimulation observed in the study by Falco and colleagues (45).

Hamm-Faber and colleagues (47) reported a case series on 11 FBSS patients where SCS alone was insufficient in treating the axial low back pain. In the study, 9 patients had both SCS and PNfS implanted and 2 patients had only PNfS implanted. PNfS with and without SCS (n = 10) significantly reduced axial low back pain, with a VAS of 62 prior to implantation to a VAS of 32 at the 12 month follow-up. In addition, there was also a 70% reduction in opioid use and improvement of Quebec back pain disability scale from 61 to 49. Furthermore, 2 patients returned to work. The study used the baseline VAS score as an internal control, adding the possibility of the placebo effect being a confounding variable (47).

McRoberts and colleagues (48) reported a prospective, multi-center, randomized, controlled, crossover study of patients with chronic intractable back pain who failed CMM (n = 44). Twenty-three patients ultimately received permanent PNfS (without SCS) and 70% of patients reported 50% – 100% pain relief for axial low back pain at one year follow-up. Baseline VAS score was also used as an internal control for this study, adding the possibility of the placebo effect being a confounding variable (48).

Nerve Root Stimulation and Dorsal Root Ganglion Stimulation

Nerve root stimulation involves the stimulation of the dorsal root entry zone and the dorsal root ganglion stimulation involves the direct stimulation of the dorsal root ganglion. Both of these techniques are employed to address primary low back pain or isolated foot pain that may be difficult to cover using traditional SCS. It is believed that the anatomy of the spinal cord limits the ability of the SCS to stimulate the deeper tracts that would cover the sacral dermatomes, including the dermatomes to the feet (49).

In nerve root stimulation, the technique is very similar to traditional SCS, except the leads are placed laterally to stimulate the dorsal root entry zone versus the dorsal columns employed by traditional SCS. This technique can cover multiple levels versus the more selective dorsal root ganglion stimulation. In nerve root stimulation, the lead is placed medial to the pedicle of the exiting nerve root. For cervical, thoracic, and upper lumbar nerve roots, an anterograde approach is

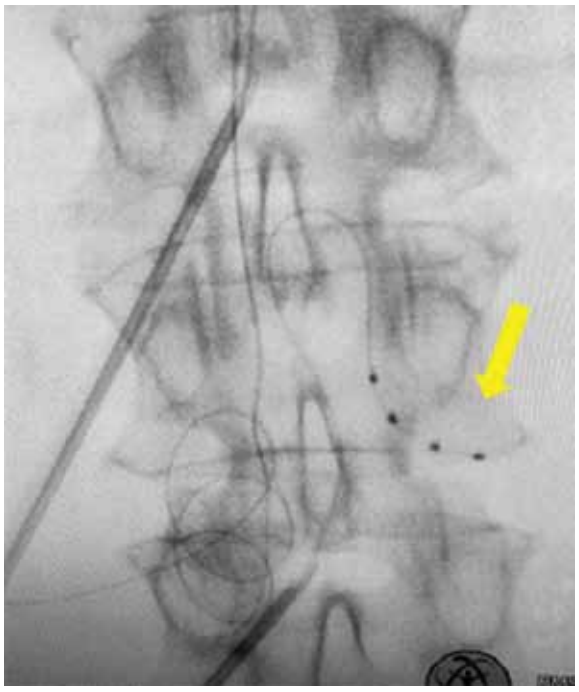

Fig. 3. *Anterior-posterior fluoroscopic image of a percutaneous lead implanted into the L2-L3 neuroforamen to stimulate the L2 dorsal root ganglion (arrow). (Image courtesy of Spinal Modulation, Inc.)*

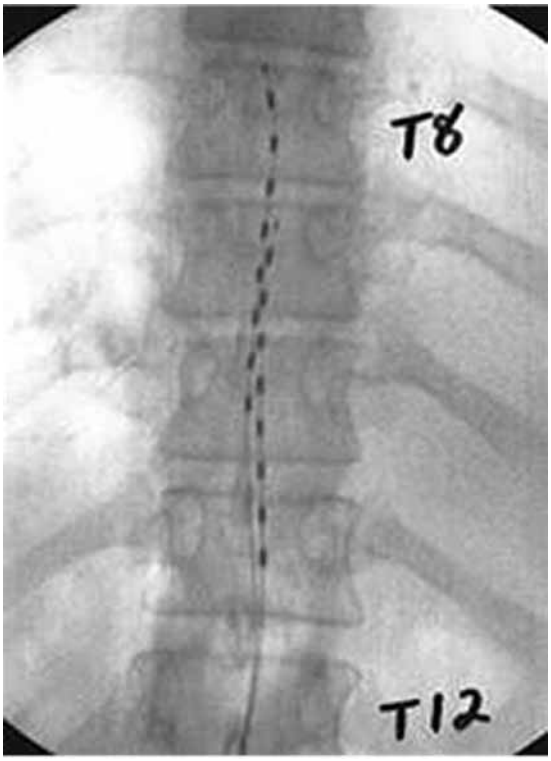

Fig. 4. *Anterior-posterior fluoroscopic image of percutaneous leads implanted in a staggered fashion in the midline thoracic epidural space for HF10 SCS.)Courtesy Van Buyten et al. Neuromodulation 2013 (51).*

generally used. For lower lumbar and sacral roots, a retrograde approach is used (49).

Dorsal root ganglion stimulation involves introducing the electrode into the epidural space and then steering the electrode laterally into the neural foramen to stimulate the dorsal root ganglion (Fig. 3). Liem and colleagues (43) conducted a multi-center, prospective, open-label observational study (n = 39) where patients were implanted with a dorsal root ganglion stimulator and followed for 6 months. The study included patients with several diagnoses, including FBSS, CRPS, radiculopathy, lumbar stenosis, and post-surgical pain. The percentage of patients who reported 50% reduction of back, leg, and foot pain were 57%, 70%, and 89%, respectively (43). The study reported a 10% rate of infection, 8.6% cerebrospinal fluid leak, 4% uncomfortable stimulation, and 3% lead migration. The study did not have a separate control and used the baseline VAS score when the stimulator was turned off as an internal control. The authors have acknowledged the placebo effect as a possible confounding variable to the study. Although, the results are encouraging, large RCTs are needed to make an evidenced-based determination on this emerging technology.

High Frequency Stimulation

High frequency spinal cord stimulation (HF-SCS) is heralded as providing analgesia without paresthesia. In HF-SCS, 1 kHz to 10 kHz is delivered instead of 50 – 100 Hz typically given for traditional SCS. HF-SCS with 10 kHz stimulation (HF10 SCS) is currently being used in Europe and Australia. HF10 SCS is also currently undergoing a pivotal RCT in the United States. Percutaneous implantation of the electrodes and placement of the implantable pulse generator is identical to the traditional method. A distinguishing aspect of HF10 SCS is the electrodes are placed using only anatomical landmarks, instead of adjusting based on patient's feedback. The 2 electrodes are staggered to facilitate contiguous stimulation and maximize coverage (Fig. 4). For the patient having back and/or leg pain, the tip of the first electrode is placed at T8 and the second electrode tip is placed at T9 in a staggered fashion to stimulate the dorsal column of T9-T11 (50-52).

Van Buyten and colleagues (51) conducted an open label, prospective, multi-center European obser-

vational study (n = 83) on HF10 SCS. The majority of the participants of this study were patients with FBSS with predominantly low back pain. At the 6 month follow-up, 75% of the patients implanted with HF-SCS reported 50% back pain and this was achieved without evoking paresthesia. Furthermore, mean VAS for back pain improved from 8.4 to 2.7 and mean VAS for leg pain improved from 5.4 to 1.4 at the 6 month follow-up. Adverse events were reported in 46% of patients with pocket pain (31% of events) and lead migration (22% of events) being the most common (51). At 24 months, 60% of the implanted patients continued to have at least 50% back pain relief and 71% continued to have at least 50% leg pain relief. There was also significant improvement in Oswestry Disability Index score and sleep disturbances. There was a 57% reduction in opioid use from baseline at the 24 month follow-up. Of the patients implanted with HF10 SCS, 81% of the patients were satisfied or very satisfied and 88% would recommend it to others with similar pain. Adverse events included 8.4% pocket pain, 6% wound infection, 4.8% lead migration, 2.4% loss of therapy effect, 1.2% suboptimal lead placement, and 1.2% skin erosion (53).

The trial did not mention whether analgesia changed with body position. Two weaknesses to this study were that it was an open label trial and it did not have a separate control, again not adequately addressing the placebo effect as a confounding variable.

Perruchoud and colleagues (54) studied 5 kHz stimulation (HF5 SCS) through a randomized, double blinded control trial (n = 33) on patients with chronic back and leg pain. The selected patients had been using low frequency traditional SCS, and the 5 kHz frequency programming was done activating contacts selected from paresthesia mapping. Sham control (no stimulation after achieving paresthesia-free stimulation) was the comparator. After 2 weeks stimulation, HF5 SCS and sham reported no statistical difference in global impression of change, VAS, and EQ-5D quality of life scales (54).

Discussion

The gate control theory may have been the inspiration for SCS in pain control. However, it is inadequate to explain the full complexity of SCS in neuromodulation. More specifically, the gate control theory cannot account for why neuropathic pain is targeted, but nociceptive pain is largely spared (2). Furthermore, it cannot explain how stimulating beyond physiologic levels, as in HF-SCS, produces paresthesia-free analgesia. A possible adjunct theory to the gate control theory is the effect of SCS on wide dynamic range (WDR) neurons. Increased sensitization of WDR neurons in the dorsal horn of the spinal cord is believed to contribute to allodynia and neuropathic pain. In animal models, SCS has been shown to inhibit the WDR cell activity and correlate with decreased hypersensitivity, which would be analogous to allodynia in pain patients (25,55). Furthermore, SCS at the 50 Hz frequency was found to inhibit windup of WDR neurons in rats (13). However, in the same study, HF-SCS (1 Hz) did not inhibit windup of WDR in rats. SCS has also been shown to suppress the sympathetic system in rats and subsequently causes vasodilation (25). This may explain the benefits of SCS in CRPS, refractory angina pectoris, and critical limb ischemia.

Despite the lack of a comprehensive mechanism, SCS demonstrates clinical utility in several pain syndromes refractory to conservative management. Pain from FBSS appears to have the strongest support for the use of SCS. SCS was found to be superior to CMM and reoperation (14,15). Furthermore, SCS was reported to be cost effective, although the overall cost for SCS was higher versus CMM alone (17-19). SCS appears to favor leg pain relief and axial low back pain appears to be more difficult to treat (20).

In observational studies, paddle leads have been reported to have around a 70% relief of low back pain (21,22). However, the benefits of paddle lead are tempered by the more invasive nature of implantation versus the percutaneous leads. To offer the benefits of paddle leads, but allow for a less invasive nature of percutaneous leads, a percutaneously implanted hybrid paddle lead was developed. De Vos and colleagues reported an open label, observational study of hybrid lead in patients with FBSS where 51% of patients reported low back pain relief and 71% reported leg pain relief by the one year follow-up (44). Baseline VAS score was used as an internal control for this study and the study did not adequately address the placebo effect as a confounding variable.

Several observational studies demonstrated that PNfS when used as either a stand-alone therapy or as an adjunct to SCS decreased axial low back pain (45-48). These observational studies used the baseline VAS as the internal control, adding the possibility of the placebo effect being a confounding variable. For this reason, large RCTs are needed to strengthen the evidence-based support for PNfS as either a stand-alone or adjunct therapy for axial low back pain. The

larger area of analgesia provided by PNfS may be due to inter-lead stimulation ("cross-talk") between the 2 separate subcutaneous leads as demonstrated in cadavers by Falco and colleagues (45). The mechanism for PNfS is unknown, but is speculated to be similar to SCS.

Nerve root stimulation and dorsal root ganglion stimulation are other techniques that some pain physicians have employed to address axial low back pain. Liem and colleagues in their multi-center, prospective, open-label, observational study reported 50% reduction of back, leg, and foot pain in 57%, 70%, and 89% of patients, respectively (43). However, the study used the baseline VAS when the stimulator was turned off as an internal control, which brings up the placebo effect as a possible confounding variable to the study. Although, the results are encouraging, the literature is still lacking large RCTs that are needed for evidence-based support for this emerging technology.

HF-SCS in particular is intriguing due to its claim to provide paresthesia-free analgesia; however, current studies provide mixed results. In the larger observational study (n = 83) using HF10 SCS (10 kHz stimulation), favorable outcomes were reported at the 6 week follow-up (51). These favorable outcomes were sustained at the 24 month follow-up (53). However, without a separate comparator, the placebo effect could not be discounted (51,53). In the smaller randomized, double blinded study (n = 40) by Perruchoud and colleagues (54), no difference was reported between HF5 SCS (5 kHz stimulation) and sham control after 2 weeks of stimulation. Sham control (no stimulation after achieving paresthesia-free stimulation) was the comparator. Assessing the results from the 2 studies (HF10 SCS and HF5 SCS), it is possible that different frequencies may have different effects. Furthermore, the study using HF10 SCS looked at the 6 month and 24 month follow-ups, while the HF5 SCS study looked at the 2 week follow-up. This further makes comparisons between the 2 studies challenging. HF10 SCS is in phase III trials in the United States and a multi-center, prospective, RCT is underway and the results may shed further light on the future of paresthesia-free, high frequency analgesia.

Foot pain may be another area that may be difficult to cover with traditional SCS. A technique has been reported of threading the electrode in a retrograde fashion to address foot pain (10). Dorsal root stimulation is also being investigated as a potential modality, with some encouraging results (43). However, the study was an open label observational study with only an internal control that inadequately addresses the placebo effect. RCTs are needed before evidence-based recommendations can be given.

SCS has demonstrated pain relief for patients with CRPS; however, the benefits appear to wane by the 3 year follow-up. Some have criticized the Kemler study that reported these results as being underpowered and lacking sufficient sample size to base clinical recommendations (56). A retrospective outcome study (n = 18) by Sears and colleagues (57) reported better results with 50% or greater pain relief in 50% of the patients at a mean follow-up of 4.4 years. Ultimately, a higher powered RCT may be needed to resolve the controversy. However, Kemler did report that 95% of the patients implanted with a SCS reported that they would undergo the treatment again (28). Long-term cost analysis studies have reported that SCS was cost effective for CRPS, but the overall cost was more than CMM alone (19,29).

Critical limb ischemia appears to have mixed results for pain relief and limb salvage, however a meta-analysis of several RCTs demonstrated clear benefit for SCS in limb salvage (35). SCS was reported to be superior to conservative management for refractory angina pectoris, but equivocal to CABG (37-39). Kumar and colleagues reported that although SCS had a higher overall cost versus CMM, it was cost effective in the treatment of both critical limb ischemia and refractory angina pectoris over a 20 year period (19).

Careful patient selection is paramount to ensure a high probability of success with SCS. Poor patient selection and indiscriminate use of SCS for a variety of pain conditions were attributed to low efficacy rates of < 25% in early SCS studies (41). However, more recent RCTs have demonstrated that with careful patient selection, SCS can be clinically efficacious and cost effective in FBSS, CRPS, refractory angina, and critical limb ischemia (14,15,19,26,30,33,35,37-39,58). The disciplined pain physician generally selects patients that first failed conservative treatment and have the patient undergo psychological evaluation prior to performing a SCS trial. The psychological evaluation is to assess a patient's understanding of the procedure, gauge expectations of the patient, and to document the absence of malingering, somatoform disorders, severe mood disorder, active substance abuse, psychosis, and major personality disorders (59). Patients that report at least 50% pain relief with the SCS trial move forward with a permanent SCS implantation.

Conclusions

Even in the absence of a unifying mechanism, the technology and the complexity in which SCS is being utilized is growing. There are several promising studies on the horizon that may open the next chapter in neuromodulation. However, there are also some lingering questions that remain. SCS is considered a long-term pain therapy, however, RCTs reporting long-term results of SCS are currently lacking. In addition, several open label studies on hybrid leads, peripheral nerve field stimulation, dorsal root ganglion stimulation, and high frequency stimulation show some promising results. However, future studies should place more emphasis on addressing the placebo effect. Avoiding internal controls and having a separate comparator would be one possible solution. Randomization would also decrease the risk of bias, thereby increasing the strength of the studies. In the end, evidence-based medicine is driven by high quality RCTs that validate the current and future use of these emerging technologies. This is crucial in continuing the transformation from the art of medicine to the state of the art.

References

1. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965; 150:971-979.
2. Epstein LJ, Palmieri M. Managing chronic pain with spinal cord stimulation. *Mt Sinai J Med* 2012; 79:123-132.
3. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. Cochrane Database Syst Rev 2004; 3:CD003783.
4. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science* 1967; 155:108-109.
5. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns. Preliminary clinical report. *Anesth Analg* 1967; 46:489-491.
6. Villavicencio AT, Leveque JC, Rubin L, Bulsara K, Gorecki JP. Laminectomy versus percutaneous electrode placement for spinal cord stimulation. *Neurosurgery* 2000; 46:399-405; discussion 405-396.
7. Babu R, Hazzard MA, Huang KT, Ugiliweneza B, Patil CG, Boakye M, Lad SP. Outcomes of percutaneous and paddle lead implantation for spinal cord stimulation. A comparative analysis of complications, reoperation rates, and healthcare costs. *Neuromodulation* 2013; 16: 418-426:
8. Mekhail NA, Cheng J, Narouze S, Kapural L, Mekhail MN, Deer T. Clinical applications of neurostimulation. Forty years later. *Pain Pract* 2010; 10;103-112.
9. Falowski S, Celii A, Sharan A. Spinal cord stimulation. An update. *Neurotherapeutics* 2008; 5:86-99.
10. de Leon-Casasola OA. Spinal cord and peripheral nerve stimulation techniques for neuropathic pain. *J Pain Symptom Manage* 2009; 38:S28-38.
11. Mazloomdoost D, Perez-Toro, MR, Burton, AW. Spinal cord stimulation. In: *Essentials of Pain Medicine*. Third Ed. Benzon H, Raja, SN, Fishman, SM, Liu, S, (eds). Saunders. Philadelphia, PA 2011, 439-447.
12. Gao J, Wu M, Li L, Qin C, Farber JP, Linderoth B, Foreman RD. Effects of spinal cord stimulation with "standard clinical" and higher frequencies on peripheral blood flow in rats. *Brain Res* 2010; 1313:53-61.
13. Shechter R, Yang F, Xu Q, Cheong YK, He SQ, Sdrulla A, Carteret AF, Wacnik PW, Dong X, Meyer RA, Raja SN, Guan Y. Conventional and Kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. *Anesthesiology* 2013; 119:422-432.
14. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain. A randomized, controlled trial. *Neurosurgery* 2005; 56:98-106; discussion 106-107.
15. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. Spinal cord stimulation versus conventional medical management for neuropathic pain. A multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007; 132:179-188.
16. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained. A 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 2008; 63:762-770; discussion 770.
17. North RB, Kidd D, Shipley J, Taylor RS. Spinal cord stimulation versus reoperation for failed back surgery syndrome. A cost effectiveness and cost utility analysis based on a randomized, controlled trial. *Neurosurgery* 2007; 61:361-368; discussion 368-369.
18. Kumar K, Malik S, Demeria D. Treatment of chronic pain with spinal cord stimulation versus alternative therapies. Cost-effectiveness analysis. *Neurosurgery* 2002; 51:106-115; discussion 115-106.
19. Kumar K, Rizvi S. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. *Pain Med* 2013; 14: 1631-1649.
20. Nizard J, Raoul S, Nguyen JP, Lefaucheur JP. Invasive stimulation therapies for the treatment of refractory pain. *Discov Med* 2012; 14:237-246.
21. Duyvendak W. Spinal cord stimulation with a dual quadripolar surgical lead placed in general anesthesia is effective in treating intractable low back and leg pain. *Neuromodulation* 2007; 10:113-119.
22. Barolat G, Oakley JC, Law JD, North RB, Ketcik B, Sharan A. Epidural spinal cord stimulation with a multiple electrode paddle lead is effective in treating intractable low back pain. *Neuromodulation* 2001; 4:59-66.

23. North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN. Spinal cord stimulation for axial low back pain. a prospective, controlled trial comparing dual with single percutaneous electrodes. *Spine (Phila Pa 1976)* 2005; 30:1412-1418.
24. Goebel A. Complex regional pain syndrome in adults. *Rheumatology* (Oxford) 2011; 50:1739-1750.
25. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. *Int Rev Neurobiol* 2012; 107:87-119.
26. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000; 343:618-624.
27. Kemler MA, De Vet HCW, Barendse GAM, Van den Wildenberg FAJM, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. Two years' follow-up of the randomized controlled trial. Ann Neurol 2004; 55:13-18.
28. Kemler MA, De Vet HCW, Barendse GAM, den Wildenberg FAJM, Kleef M. 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. *Journal of Neurosurgery* 2008; 108:292-298.
29. Kemler MA, Raphael JH, Bentley A, Taylor RS. The cost-effectiveness of spinal cord stimulation for complex regional pain syndrome. *Value Health* 2010; 13:735-742.
30. Jivegard LE, Augustinsson LE, Holm J, Risberg B, Ortenwall P. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia. A prospective randomised controlled study. *Eur J Vasc Endovasc Surg* 1995; 9:421-425.
31. Spincemaille GH, Klomp HM, Steyerberg EW, Habbema JD. Pain and quality of life in patients with critical limb ischaemia. Results of a randomized controlled multicentre study on the effect of spinal cord stimulation. ESES Study Group. *Eur J Pain* 2000; 4:173-184.
32. Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JD, van Urk H. Spinal-cord stimulation in critical limb ischaemia. A randomised trial. ESES Study Group. *Lancet* 1999; 353:1040-1044.
33. Suy R, Gybels J, Wan Damme H, Martin D, van Maele P, Delaporte C (eds). Spinal cord stimulation for ischemic rest pain. The Belgian randomized study. 1994. In: *Spinal cord stimulation: an innovative method in the treatment of PVD*. First Ed. Horsch, S, Claeys, L. (eds). Springer. New York, NY 1994, 197-202.
34. Claeys LG, Horsch S. Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation. *Int Angiol* 1996; 15:344-349.
35. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 2013; 2:CD004001.
36. Klomp HM, Steyerberg EW, van Urk H, Habbema JD. Spinal cord stimulation is not cost-effective for non-surgical management of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2006; 31:500-508.
37. de Jongste MJ, Hautvast RW, Hillege HL, Lie KI. Efficacy of spinal cord stimulation as adjuvant therapy for intractable angina pectoris. A prospective, randomized clinical study. Working Group on Neurocardiology. *J Am Coll Cardiol* 1994; 23:1592-1597.
38. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris. A randomized, controlled efficacy study. *Am Heart J* 1998; 136:1114-1120.
39. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, Norrsell H, Hjalmarsson A. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. The ESBY study. *Circulation* 1998; 97:1157-1163.
40. 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.
41. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain. A 20-year literature review. *J Neurosurg* 2004; 100:254-267.
42. Rosenow JM, Stanton-Hicks M, Rezai AR, Henderson JM. Failure modes of spinal cord stimulation hardware. *J Neurosurg Spine* 2006; 5:183-190.
43. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation* 2013; 16: 471-482.
44. de Vos CC, Dijkstra C, Lenders MW, Holsheimer J. Spinal cord stimulation with hybrid lead relieves pain in low back and legs. *Neuromodulation* 2012; 15:118-123; discussion 123.
45. Falco FJ, Berger J, Vrable A, Onyewu O, Zhu J. Cross talk. A new method for peripheral nerve stimulation. An observational report with cadaveric verification. *Pain Physician* 2009; 12:965-983.
46. Mironer YE, Hutcheson JK, Satterthwaite JR, LaTourette PC. Prospective, two-part study of the interaction between spinal cord stimulation and peripheral nerve field stimulation in patients with low back pain. Development of a new spinal-peripheral neurostimulation method. *Neuromodulation* 2011; 14:151-154; discussion 155.
47. Hamm-Faber TE, Aukes HA, de Loos F, Gultuna I. Subcutaneous stimulation as an additional therapy to spinal cord stimulation for the treatment of lower limb pain and/or back pain. A feasibility study. *Neuromodulation* 2012; 15:108-116; discussion 116-107.
48. McRoberts WP, Wolkowitz R, Meyer DJ, Lipov E, Joshi J, Davis B, Cairns KD, Barolat G. Peripheral nerve field stimulation for the management of localized chronic intractable back pain. Results from a randomized controlled study. *Neuromodulation* 2013; 16: 565-574.
49. Kellner CP, Kellner MA, Winfree CJ. Spinal nerve root stimulation. *Prog Neurol Surg* 2011; 24:180-188.
50. Vallejo R. High-frequency spinal cord stimulation. An emerging treatment option for patients with chronic pain. *Techniques in Regional Anesthesia and Pain Management* 2012; 16:106-112.
51. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients. Results of a prospective multicenter European clinical study. *Neuromodulation* 2013; 16:59-65; discussion 65-56.
52. Tiede J, Brown L, Gekht G, Vallejo R, Yearwood T, Morgan D. Novel spinal cord stimulation parameters in patients with predominant back pain. Neuromodulation 2013; 16: 370-375.
53. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain. 24-month re-

sults of a prospective multicenter study. *Pain Med* 2013; 15:347-354.

54. Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic efficacy of high-frequency spinal cord stimulation. A randomized double-blind placebo-controlled study. *Neuromodulation* 2013; 16:363-369.
55. Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. *Pain* 1999; 79:223-233.
56. Atkinson L, Sundaraj SR, Brooker C, O'Callaghan J, Teddy P, Salmon J, Semple T, Majedi PM. Recommendations for patient selection in spinal cord stimulation. *J Clin Neurosci* 2011; 18:1295-1302.
57. Sears NC, Machado AG, Nagel SJ, Deogaonkar M, Stanton-Hicks M, Rezai AR, Henderson JM. 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; discussion 318.
58. Klomp HM, Spincemaille GH, Steyerberg EW, Berger MY, Habbema JD, van Urk H. Design issues of a randomised controlled clinical trial on spinal cord stimulation in critical limb ischaemia. ESES Study Group. *Eur J Vasc Endovasc Surg* 1995; 10:478-485.
59. Compton AK, Shah B, Hayek SM. Spinal cord stimulation. A review. *Curr Pain Headache Rep* 2012; 16:35-42.