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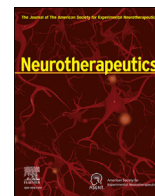
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## Review

## Disease applications of spinal cord stimulation: Chronic nonmalignant pain

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## ABSTRACT

Neuropathic pain is a chronic condition representing a significant burden for society.

It is estimated 1 out of 10 people over the age of 30 that in the US have been diagnosed with neuropathic pain. Most of the available treatments for neuropathic pain have moderate efficacy over time which limit their use; therefore, other therapeutic approaches are needed for patients. Spinal cord stimulation is an established and cost-effective modality for treating severe chronic pain. In this article we will review the current approved indications for the use of spinal cord stimulation in the US and the novel therapeutic options which are now available using this therapy.

## Introduction

Pain is commonly categorized as nociceptive (from tissue injury) or neuropathic (from nerve injury), but there is considerable overlap in the different types of pain mechanisms within and between patients, and more recently authors are defining pain as a continuum [1]. The treatment of chronic neuropathic pain with spinal cord stimulation (SCS) was initially based on the gate control theory [2]. SCS is the most frequently used neuromodulation intervention and its use has increased exponentially in the past 10 years. It is estimated that approximately 40,000 new devices are implanted each year [3], of which roughly half are in the USA alone. There has been continuous improvement in the technology along with an expansion in the approved indications. This systematic narrative reviews the current FDA-approved indications for SCS and provides an update on the long term outcomes from large case series.

## Methods

We performed a literature review on bibliographic resources, including EMBASE, PubMed Cochrane Database of Systemic Reviews from literature published from January 2000 to 2023 to identify studies and treatments using SCS to treat chronic pain. Search words included SCS, chronic pain treatment, failed back surgery syndrome, complex regional pain syndrome, peripheral neuropathy, peripheral vascular

disease. The search was limited to the English language, excluding case reports, reviews or preclinical work, limiting the results to trials and original studies only. Information on emerging technologies (e.g. trial using devices in experimental stage) was captured separately, as they did not meet the inclusion criteria. A total of 1000 citations were identified. After combining the results, removing duplicates and selections based on the title and abstract, 39 full-text studies ultimately remained and were included in the review. Case vignettes in each different pain condition are provided.

## Results

*Low back pain and persistent spinal pain syndrome (PSPS): Case vignette and literature review*

We present a case of an 81-year-old male suffering from post-laminectomy syndrome, status post L3 to pelvis fusion resulting in refractory, disabling pain. Patient experienced bilateral back and lower extremity pain on going for a 5-year period exacerbated by bending, twisting and lifting and accompanied by weakness, numbness and tingling sensations significantly impacting his ability to perform daily activities and engage in personal hobbies, as well as maintain grooming and hygiene. Patient had previously undergone both physical therapy and epidural injections but reported no relief with physical therapy and

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only temporary relief with injections. On physical examination, patient exhibited subjective sensory deficits in the L4 and L5 dermatomes. Given limited response to conservative management and symptoms suggestive of neuropathic pain, the patient was deemed an appropriate candidate for spinal cord stimulator trial.

Percutaneous spinal cord stimulator leads were placed intra-operatively by entering the epidural space at T12-L1 interspace using right paramedian approach. Electrodes were advanced in cephalad fashion to T8 level bilaterally. Using a combination of electrodes and polarities, successful stimulation of the patient's bilateral lower back and bilateral leg pain was obtained. On follow up visit patient endorsed 95 % improvement in both legs and back pain. Patient endorsed reduction in analgesic medication use, as well as improved sleep and ambulation.

Given significant improvement with trial, the patient was scheduled for permanent spinal cord stimulator placement. On subsequent follow up visits, the patient endorsed 80 % improvement in bilateral leg and back pain. Patient reported further decrease in analgesic medication requirement and sustained improvements in both ambulation and sleep, as well as return to activities of daily living. This case highlights the successful utilization of spinal cord stimulation as an effective treatment modality for patients suffering from post-laminectomy syndrome refractory to conservative management.

Chronic back pain is one of the most common health problems and causes significant burden on individuals and society. Chronic back pain is generally felt at the lower back, between the lower rib and gluteal fold, for which no specific neural compression or insult can be designated [4]. Persistent Spinal Pain Syndrome (PSPS), previously called FBSS, or post-laminectomy syndrome is a term used to define an unsatisfactory outcome of a patient who underwent spinal surgery, irrespective of type or intervention area, with persistent pain in the lumbosacral region with or without it radiating to the leg.

In 2007 Kumar et al. published the results of an international, multicenter, nonblinded, randomized controlled trial comparing outcomes of traditional low-frequency 49 Hz ( $\pm 16.4$ ) SCS plus conservative management versus conservative management alone in adults diagnosed with failed back surgery syndrome (PSPS) (PROCESS trial) [5]. Their primary outcome was the proportion of patients achieving 50 % or more pain relief in the legs, while secondary outcomes were improvement in back and leg pain, health-related quality of life, functional capacity, use of pain medication and non-drug pain treatment, level of patient satisfaction, and incidence of complications and adverse effects. Included patients were followed for 1 year after randomization to implantation ( $n = 52$ ) or conservative management ( $n = 48$ ) which included epidural injections, physical therapy and opioid analgesia. In the intention-to-treat analysis at 6 months, 24 patients in the SCS group (48 %) and 4 patients in the conservative group (9 %) ( $p < 0.001$ ) achieved the primary outcome. The within-SCS group mean back VAS decreased from 54.5 ( $\pm 24.3$ ) at baseline to 40.6 ( $\pm 24.9$ ), and the between-group mean difference was  $-11.0$  (99 % confidence interval [CI] =  $-25$  to  $3.0$ ), with a group mean Oswestry Disability Index (ODI) difference of  $-11.2$  (99 % CI =  $-21.2$  to  $-1.3$ ). By 12 months,  $n = 30$  participants in the conservative group crossed over to the SCS treatment arm. The authors were able to perform a post-hoc analysis considering crossovers treatment failures according to their initial randomization order and showed that  $n = 17$  patients in the SCS, but only  $n = 3$  in the conservative group achieved the primary outcome (leg pain reduction).

Kapural et al. [6] published the results of a multicenter, nonblinded RCT evaluating the outcomes of 10-kHz SCS compared with traditional low-frequency SCS in adults suffering from refractory chronic low back and leg pain. The primary outcome was  $\geq 50$  % VAS reduction, secondary outcomes included ODI and patient satisfaction. The authors followed one hundred seventy-one subjects ( $n = 90$  HF10 therapy,  $n = 81$  traditional SCS) for 24 months after implantation. At 12 months, 79 % (95 % CI = 70 %–87 %) of 10-kHz compared with 51 % (95 % CI = 40 %–62 %) of the low-frequency SCS group achieved  $\geq 50$  % back VAS reduction. These outcomes were maintained at 24 months, with 77 % of the 10-kHz

group compared with 49 % of the control group continuing to report  $> 50$  % back pain reduction, a proportion ratio (relative success) of 1.5 (95 % CI = 1.2 to 2.0). Also leg pain decreased in a similar trend at 24 months timepoints (reduction with HF10 therapy 65.1 %  $\pm$  36.0 % compared to traditional SCS 46.0 %  $\pm$  40.4 %,  $P < 0.001$  for non-inferiority and  $P = 0.002$  for superiority).

North et al. [7] reported the outcomes of their RCT where they compared SCS to repeated spine surgery in PSPS patients and found that, at a mean follow-up of three years, SCS patients were more successful in terms of pain relief (47 % had  $\geq 50$  % pain relief vs 12 % in the reoperation group;  $p < 0.01$ ) and the use of narcotics ( $p < 0.025$ ) and were less likely to cross over to the other treatment group ( $p = 0.02$ ).

North et al. [8] reported on their randomized,  $2 \times 2$  crossover study of low frequency supra-perception SCS vs. sub-perception SCS at 1 kHz frequency. They followed  $n = 22$  patients for 7 weeks total (three weeks of treatment, one week wash off, and another three weeks of treatment). The primary outcome was the numeric pain rating scale (NPRS) score, with ODI and Patient's Global Impression of Change (PGIC) as secondary outcome measures. They reported how  $n = 21$  subjects (95 %) had improvements in their NPRS scores, but the NPRS scores were significantly lower with sub-perception stimulation compared to paresthesia-based stimulation ( $p < 0.01$ ,  $p < 0.05$ , and  $p < 0.05$ , respectively).

Zucco et al. [9] reported the results of their multicenter longitudinal study (PRECISE study) on a total of  $n = 63$  patients implanted with SCS for PSPS with predominantly leg(s) pain which were followed up for 24 months. The mean NRS score decreased from 7.56 to 5.11 after 24 months post-SCS ( $t = 9.0026$ ,  $p < 0.0001$ ), with the highest drop in the first 6 months after the implant. The authors noted also a significant decrease in the mean ODI ( $t = 7.9845$ ,  $p < 0.0001$ ) from 61.6 at baseline to 42.4 after 24 months.

De Andres et al. [10] conducted a RCT including  $n = 55$  patients with PSPS which were randomized to conventional versus high frequency (10 kHz) stimulation and followed for 12 months. Primary outcome was reduction in numerical rating scale (NRS) and secondary outcomes included ODI and PD-Q. The authors reported an overall reduction in the average NRS scores which was not significantly different for the two groups, and they concluded that this result may have been partially linked to methodological issues.

Veizi et al. [11] published the results of a multicenter, prospective observational study with a retrospective propensity-matched cohort analysis evaluating the outcomes of both traditional and "anatomically-guided three dimensional (3D) neural targeting" SCS in adult patients suffering from chronic axial low back and leg pain. This technology (Illumina 3D) used a combination of independent current control with up to 32 contacts and a three-dimensional programming algorithm based on a realistic model of electrical conductivity of spinal column structures (CSF, electrodes,...). A total of  $n = 169$  patients were implanted and had follow-up data available at 24 months, including patients with only chronic axial low back pain (42 %), with both leg and low back pain (38 %) and patients with only leg pain (21 %). Primary diagnosis was PSPS although a minority of patients had CRPS or neuropathy as their primary. The main outcome was the proportion of patients with  $\geq 50$  % improvement on the NRS at 24 months. At 24 months, 71 % (99 % CI = 59 %–82 %) of 3D neural targeted SCS recipients reported a  $\geq 50$  % NRS improvement in axial LBP compared with 41 % (99 % CI = 29 %–54 %) in the traditional low-frequency SCS group, with similar amounts of relief in all subgroups regardless of pain location.

Russo et al. [12] published a prospective cohort study evaluating outcomes of closed-loop, feedback-controlled, paresthesia-based SCS in  $n = 36$  individuals suffering from chronic pain of the back and/or legs due to diagnoses including PSPS, radiculopathy, lumbar spondylosis, neuropathic pain, and discogenic back pain. The patients were implanted with a novel closed-loop system comprising two 12-contact percutaneous leads and an integrated feedback control system based on evoked compound action potentials to maintain stimulation within an individualized therapeutic range. The primary outcome was the responder rate ( $\geq 50$  %

pain reduction on the VAS) at six months; additional outcomes measured included quality of life (EQ-5D-DL), function (ODI), and sleep quality (PSQI). After six months 86 % (95 % CI = 67 %–96 %) of respondents reported ≥50 % back pain relief, and 70 % (95 % CI = 41 %–78 %) reported ≥80 % improvement.

Deer et al. [13] reported the results of their randomized, controlled, unblinded trial (SUNBURST study) which included a 24-week cross-over phase during which subjects used one stimulation mode (burst vs tonic) for 12 weeks and then crossed over to the other for the remaining 12 weeks, followed by an open-label phase during which study participants could use either waveform. Most subjects were diagnosed with either PSPS (59/141, 41.8 %) or radiculopathy (52/141, 36.9 %) and were followed up to 24 weeks. The primary outcome was 30 % or greater change from baseline in overall VAS score, whereas the secondary outcome was the result of the superiority test to demonstrate that the change in VAS score with burst stimulation is superior to that of using tonic stimulation. At 24 weeks significantly more subjects preferred burst stimulation over tonic stimulation (70.8 % vs. 18.8 %,  $p < 0.001$ , and of the  $n = 88$  patients who completed the 1 year visit still 68.2 % (60/88) preferred burst stimulation.

Al-Kaisy et al. [14] published a multicenter single-group prospective cohort study evaluating the outcomes of 10-kHz SCS in adults suffering from chronic low back and leg pain. A total of 65 patients (80 % diagnosed with PSPS) were implanted and followed up to 24 months. Primary outcomes included VAS ratings for back and leg pain, sleep disturbance as assessed by the subjective number of awakenings per night, Oswestry Disability Index (ODI). At 24 months, 60 % of the implanted patients had at least 50 % back pain relief and 71 % had at

least 50 % leg pain relief ( $P < 0.001$  when 24 months VAS was compared to baseline).

Mekhail et al. [15] reported the results of their multicenter RCT trial using the Evoke® physiologic closed-loop SCS system in patients with chronic, intractable pain of the trunk and/or limbs. This was the first double-blind randomized-controlled trial to compare evoked compound action potentials (ECAP)-controlled closed-loop spinal cord stimulation with fixed-output, open-loop spinal cord stimulation and to measure spinal cord activation in both groups. The most frequent pain etiologies in both groups were radiculopathy, persistent spinal pain syndrome type 2 and degenerative disc disease. The study randomized a total of  $n = 134$  patients (67 to each group, conventional vs closed loop SCS), and the primary outcome was the proportion of patients with a reduction of 50 % or more in overall back and leg pain, with no increase in baseline pain medications. At 3 months, a greater proportion of patients in the closed-loop group than in the open-loop group had achieved the primary outcome (51 [82.3 %] of 62 patients vs 38 [60.3 %] of 63 patients; difference 21.9 %, 95 % CI 6.6–37.3;

$p = 0.0052$ ). This trend was maintained at the 12 months follow up (49 [83.1 %] of 59 patients vs 36 [61.0 %] of 59 patients; difference 22.0 %, 6.3–37.7;  $p = 0.0060$ ). The authors later reported the results of the 24 months follow up [16] which again confirmed that significantly more closed-loop than open-loop patients were responders (50 % reduction) in overall pain (53 of 67 [79.1 %] in the closed-loop group; 36 of 67 [53.7 %] in the open-loop group; difference, 25.4 % [95 % CI, 10.0%–40.8 %];  $P = 0.001$ ).

A total of 11 out of 600 existing studies were ultimately included in this section.

Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
Kumar et al. 2007	Low-frequency SCS + conventional therapy vs conventional therapy alone	Synergy system Medtronic	mean (standard deviation) settings were an amplitude of 3.7 V (2.0), a pulse width of 350 $\mu$ s (95.5) and a rate of 49 Hz (16.4)	h/o previous spine surgery, neuropathic pain of radicular origin exceeding back pain for at least 6 months N = 135	Medtronic, Inc.	multicenter, nonblinded, randomized controlled trial 12 months
Kapur et al., 2016	10-kHz SCS vs traditional low-frequency SCS	Nevro Senza system	10 kHz vs tonic SCS 39.2 $\pm$ 15.0 Hz	h/o chronic, intractable pain of the trunk and/or limbs, refractory to conservative therapy for a minimum of 3 months N = 171	Nevro Corp., Inc.	multicenter, nonblinded RCT 24 months
North et al. 2005	SCS Vs repeated spine surgery in PSPS patients	Medtronic	Not reported	Patients with surgically remediable nerve root compression and concordant complaints of persistent or recurrent radicular pain N = 45	Medtronic, Inc.	RCT, nonblinded 24 months
North et al. , 2016	Two groups, patients randomized to either receive 1 kHz subperception stimulation or paresthesia-based stimulation	Boston Scientific Precision Plus or Precision Spectra SCS system	Not reported	Precision Plus or Precision Spectra SCS system implanted for chronic pain (PSPS but also low back pain), and a baseline numeric pain rating scale (NPRS) score $\geq 5$ N = 22	Boston Scientific, Inc.	randomized, 2 $\times$ 2 crossover study three weeks of each stimulation paradigm, with a 7–10 day washout period between treatments
Zucco et al. , 2015	One group only	Medtronic hardware (not rechargeable)	Various settings (not available)	Patients with PSPS pain that radiates to lower limbs, mono or	Partly Medtronic, Inc. (technical support)	multicenter longitudinal study 24 months

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Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
De Andres et al., 2017	Conventional vs high frequency SCS	Medtronic Surescan (Conventional SCS) and Nevro Senza (HF SCS)	HF group: frequency, 2 Hz to 10,000 Hz; pulse width, 20 µs to 1 ms; amplitude, 0 mA–15 mA CF group: frequency 40Hz, pulse width 300–450 µs, amplitude 4.5–7V	bilaterally, NRS >5 N = 80 Patients with PSPS, pain of the trunk and/or limbs for at least six months, NRS >5. N = 55	Authors' departmental funds	Prospective blind RCT 12 months
Veizi et al., 2017	Traditional SCS vs '3D Neural targeting' SCS	Boston Scientific Precision Spectra (3D Neural targeting) and Precision (conventional SCS) System	Variety of settings, amplitude 5.64 (±3.43) mA, pulse width 392 (±232) µsec, frequency 59.8 (±109.3) Hz	Patients with mainly PSPS and related radiculopathy, but also CRPS (5 %) N = 213	Boston Scientific, Inc.	multicenter, open-label observational study with retrospective cohort 24 months
Russo et al., 2018	One group only	Evoke SCS system, Saluda Medical (closed-loop rechargeable implantable pulse generator)	Variety of settings based on patient's specific evoked compound action potential (ECAP)	Patients with chronic pain of the back and/or legs for at least 3 months, PSPS with or without radiculopathy, or other discogenic pain N = 51	Saluda Medical, Inc.	prospective cohort study 6 months
Deer et al., 2018	Tonic vs burst stimulation	Prodigy SCS IPG, Abbott	Tonic: pulse width range of 100–500 µsec, frequencies between 30 and 100 Hz, variable amplitude. Burst: 500 Hz stimulation was delivered in groups of five pulses with a 1 msec pulse width, with the five pulses repeated at a frequency of 40 Hz	Patients with chronic intractable pain of the trunk and/or limbs (78 % between PSPS and other radiculopathy) N = 100	Institutional funds	randomized, controlled, unblinded trial 6 months
Al-Kaisy et al., 2018	Tonic vs different subperception SCS parameters	Medtronic RestoreSensor IPG (AdaptiveStim feature remained off during the crossover phase of the study)	1200 Hz @ 180 µsec, 3030 Hz @ 60 µsec, and 5882 Hz @ 30 µsec. Variable amplitude (individual subthreshold)	Patients with PSPS, VAS score >6 cm N = 24	Institutional funds	Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial 12 months
Mekhail et al., 2020, 2022, 2023	Closed-loop SCS based on ECAPs vs conventional 'open-loop' SCS	Evoke System, Saluda Medical used for both groups	Parameters were consistent within groups. At 3 months the mean used frequency was 42.0 Hz [range: 10.0–80.0] and mean pulse width was 313.9 µs [range: 150.0–500.0], variable amplitude	Patients with chronic, intractable pain of the trunk and/or limbs N = 134	Saluda Medical, Inc.	Prospective, multicenter, participant, investigator, and outcome assessor-blind parallel arm RCT 3 year follow up 12 months

### SCS for peripheral neuropathy: case vignette and literature review

A 53-year-old female patient with a history of hypertension, hyperlipidemia, obesity, and diabetes mellitus presented to the clinic with a 4-year history of bilateral hand pain in the C5, C6, C7, and occasionally T1 distribution. When asked to describe the character of the pain, the patient stated it was sharp, achy, and burning in nature. The pain worsened in the morning and was exacerbated by cold weather, touch, and hand use. The patient had undergone an extensive workup, including consultations with rheumatology, neurology, hand ultrasound, MRI imaging, EMG studies, and skin biopsy. Hand ultrasound was negative for inflammatory arthritis, rheumatoid arthritis, and synovitis. EMG studies showed no evidence of compressive neuropathy but indicated a risk for mono-neuropathy. Cervical MRI was negative for herniated disks or foraminal

stenosis to explain the patient's symptoms. Various treatment modalities, such as celecoxib, gabapentin, hand injections, dry needling, physical therapy, and carpal tunnel release surgery were attempted. Following carpal tunnel release surgery, the patient expressed improved right-hand pain but unchanged pain in her left hand. A skin biopsy on the left hand was then performed and revealed idiopathic, non-length-dependent small fiber neuropathy.

To address the persistent neuropathic pain in her left hand, the patient underwent a trial of percutaneous spinal cord stimulation with the lead tip placed at C2. There were no complications during surgery, but X-ray imaging demonstrated lead migration to the right on the follow-up visit. Unsurprisingly, the patient reported no improvement in left-hand pain, presumed to result from lead migration. A second trial was conducted with two spinal cord stimulator leads placed at the level of C2,

and this time, a cervical collar was used postoperatively to limit cervical motion and reduce the risk of lead migration. The patient reported a 70 % improvement in neuropathic pain, enhanced ambulation, sleep quality, activities of daily living, and overall quality of life. As a result, the patient underwent permanent placement of a spinal cord stimulator paddle at the level of C2. Following the surgery, the patient experienced a 50 % reduction in pain in her left hand.

This case highlights the challenging management of peripheral neuropathy and the potential role of spinal cord stimulators in providing relief for chronic neuropathic pain when other treatments have been unsuccessful. Spinal cord stimulation offers a promising option for patients with peripheral neuropathy who have exhausted conventional treatments and can significantly improve their quality of life.

Peripheral neuropathies are divided into mononeuropathies, multifocal neuropathies, and polyneuropathies. Symptoms usually include numbness and paresthesia, and they are often accompanied by weakness and pain. Diabetes is the most common cause of peripheral neuropathy and is associated with both mono- and polyneuropathies. Up to 50 % of persons with diabetes will ultimately develop polyneuropathy during the course of the disease [17], and the prevalence of diabetic polyneuropathy in individuals over 65 years of age is 3 %. DN involves distal autonomic and sensory dysfunction, predominantly affecting the feet, but often progressing proximally and/or involving the upper limbs as time passes. Neuromodulation has been used mainly for chronic polyneuropathies but the data on those are scarce.

Plujims et al. [18] presented their study results on n = 15 patients implanted with SCS for diabetic neuropathy. Primary outcome was a reduction in the NRS scale diary, while secondary outcomes included EQ-5D questionnaire and sleep quality. Patients were followed up to 12 months after surgery, and pain decreased 50 % from baseline in >60 % of the patients during the day (slight less reduction in median pain at night, but still significant).

De Vos et al. [19] reported the results of their open randomized parallel-group design trial of SCS in patients with DN which were randomized to either receive SCS (n = 40) or optimal medical treatment (n = 20) in Europe. Patients with PAD-related pain were excluded, as well as patients experiencing upper extremities neuropathy. The study's primary outcome parameter was the percentage of patients with more than 50 % pain reduction at 6 months of treatment in each study group. Secondary outcome parameters were average reduction in pain intensity, pain characteristics and quality of life. After 6 months, 25 patients in the SCS had over 50 % pain reduction while in the control group the pain rating did not change (p < 0.001).

The same group [20] published about their prospective trial on n = 48 patients (12 with diabetic neuropathy) with conventional (tonic) stimulation which were switched to burst protocol for 2 weeks. Tonic

stimulation caused an average reduction of 37 % in VAS score in comparison with the baseline situation. Burst stimulation caused a 25 % further pain reduction compared with tonic stimulation which resulted in an average reduction of 52 % in VAS score in comparison with the baseline, and the improvement was higher in the neuropathy group compared to the PSPS group (p < 0.05).

Petersen et al. [21] reported the results of the open-label SENZA-PDN randomized clinical trial comparing conventional medical management (CMM) with 10-kHz SCS plus CMM. N = 216 patients were randomized to either of these 2 groups (90 implanted with SCS) and the primary outcome was a 50 % or more pain relief by VAS. In the SCS group 75 patients met the outcome compared to the CMM alone group (79 %; difference, 73.6 %; 95 % CI, 64.2–83.0; P < 0.001). At 6 months the lower limb pain VAS scores in the SCS group decreased by a mean of 76.3 % (95 % CI, 70.8–81.8) while there was no change in mean pain VAS scores for the CMM group. The proportion of responders was 5 % (5 of 93) in the CMM group compared with 85 % (74 of 87) in the 10-kHz SCS plus CMM group at 6 months (P < 0.001).

Van Beek et al. [22] reported the 5 year follow up data in their prospective cohort of SCS for DN. NRS score for pain during the day and night was the primary outcome measure of the study, with treatment success defined as >50 % pain relief for 4 days. A total of n = 40 patients were permanently implanted and completed the follow up at 5 years. The authors reported that after 1-year follow-up, both day and night mean NRS pain scores decreased from 6.7 to 3.8 and 3.9 (P < 0.001, and the improvement was still present at 5 years follow up (NRS 4.3 and 4.6) although decreased.

Zuidema et al. [23] published the long term follow up results (8 years) of the European cohort prospective cohort study. The primary outcome was pain intensities (NRS) for both day and night. N = 19 patients were included in the follow up and experienced a mean NRS reduction of >2 points, with a pain reduction ≥30 % (day and night) achieved in >50 % of the patients.

Eldabe et al. [24] performed a retrospective study of n = 10 participants with chronic intractable PDN who trialed DRG-S. Of the seven patients who proceeded to implantation, five patients followed to six months reported a mean VAS reduction of 49.4 mm, and four patients followed to twelve months reported a mean VAS reduction of 48.2 mm. Overall, this study reported a 70 % success rate for trial-to-implant ratio and clinically significant pain relief in most patients followed to 12 months. Unfortunately, 2 patients (29 % of the sample) had their stimulator removed due to complications or personal choice before the one-month follow-up visit. Overall the current evidence for DRG stimulation in DN is still not as robust.

A total of 7 out of 625 existing studies were ultimately included in this section.

Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
Plujims et al., 2012	One group only	Synergy Versitrel, Medtronic	Not available	Patients with diabetes, pain in lower extremities >12 months with NRS score >5 N = 15	Medtronic, Inc.	prospective open-label cohort study 12 months
De Vos et al., 2014	Best medical therapy with SCS vs best medical therapy alone	EonC, Eon, or Eon Mini; St. Jude Medical	Not available	Patients with refractory diabetic neuropathic pain in the lower extremities N = 60	St. Jude Medical, Inc.	open randomized parallel-group design trial 6 months
De Vos et al., 2014	Tonic vs burst stimulation	Eon implantable pulse generators (IPG) (St. Jude Medical)	Burst stimulation: five spikes at 500 Hz spike mode, 40 Hz burst mode, 1 msec pulse width,	12 patients with diabetic neuropathy, 24 patients with PSPS, and 12 patients with PSPS which	St. Jude Medical, Inc.	Prospective cohort study 6 months tonic stim followed by 2 weeks burst stim

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Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
Petersen et al., 2021	medical management (CMM) with 10-kHz SCS plus CMM	Nevro Senza IPG	amplitude set to 90 % of paresthesia threshold 10-kHz frequency, 30- $\mu$ s pulse width delivered via bipole, and amplitude range of 0.5–3.5 mA	failed SCS N = 12 Patients with PDN diagnosis with symptoms for 12 months, VAS > 5 cm N = 216	Nevro Corp.,Inc.	prospective, multicenter, open-label RCT 6 months
Van Beek et al., 2018	One group only	Synergy Versitrel or PrimeAdvanced; Medtronic	Not available	Patients with PDN, pain present for >12 months, mean NRS score $\geq$ 5 N = 48	Medtronic,Inc.	Prospective cohort, multicenter 5 years
Zuidema et al., 2022	One group only	Synergy Versitrel or PrimeAdvanced, Medtronic	pulse width 150–450 $\mu$ m, frequency 30–60Hz, varied amplitude	Patients with PDN, pain present for >12 months, mean NRS score $\geq$ 5 N = 19	Medtronic, Inc.	Prospective cohort study 10 years
Eldabe et al., 2018	One group only	Abbott	Not available	Patients with PDN, chronic intractable pain of the lower limbs >6 months, VAS >6 cm N = 10	Abbott, Inc.	Retrospective case series 12 months

### CRPS: case vignette and literature review

A 31-year-old male presented to the clinic with complex regional pain syndrome (CRPS type 1) in the L1 distribution secondary to right-sided unilateral inguinal hernia repair. This patient reported a 1.5 years history of sharp and burning pain that radiated throughout the right L1 dermatomal distribution. Intensity ranged from 2 to 9 and was exacerbated by bending, twisting, lifting and walking. On physical exam he endorsed subjective sensory deficits in the L1 distribution, his exam was otherwise unremarkable. He had previously undergone conservative management in the form of ilioinguinal nerve blocks and physical therapy without relief.

Given his clinical presentation, failed conservative management and presence of neuropathic pain secondary to CRPS, he was deemed a candidate for spinal cord stimulator trial with percutaneous lead placement. Intraoperatively the epidural space was accessed at the level of T12 and L1. Leads were advanced to the T10 level bilaterally. On follow up examination, the patient reported a remarkable 65–70 % improvement in his neuropathic pain. He additionally endorsed improvement in sleep and ambulation, particularly highlighting the resolution of his radiating burning pain.

Based on positive trial results, he was scheduled for permanent placement of spinal cord stimulator. During the permanent implantation procedure, a thoracic laminectomy was performed at the level of T11 and a spinal cord stimulator paddle was placed with the tip located at the level of T10. Laminoplasty was then performed to reduce the risk of post laminectomy syndrome. On subsequent follow up visit, patient reported an overall 60 % improvement in pain. He endorsed a stable improvement in ambulation and proudly noted his ability to ambulate a total of 1.5 miles without inguinal pain, which he had previously been unable to do. This case vignette highlights the potential benefits of spinal cord stimulation in the management of refractory complex regional pain syndrome.

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by a spontaneous and evoked regional pain, usually beginning in a distal extremity, that is disproportionate to the inciting pain stimulus and it is associated with prominent regional autonomic and inflammatory changes. The syndrome is quite disabling and it is associated with extreme hyperalgesia and allodynia, skin color and temperature changes, edema and altered patterns of hair or skin trophism in the

affected limb. CRPS is subdivided into type I and type II on the basis of absence or presence, respectively, of clinical signs of major peripheral nerve injury (such as nerve conduction study abnormalities). Authors have postulated about the modulatory effect of SCS as one of the mechanisms of action of SCS in this population [25].

Kemler et al. [26] performed one of the first RCT on patients with CRPS type one who were either randomized to SCS plus PT (n = 24) or PT alone (n = 18) and followed up to 6 months. Among the 24 patients who were actually treated with spinal cord stimulation, the score on the visual-analogue scale decreased by a mean of 3.6 cm, whereas the score increased by a mean of 0.2 cm among the 18 patients who received physical therapy (P < 0.001). The same group reported the results of their 2 and 5 years follow up on these patients [27]. At 5 years post-treatment, SCS + PT produced results similar to those following PT for pain relief and all other measured variables. In a subgroup analysis, the results with regard to global perceived effect (p = 0.02) and pain relief (p = 0.06) in n = 20 patients with an implant exceeded those in 13 patients who received only PT.

Forounzafar et al. [28] followed n = 36 patients with CRPS I implanted with SCS (either in the cervical [19] or lumbar spine [17]) for up to 24 months. The primary outcome was the reduction in VAS score, and secondary outcome included the Euroqol 5D (EQ-5D) questionnaire. At all follow-up periods the pain intensity was decreased compared with the baseline (P < 0.001), with at least 50 % improvement in the VAS which was maintained at 2 years. Interestingly there was no significant difference between the cervical or lumbar location of the implant and the degree of pain reduction over time.

Geurts et al. [29] presented the results of their prospective study of n = 87 patients with CRPS I & II (90 % of the total diagnosis) implanted with SCS. At 1 year follow up (79 patients) at least 63 % of patients reported pain relief, which stabilized at 30 % or more at the last follow up. 60 % of patients still used the SCS system during 12 years of follow up although the number of revisions was important, as thirteen complications occurred in 11 of the 84 patients (13 %).

Kriek et al. [30] published the results of their RCT on SCS in patients with CRPS who were either unresponsive to conventional therapies, or who already had SCS therapy but with loss of therapeutic effect over time. The primary outcomes of the study were pain reduction and patient satisfaction, while the secondary outcomes included the use of a dynamometer to measure muscle strength of the flexors and extensors of the

elbow in case of the upper extremity, and of the knee and the foot in case of CRPS in the lower extremity. The protocol included 3 months of conventional tonic SCS followed by a crossover phase with 5 different frequencies tested each beginning with a 2 days washout period. At the end of the crossover phase the patients were left with the frequency of choice for the next 3 months. Of the  $n = 29$  patients that completed the trial, significant pain reduction was achieved for the main primary outcome parameter VAS with 40, 500, 1200 Hz and burst SCS, compared with placebo stimulation, whereas there were no significant differences between 40, 500, 1200 Hz and burst SCS. At the end of the crossover period, 48 % of the patients preferred standard to non-standard stimulation (52 %), and the authors postulated that this result may be due to a lower energy consumption using standard stimulation which had less drawbacks.

Levy et al. [31] published the results of the ACCURATE randomized, controlled multicenter trial which compared outcomes of dorsal root ganglion (DRG) stimulation versus tonic spinal cord stimulation (SCS) in  $n = 152$  subjects with chronic lower extremity pain due to complex regional pain syndrome (CRPS) type I or II. The main idea behind the study was to investigate the effect of reduced habituation to tonic SCS on long term pain reduction. 76 patients were randomized to either receive SCS or DRG and were followed up to 12 months. The responder rate was highest at the end of the trial stimulation period for both groups, in which 89.0 % of DRG stimulation subjects and 86.1 % of SCS subjects had at least 50 % pain relief from baseline. In the DRG stimulation group the VAS declined to 69.8 % at 1 month and remained stable from 1 month through 12 months, when pain relief was 69.3 %. In the SCS group it decreased to 66.9 %, but this declined significantly to 58.3 % at 9 months and 57.9 % at 12 months ( $P < 0.01$ ). For the DRG stimulation group, the responder rate declined to 74.0 % at 1 month, but remained relatively stable at 75.3 % by 12 months. In contrast, for the SCS group, the responder rate declined to 68.1 % at 1 month, and continued to fall to 61.1 % at 12 months.

A total of 5 out of 200 existing studies were ultimately included in this section.

### Limb ischemia: case vignette and literature review

A 58-year-old female patient with a complex medical history, including anxiety, arthritis, asthma, depression, hypertension, prior anterior cervical discectomy and fusion (ACDF), prior lumbar fusion at L5/S1, and thromboangiitis obliterans presented with debilitating pain in her bilateral feet, right leg, and right lower back. She underwent a posterior lumbar interbody fusion in 2008 for chronic L5 radicular pain, which did not relieve her symptoms. Despite negative findings on cervical and thoracic MRI scans, the patient continued to experience severe pain which was unresponsive to NSAIDs, oral steroids, muscle relaxants, neuropathic pain medications, and opioids.

After an extensive workup, the patient was diagnosed with thromboangiitis obliterans, a condition resulting from a long-standing smoking history, causing inflammation and thrombosis in the small vessels of the hands and feet, leading to ischemic limb pain. In 2022, the patient underwent a spinal cord stimulation (SCS) procedure, initially experiencing good results.

The patient presented with worsening bilateral feet, right leg, and right lower back with reduced benefit from SCS over time. The pain was worse in the morning and was aggravated by standing, changing positions, and lying down. A monopolar review using a combination of electrodes and polarities was performed. Successful stimulation was achieved, providing coverage to the bilateral legs, back, and feet. The patient reported complete pain coverage, endorsing 100 % relief with reprogramming.

This case highlights the potential benefits of spinal cord stimulation in managing vascular disease resulting in limb ischemia. Despite unsuccessful prior interventions, the patient achieved significant pain relief through SCS. The ability to adjust the device settings and stimulation parameters allowed for optimal pain management and long-term improved quality of life.

The symptoms of arteriosclerotic occlusive arterial disease include intermittent claudication, ischemic pain and ulceration/gangrene as the disease progresses. For patients in advanced stage (stage IV according to

Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
Kemler et al., 2000	SCS vs conservative treatment	Itrel III, model 7425, Medtronic	rate, 85 Hz; pulse width, 210 $\mu$ sec; 0–10V	Patients with CRPS for at least 6mo restricted to one hand or foot, pain VAS >5 cm N = 24	Dutch Health Insurance Council	prospective, randomized, controlled trial 6 months
Forouzfahar et al., 2004	Cervical vs lumbar SCS	Itrel 3, model 7425; Medtronic	Frequency 85 Hz, pulse width of 210 $\mu$ s, amplitude 0–10V	Patients with CRPS I for >6 months, failed other treatments N = 36	Institutional funds	Prospective cohort 2 years
Geurts et al., 2013	Only one group	Itrel III, model 7425, Medtronic	Not available	Patients with CRPS I, VAS > 5 cm N = 84	Dutch government grant	Prospective cohort 12 years
Kriek et al., 2017	Different frequencies	Eon IPG, St Jude	40-, 500-, and 1200-Hz stimulation, burst and placebo (sham) stimulation	Patients with CRPS diagnosis in one single extremity, therapy resistant CRPS with a pain score of $\geq 5$ cm VAS N = 29	St. Jude Medical, Inc.	Double blind randomized controlled trial 10 weeks
Levy et al., 2020	DRG stim vs SCS for lower extremities CRPS	DRG stim: Axium Neurostimulation System, Abbott SCS: RestoreUltra and RestoreSensor, Medtronic	Not available in details	Patients with CRPS I & II, pain VAS >6 cm N = 145	Abbott, Inc.	Unblinded RCT 12 months



Fontaine) often there is no available reconstructive indications, and there are limited options to avoid limb amputation. Neuromodulation with SCS has been proposed as a therapeutic option in these patients to treat ischemic pain, and it has been shown to increase perfusion to the limb [32].

Petrakis et al. [33] reported the outcome of their prospective study on  $n = 60$  patients with type I diabetes and non-surgical painful peripheral arterial occlusive disease. Patients were screened for the presence of autonomic neuropathy at the beginning of the study, and the authors also monitored the Transcutaneous oxygen tension on the dorsum of the foot in addition to the change in VAS scale during the 18 months follow up period. A total of  $n = 47$  patients achieved  $>50\%$  pain relief (35 patients had more than 75 % relief), with statistically significant improvement in tissue oxygenation as defined by cutaneous oxygen tension in as early as 2–3 weeks after the implant.

Amann et al. [34] reported the outcomes of the SCS-EPOS multicenter trial in Europe. The primary endpoint was limb survival, defined as a lack of amputation of the target leg in or above the level of the ankle during the follow-up period, while secondary objectives included pain relief, wound healing and quality of life. Patients were divided based on transcutaneous oxygen tension (TcPO<sub>2</sub>) measurements (73 received SCS implant, 39 only conservative management) and followed up for 12 months. After 12 months, 43 % of the SCS patients with lower TcPO<sub>2</sub> had improved from Fontaine stage III or IV to stage I or II, with limb survival significantly improved in the SCS group compared to those who only received conservative treatment ( $p < 0.003$ ). The pain relief was also greater in the SCS group ( $p < 0.005$ ).

Horsch et al. [35] reported the results of their retrospective study on  $n = 258$  patients which were implanted with SCS for PVD and they were followed for up to 18 months. The limb survival in the medium baseline TcPO<sub>2</sub> group was 89.5 % compared to the low TcPO<sub>2</sub> group 77.8 % (statistically significant  $p = 0.014$ ), and the time until major amputation was significantly longer again in the medium TcPO<sub>2</sub> group ( $p = 0.028$ ).

Brummer et al. [36] reported the results of their prospective study on 8 patients with ESRD and lower limb PAOD which were followed for up to 12 months after implant. The primary outcomes were severity of pain and quality of life. VAS decreased significantly throughout the observation period (T0,  $87 \pm 13$  mm; at 6 months,  $19 \pm 10$  mm; at 12 months,  $16 \pm 6$  mm;  $P < 0.001$ , T0 versus 6 and 12 months). 3 patients initially assessed at stage III improved to stage II by the end of the follow up.

Liu et al. [32] have recently reported the outcomes of their prospective study on SCS for critical limb ischemia.  $N = 37$  out of 78 patients were implanted with SCS and followed up to 12 months post implant. The authors used Lower-limb 201 Tl scintigraphy to diagnose and monitor the lower limb perfusion insufficiency, together with pain relief and walking distance as additional outcome parameters. In the SCS group the authors reported improved pain relief at 12 months (VAS score  $2.35 \pm 0.62$ ,  $p < 0.001$ ), but they also noticed improvement in the walking distance ( $1595.00 \pm 483.60$ ,  $p < 0.001$ ), walking time ( $48.92 \pm 14.10$ ,  $p < 0.001$ ), and sleep quality ( $4.65 \pm 0.92$ ,  $p < 0.001$ ). In addition, the authors noticed an increased intensity of microcirculation in the calves after SCS implantation.

A total of 5 out of 20 existing studies were ultimately included in this section.

Author, year	Study comparison	SCS system	Stimulation parameters	Patient population	Funding	Type of study & Duration of study
Petrakis et al., 2000	One group only	Itrel II, Medtronic	Amplitude 1–5V, frequency 40–120Hz, pulse width 150–450 ms	Patients with type I diabetes, non-reconstructible PAOD $N = 60$	Institutional funds	Prospective cohort 6 months
Amann et al., 2003	SCS in patients with PAOD and different levels of TcPO <sub>2</sub> and response to stim	IPG Itrel or Synergy; Medtronic	Not available	Patients with chronic, stable limb ischemia and not suitable for vascular reconstruction $N = 41$	Institutional funds	Prospective cohort 12 months
Horsch et al., 2004	Patients with different outcomes based on TcPO <sub>2</sub> baseline measurement	Itrel II or III, Medtronic	pulse amplitude of 2.2 V, a pulse width of 300 $\mu$ s, and frequency of 70 Hz	H/o PAOD with TcPO <sub>2</sub> $< 30$ mmHg $N = 258$	Medtronic, Inc.	Retrospective study 18 months
Brummer et al., 2006	One group only	Medtronic	Not available	Patients on regular hemodialysis treatment and with lower-limb PAOD-pain $N = 8$	None	Prospective cohort 12 months
Liu et al., 2018	SCS vs conventional medical treatment for PAOD-pain	Medtronic	stimulation intensity, $2.39 \pm 0.45$ , $1.1–4.7$ V; frequency, $96.35 \pm 13.12$ , 50–130 Hz; pulse width, $276.10 \pm 41.12$ , 150–360 $\mu$ sec	Patients with a perfusion difference of $< 0.95$ between two legs and pain in the legs $N = 78$ (37 received SCS)	National Science Council	Prospective case-control study 12 months

## Future directions

This review has been intentionally focused on providing an update on the major clinical trials and case series for the currently FDA-approved SCS indications.

Chronic nonmalignant, intractable pain is a common condition which exerts an enormous personal and economic burden, affecting more than 30 % of people worldwide according to some studies [1]. There is little doubt that SCS represents a safe and effective therapy for patients with chronic nonmalignant pain conditions, especially those with PSPS or CRPS [37]. SCS effect is mediated through a number of different pathways and neurotransmitters in the spinal cord as well as in the CNS [38]. There remain challenges with SCS therapy including loss of efficacy over time. For example, the most common reason for failure over the first 12 months after implant has been shown to be lack or loss of efficacy due to the device migrating leading to change in stimulations, implantable pulse generator (IPG) pocket pain, and infection [39]. Another challenge is represented by true ‘habituation’ to SCS: habituation can be defined as synaptic suppression when a constant stimulation is detected by sensory neurons. This suppression of signal has been associated with the use of tonic stimulation [40] and can possibly be circumvented by using a different stimulation paradigm (waveform and contacts configuration). Further large, non-industry-sponsored clinical trials are needed to establish what stimulation paradigms and hardware constructs are superior for specific neuropathic conditions and to better understand the reasons behind the loss of efficacy that occurs over time.

## Limitations

There are several limitations with this review. Although the bulk of the literature appears to support a role for spinal cord stimulation, primarily in neuropathically driven pain syndromes, the quality of the literature must be considered. There are only a few randomized prospective studies on the efficacy of SCS. By only including large retrospective case series and clinical trials, it is possible that we excluded high quality studies that could have informed on the efficacy of SCS in different pain states. Overall, the present literature suggests an important role for spinal cord stimulation, but these authors conclude that the limitations of the literature must be acknowledged.

## Authors contributions

Dr. Francesco Sammartino performed the literature search, analysis, and drafted the article.

Dr. Jacquelyn MacDonell drafted the clinical vignettes.

All authors including Richard B North, MD, Vibhor Krishna, MBBS, Lawrence Poree performed critical review of the draft and approved the final version of the manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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