Spinal Cord Stimulation: The Use of Neuromodulation for Treatment of Chronic Pain
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INTRODUCTION

Chronic Pain and the Role of Neuromodulation

Chronic pain, defined as pain persistent for more than 3–6 months, affects 100 million adults in the United States (US) and impacts all dimensions of health-related quality of life (QOL) and healthcare expenditures.1 Low back pain is the leading cause of disability, with healthcare expenditures estimated to be as much as $560–$635 billion, more than the combined spending on heart disease and diabetes.1 Despite lack of consistent evidence, rates of spine surgeries have increased, while other forms of chronic pain management, including narcotics, contribute to both adverse medical side effects and the ongoing opioid epidemic.2

As such, additional treatment options for chronic pain are being studied. One promising option is spinal cord stimulation (SCS), a form of neuromodulation used since the 1960s. Recently, a paradigm shift has occurred, with SCS increasingly accepted as a first-line therapy after noninvasive treatment (physical therapy, medications, etc). SCS reduces pain, decreases use of analgesic medication, and improves function. Level I evidence supports the use of SCS for chronic neuropathic pain from failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and painful diabetic peripheral neuropathy (DPN).3 Recent guidelines suggest that appropriately selected patients who have failed conventional medical management (CMM) for neuropathic pain may benefit from SCS.4

Neuromodulation involves the application of electricity to the central or peripheral nervous systems for therapeutic benefit. The strengths of this approach include reversibility and a low-risk profile. Furthermore, studies demonstrate improved pain relief, health-related QOL, and functional status.5,6 Multiple neuromodulatory techniques exist, including spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), dorsal root ganglion (DRG) stimulation, and deep brain stimulation (DBS). Among these, SCS is most commonly performed in the US, with an estimated 50,000 implants annually, accounting for 70% of all neuromodulation treatments. The valuation of the SCS marketplace was $1.3 billion in 2014.7

Spinal Cord Stimulation and Mechanisms of Action

Spinal cord stimulation (SCS) involves the application of electricity to the spinal dorsal columns, which modulate pain signals relayed by ascending pain pathways to the brain. Although precise mechanisms are complex and not fully understood, the concept derives from the gate control theory, first described by Melzack and Wall.8 This theory describes the presence of a “gate” in the dorsal horn, relaying neuronal signals from sensory afferent fibers to brain centers involved in pain perception. Ab fibers [myelinated] carrying non-nociceptive stimuli and C fibers [non-myelinated] relaying painful stimuli both synapse in the dorsal horn with the spinothalamic tract; the gate theory postulates that stimulating the faster Ab fibers leads to closure of nerve “gates,” blocking the transmission of pain signals by slower C fibers [Figure 1]. This theory provides insight into why non-nociceptive stimuli, such as tapping or massaging a painful area, provides temporary relief.

Figure 1. Gate theory of pain postulates that sending electrical current to the dorsal column leads to stimulation of faster, myelinated Ab fibers carrying non-nociceptive stimuli, resulting in closure of nerve “gates” and blocking slower, non-myelinated C fibers from transmitting pain signals via the spinothalamic tract.
b and C fibers are segregated from afferent pain signals with more tolerable paresthesias in the distribution of the patient’s pain. Recent devices employ higher frequencies, which minimizes paresthesias. Other stimulation paradigms deliver electricity in short bursts, clusters, and via closed-loop feedback.

The exact mechanism for the modulation of neuronal pain in the dorsal columns is probably complex. In animal models, SCS leads to enhancement of inhibitory neurotransmitters such as GABA and the release of acetylcholine, which acts on muscarinic M4 spinal cord receptors involved in analgesia. SCS may also modulate supraspinal pathways to mediate analgesia, as functional MRI demonstrates changes in the thalamus and somatosensory cortex corresponding to altered pain processing.

**Common Indications for Spinal Cord Stimulation**

SCS is approved by the Food and Drug Administration (FDA) for chronic neuropathic pain disorders of the trunk and extremities, including failed back surgery syndrome (FBSS), complex regional pain syndrome, neuropathy, and radiculopathy. SCS is also used for refractory angina pectoris, peripheral limb ischemia, and irritable bowel syndrome.

SCS has been most widely studied in FBSS, which broadly encompasses pain that persists despite spine surgery. Randomized controlled trials (RCTs) have studied the efficacy of SCS, particularly in cases of leg-predominant symptoms. A landmark RCT compared patients undergoing SCS with those who had re-operation of the lumbar spine. Significant pain relief, defined as 50% reduction, was achieved in 39% of the SCS group vs. 12% in the re-operation group ($p<0.01$); in addition, there was an 87% reduction in opiate analgesic use with SCS vs. 58% with re-operation ($p=0.025$). Furthermore, after a 6-month post-operative period, 54% of re-operation patients elected to cross-over and undergo SCS, vs. 26% of SCS patients who crossed over from SCS to re-operation ($p=0.02$). A recent review including 2 RCTs and 9 prospective observational trials demonstrated efficacy of SCS for FBBS, with the pooled 1035 observational patients experiencing between 48–77% treatment efficacy at 1-year follow-up.

Evidence also supports the use of SCS in complex regional pain syndrome (CRPS), which involves pain dysregulation and nerve dysfunction in both the sympathetic and central nervous systems, leading to sensory, vasomotor, and sudomotor changes as well as pain and weakness. Management is difficult and symptom-based, with limited structural pathology to target. A systematic review of SCS in CRPS (1 RCT and 25 observational studies) found that in addition to reducing analgesic use and improving QOL, SCS led to a pooled decrease of 47% on the visual analog pain scale.

Beyond current FDA-approved indications, RCTs have shown that SCS can benefit ischemic vascular disease, including chronic inoperable limb ischemia and treatment refractory angina. The mechanism of action is thought to involve modulation of the sympathetic nervous system, levels of prostaglandin, and nitric oxide production. Compared to CMM, SCS therapy leads to greater pain relief, improved ankle-brachial pressure indices, and higher rates of limb salvage. In patients with treatment refractory angina, no differences were found in exercise function and QOL measures when comparing SCS and coronary artery bypass grafting (CABG), although total mortality was increased in the CABG group at 6-month follow-up. There is also Level I evidence supporting SCS use in peripheral neuropathic pain syndromes, including diabetic and post-chemotherapy neuropathy. Other conditions involving nerve pathology such as post-herpetic neuralgia, post-thoracotomy neuralgia, and phantom-limb pain have been successfully treated with SCS but with less robust evidence.

**Complications of Spinal Cord Stimulation and Patient Selection**

SCS is widely reported to be a safe procedure, owing to its reversibility and minimal invasiveness. Catastrophic surgical complications are rare, with neurologic injury reported as 0.25% in one review of 44,587 cases. Some causes include formation of epidural hematoma (0.19%) and spinal cord injury. SCS has been most widely studied in FBSS, which broadly encompasses pain that persists despite spine surgery. Randomized controlled trials (RCTs) have studied the efficacy of SCS, particularly in cases of leg-predominant symptoms. A landmark RCT compared patients undergoing SCS with those who had re-operation of the lumbar spine. Significant pain relief, defined as 50% reduction, was achieved in 39% of the SCS group vs. 12% in the re-operation group ($p<0.01$); in addition, there was an 87% reduction in opiate analgesic use with SCS vs. 58% with re-operation ($p=0.025$). Furthermore, after a 6-month post-operative period, 54% of re-operation patients elected to cross-over and undergo SCS, vs. 26% of SCS patients who crossed over from SCS to re-operation ($p=0.02$). A recent review including 2 RCTs and 9 prospective observational trials demonstrated efficacy of SCS for FBBS, with the pooled 1035 observational patients experiencing between 48–77% treatment efficacy at 1-year follow-up.

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contusion (0.1%). Minor complications mostly occur within 12 months after implantation and are generally reversible.

The most common mechanical complication is lead migration (14%), which may require revision if it results in loss of targeted stimulation.\textsuperscript{19} Lead migration typically occurs within several days of implantation. Post-operative scarring keeps leads in place longitudinally. Migration is mitigated by appropriately anchoring leads. Recently, a lower incidence of migration is attributed to improvements in lead design and anchoring systems. Hardware malfunction or lead fracture necessitating device removal occurs less frequently (7-10%). Subcutaneous implantation of the SCS impulse generator may lead to incisional or pocket pain (10%).

The most common medical complication is infection (3.8%), which is generally superficial and minimized with pre-operative broad-spectrum antibiotic use. There is no evidence supporting routine post-operative antibiotics.\textsuperscript{10} Other medical complications are less common (2.5%) and include hematoma, seroma, epidural fibrosis, dural puncture, and neurologic injury.

Appropriate patient selection is crucial for reducing SCS complications and treatment failures.\textsuperscript{20} SCS candidates should undergo behavioral assessment before a trial of therapy. Untreated depression, major psychiatric illness, and unrealistic expectations lead to less improvement of pain and disability scores. Obesity, younger age, and male gender also predict early failure.\textsuperscript{21}

**MRI Compatibility and Cost-Effectiveness**

Historically, SCS was not compatible with magnetic resonance imaging (MRI). Recent technological advancements allow use of MRI under specific conditions. Although the initial costs of SCS are high, they are offset by improved QOL measures and decreased use of drug and non-drug therapies over time.\textsuperscript{19} SCS is particularly cost-effective in long-term studies (>6 months) and for back and leg pain refractory to CMM; SCS was shown to be cost-effective as an adjunct to CMM and when compared to re-operation, with >80% greater likelihood of cost-effectiveness versus CMM and re-operation in predictive models.\textsuperscript{22} In FBSS patients, SCS decreased annual healthcare costs by an average of 40% over 9-year follow-up compared to CMM.\textsuperscript{23} Additionally, newer high-frequency stimulators and rechargeable battery systems have led to increased cost-effectiveness.

**Emerging Approaches in Neuromodulation**

Traditionally, SCS stimulates dorsal columns in the 50-100 Hz range, creating perceptible paresthesias in the distribution of the patient’s pain. Recently, the application of sub-threshold high-frequency stimulation (HFS) or burst stimuli has reduced or eliminated paresthesias while providing similar or improved pain relief versus traditional SCS.\textsuperscript{7} HFS was FDA-approved in 2015 for chronic refractory trunk and/ or limb pain. Its unique waveform at 10kHz preferentially blocks large-diameter nerve fibers (responsible for paresthesias) while recruiting smaller and medium fibers (involved in vibration and pressure signaling), resulting in paresthesia-free SCS. Burst stimulation delivers higher-frequency stimulation in closely-spaced bursts, rather than constant lower-frequency tonic stimulation used in traditional SCS, which reduces pulse amplitudes and provides subthreshold stimulation with minimal paresthesia. This approach may improve the tachyphylaxis and physiologic tolerance seen with constant stimulation.

Neuromodulation techniques targeting the dorsal root ganglion (DRG) and peripheral nervous system (PNS) allow for greater anatomic specificity. Stimulation of the DRG, which is located at the transition between the spinal cord and peripheral nervous system and contains the primary sensory neuron cell body, can block or reduce painful peripheral signals to the CNS. Anatomically, the vertebral forams housing the DRG form an ideal enclosure for leads, reducing migration and positional issues seen with SCS ([Figure 3](#Figure3)). Minimal cerebrospinal fluid at the forams also allows for lower energy requirements, improving battery longevity. Targeting the DRG of a specific dermatome provides focal pain relief, particularly for refractory CRPS and focal neuralgias that are less effectively treated by traditional SCS, such as the groin and foot.\textsuperscript{20}

**Figure 3.** AP fluoroscopic image of bilateral dorsal root ganglion stimulation, with leads in place at L1.
CONCLUSIONS

Growing Level I evidence supports the use of SCS as a safe and cost-effective therapeutic option for numerous chronic pain conditions. SCS is a minimally-invasive procedure that may be implemented earlier in the treatment continuum to reduce pain and disability, particularly in cases of refractory neuropathic pain complicated by analgesic side effects, drug tolerance, or the need for re-operation. Advancements such as high-frequency, burst, and dorsal root ganglion stimulation have further improved pain relief and patient satisfaction, while mitigating risk and improving outcomes.

References


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