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REGENERATIVE PAIN MEDICINE/INTERVENTIONAL PAIN MEDICINE (EC BRADLEY, SECTION EDITORS)

Dorsal Column Stimulation and Cannabinoids in the Treatment of Chronic Nociceptive and Neuropathic Pain: a Review of the Clinical and Pre-clinical Data

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Abstract

Purpose of Review The main objective of this review is to appraise the literature on the role of spinal cord stimulation (SCS), cannabinoid therapy, as well as SCS and cannabinoid combination therapy for the management of chronic neuropathic and nociceptive pain. Current research suggests that SCS reduces pain and increases functional status in carefully selected patients with minimal side effects.

Recent Findings As cannabinoid-based medications become a topic of increasing interest in pain management, data remains limited regarding the clinical efficacy of cannabinoids for pain relief. Furthermore, from a mechanistic perspective, although various pain treatment modalities utilize overlapping pain-signaling pathways, clarifying whether cannabinoids work synergistically with SCS via shared mechanisms remains to be determined. In considering secondary outcomes, the current literature suggests cannabinoids improve quality of life, specifically sleep quality, and that SCS decreases opioid consumption, increases functional capacity, and decreases long-term healthcare costs.

Summary These findings, along with the high safety profiles of SCS and cannabinoids overall, incentivize further exploration of cannabinoids as an adjunctive therapy to SCS in the treatment of neuropathic and nociceptive pain.

Keywords Spinal · Cord · Stimulation · Cannabinoids · Cannabis · CBD

Introduction

Nociceptive and Neuropathic Pain

In the US population, it is estimated that approximately one-third of adults suffer from chronic pain. In this regard, the Institute of Medicine estimates that $635 billion in direct costs and productivity is lost as a result [1••]. A more recent study of pain-related costs in a large healthcare system performed by Park et al. suggests a positive, causal relationship between chronic pain conditions and medical resource consumption [2••]. As chronic pain cannot be quantified or monitored by precise means and can result from a wide variety of conditions

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[1••, 3•, 4••], further studies are needed to establish objective clinical correlates of pain and to provide targeted therapies for patients with poorly managed chronic pain.

Nociceptive pain can be broadly described as the detection of noxious stimuli by peripheral neurons and the transduction of these signals to the central nervous system through well-defined anatomic tracts. Our understanding of canonical electrochemical nociceptive signaling via voltage-gated Na^+ channels remains the basis of modern local anesthetics [5]. However, sensory neurons are substantially more complex, varying widely by tissue type and function through biochemically diverse mechanisms to facilitate specialized detection of one or many stimuli [6]. Tissue-specific afferent nociception at the periphery has been extensively described, [7, 8•] and downstream signaling at the central nervous system is similarly well-mapped through the cortex. However, recent literature suggests that emerging pathways in central processing of nociceptive signals may explain differential perception of and adaptation to pain across patient populations and conditions [9, 10]. Common conditions classically presenting with nociceptive pain include acute or chronic musculoskeletal injuries such as burns, bruises, fractures, osteoarthritis, tendinitis, muscle strains, ligament sprains, meniscal tears, generally affecting the bone and joints, tendons, ligaments, muscles, and skin.

Unlike nociceptive pain, which is triggered by external stimuli, neuropathic pain is caused by damaged or diseased sensory neurons in the nociceptive pathway. Injuries to nerves can vary widely (mechanical, infectious, autoimmune, etc.), and often present with distinct symptoms and pathophysiologic underpinnings [11, 12•, 13]. Common neuropathic pain conditions include multiple sclerosis, complex regional pain syndrome, diabetes, vitamin deficiencies, and nerve sheath tumors. While neuropathic pain as a symptom can be diagnostically useful, it chronically burdens up to 8% of the general population with decreased quality of life [12•]. Limited treatment options exist for the management of neuropathic pain, which may persist long after resolution of the initial insult to the nervous system [13].

Current Treatment Modalities

Opioids and Adjuvant Medications

According to a 2015 estimate published by the American College of Physicians, opioid medications are prescribed to over one-third of the US population and currently the most common therapy for chronic nociceptive pain [15]. Opioids prevent neurotransmitter release in nociceptive signals through mu-receptor agonism at the pre- and post-synaptic terminals of spinal neurons [16]. Mu receptors has been shown to play a key role in spinal, supraspinal analgesia with absence of mu-receptor in knockout mice influencing response to mechanical, chemical, and supraspinal thermal nociception [17]. Mu receptors belong to one of three established classes of opiate receptors: μ-mu, δ-delta, and κ-kappa, which are widely distributed in the brain (periaqueductal gray, nucleus raphe magnus, caudate nucleus, hypothalamus, habenula, and hippocampus) and dorsal horn of the spinal cord (Rexed laminae I, II, and V) [17, 18]. Endogenous opioid peptides—beta-endorphins, enkephalins, and the dynorphins—bind the opiate receptors and modulate nociception by (a) inhibiting presynaptic influx of Ca^{2+}, which prevents neurotransmitter release, or (b) opening up potassium channels, leading to neuron hyperpolarization and blocking spike activity and pain transmission with release of substance P [17]. Beta-endorphins are considered the putative ligands for the mu-receptors, which modulate inhibitory effects on dorsal horn nociception. Exogenous and endogenous opioids act on mu-receptors in central and peripheral terminals of nociceptive afferent fibers to modulate nociception. Binding of mu and opiate receptors activates descending pain suppression pathways, and simultaneously modifies firing threshold of neurons that block ascending nociceptive information [18, 19]. Due to widespread localization of endogenous opiate receptors in the brainstem parabrachial nuclei, opioids are known to activate the pre-Bötzinger complex, a respiratory rhythm generator area in the pons and subsequently induce respiratory depression [18, 19]. Due to the risks of respiratory depression, long-term misuse, and dependence associated with opioids, alternative therapies are of interest to practitioners, patients, and policymakers [15].

The management of neuropathic pain is distinct from that of nociceptive pain, employing first-line agents in the antidepressant and anticonvulsant classes [14, 20, 21]. Tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are thought to oppose neuropathic nociceptive signaling at multiple steps: (i) inhibiting serotonin and noradrenaline reuptake between first- and second-order neurons and (ii) potentiating inhibitory GABAergic spinal interneurons [14, 16]. Pregabalin and gabapentin are anticonvulsant GABA analogs, which promote the internalization of calcium channels at the synaptic cleft. Both work by destabilizing association of calcium with the plasma membrane and decrease neurotransmitter release from the axon terminal [14, 16, 21, 22•]. Opioid analgesics are generally considered to be second-line due to aforementioned concerns for respiratory depression, long-term misuse, dependence, and abuse [16, 20, 21, 23]. Moreover, opioid sensitivity for neuropathic pain control may be reduced through down-regulation of opioid receptors, elevated Aβ fiber–mediated allodynia, elevated cholecystokinin (CCK) antagonism of opioid actions and *N*-methyl-D-aspartate (NMDA)-mediated dorsal horn neuronal hyperexcitability. All of this increases the threshold needed for opioid analgesia and decreases opioid efficacy for neuropathic pain [24, 25].

Ketamine has been suggested as a potential option for managing neuropathic pain. It works as a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist and has been shown to have a role in central sensitization, reduce opioid tolerance, enhance endogenous antinociception pathways, and block astrocyte and microglial activation [26]. Limited data reviewed by Maher et al. provides evidence for the use of intravenous ketamine for moderate-term relief (< 1 month) of chronic neuropathic pain. However, existing trials do not provide robust guidelines for widespread clinical use [27]. Current literature suggests that medical therapy provides some level of relief in ≤ 50% of patients with chronic neuropathic and nociceptive pain [20, 21]. As such, there is a clear need for further investigation and development of pharmacologic interventions targeting both nociceptive and neuropathic pain pathways.

Surgical vs. Non-surgical Interventions

Outpatient spine surgery to address chronic back pain offers a shorter-term treatment course relative to medical management and can be optimal for select patients. However, clinical trials performed comparing spinal fusion and physical therapy programs offer conflicting results as to reduction in pain and functional benefits of surgery. Moreover, these studies do not use comparable controls and study outcomes are heterogenous making meaningful comparisons difficult [28, 29]. Furthermore, physical therapy and conservative management including pharmacotherapy are often more cost effective than surgical options. Nonetheless, a subset of patients suffering from chronic low back and leg pain have been shown to recover significantly with post-surgical improvement in function and quality-of-life [30]. More randomized controlled clinical trial data may be needed to refine surgical inclusion criteria and pertinent outcomes.

Despite the role of surgical vs. non-surgical management of chronic nociceptive vs. neuropathic pain, several non-traditional and procedural therapies have been proposed as adjuvants or replacements for traditional medical and surgical management of chronic pain. Radiofrequency ablation (RFA) of peripheral sensory nerves demonstrated effective, short-term pain relief in randomized control trials in a 2014 review by Leggett et al. [31]. More recent prospective trials have shown longer-term pain relief (> 6 months) in a subset of patients treated with RFA [32, 33]. Other minimally invasive procedures like stimulation of the dorsal column, traditionally referred to as spinal cord stimulation (SCS) have emerged as promising therapies to treat neuropathic and nociceptive pain. Current approved indication for SCS includes failed back surgery syndrome with radiculopathy, complex regional pain syndrome, chronic peripheral diabetic neuropathy, refractory angina, ischemic limb pain, and phantom limb pain. A review of the literature on SCS trials [34, 35] demonstrates that spinal cord stimulation reduces pain and increases functional status in carefully selected patients with the above indications [36, 37]. Most conservatively, mindfulness and meditation, alone or in combination with pharmacologic therapy is supported by several small trials [36] as an effective approach to reduce chronic pain at rates similar to traditional interventions.

More recently, cannabinoid-based medications have become a topic of increasing interest in pain management for use in a variety of clinical conditions [41]. Nonetheless, data are limited with regards to the clinical efficacy of cannabinoids for pain relief. The dearth of evidence highlights the need for further studies regarding whether cannabinoids, alone or as an adjuvant, are effective in relieving chronic nociceptive vs. neuropathic pain. From a mechanistic perspective, although various pain treatment modalities may utilize overlapping pain-signaling pathways, clarifying whether cannabinoids work synergistically with SCS via shared mechanisms remains to be determined. With rapid advances in SCS technology, clinicians will be well served by understanding the evidence for SCS and related supporting therapeutic modalities for nociceptive and neuropathic pain. It is therefore instructive to explore the role of cannabinoids as an adjunctive therapy to SCS in the treatment of neuropathic vs. nociceptive pain. The goal of this review, therefore, is to evaluate the clinical and pre-clinical data for the use of cannabinoids as an adjunct to SCS for treatment of neuropathic or nociceptive pain.

SCS and Cannabinoids

Spinal cord stimulation involves implantation of single or dual electrodes in the epidural space posterior to the dorsal columns with the aim of reducing chronic neuropathic and nociceptive pain. An increasing variety of stimulation waveforms, intensities, and frequencies are the focus of various ongoing clinical trials [35, 37, 39]. The postulated electrochemical and neurophysiological mechanisms that underlie SCS-mediated attenuation of nociceptive signaling have been well delineated by others. Briefly, stimulation of large sensory afferents (i) potentiate inhibitory neurotransmitter (GABA and others) release from peripheral neurons, (ii) decrease excitatory glutamatergic signaling, and (iii) may activate central, descending inhibitory pathways. While understanding of the underlying mechanisms of SCS continues to evolve, it is premised partly on the gate control theory by facilitation of pain transmission through activation of tactile A-beta fibers in the dorsal column and gating of sensory afferent fiber input. Other proposed mechanisms include activation of neurotransmitters, supra spinal pain inhibition, and blocking of transmissions in the spinothalamic tract [39, 40]. Interestingly, SCS analgesia arises independently of mu-receptor-tied signaling and is not counteracted by mu-antagonists [39–42].

In a 2007 RCT, Kumar et al. showed that SCS is significantly more effective than medical management alone in reducing discomfort and increasing function at the 1-year and 2-year follow-up in patients with neuropathic pain after failed back surgery [43]. Similarly, a more recent RCT supports the long-term efficacy of SCS in treating diabetic neuropathy, a major component of neuropathic pain in this population [44]. Studies by Kapural et al. suggest that the use of high-frequency SCS further increases the proportion of patients who respond to this procedure, especially those with nociceptive and neuropathic back and leg pain [45, 46]. However, this did not necessarily translate into better outcomes for pain alleviation.

In 2017, Deer et al. performed a randomized, unblinded, crossover study titled "Success Using Neuromodulation with BURST (SUNBURST)." The study concluded that in comparison to tonic stimulation, burst stimulation may be superior for the treatment of chronic pain [47]. Superiority of burst stimulation is premised on the delivery of packets of stimulation, which mimic the naturally occurring firing patterns in the central nervous system [39–43]. This modulates pathways that reduces the behavioral unpleasantness of tonic stimulation and any associated suffering [40, 41]. Unlike tonic stimulation, burst has been described as a "wakeup call from the thalamus" and signaling to the cortex of changes in the sensory environment. By multiplexing signaling information in addition to selective routing, burst stimulation is able to create synchrony in spatially segregated but functionally connected regions of the central nervous system [40–42]. Burst stimulation therefore increases the signal to noise ratio compared to tonic stimulation. Because some neurons naturally fire in bursts, being able to mimic this natural pattern with trains of rapid high frequency actional potentials in active phase, then followed by a quiescent silent phase, purportedly allows activation of ascending medial vs. lateral ascending pathways, and descending pathways [40–42]. To date, however, there are no studies evaluating combination therapy of tonic frequency, higher frequency and burst stimulation for treatment of pain. Finally, a 2018 meta-analysis by Moens et al. revealed that SCS in general may confer a higher likelihood of returning to work activities (a key functional metric) post-SCS as compared to non-SCS treatments [34].

Whereas SCS works on the dorsal column, cannabinoids affect central vs. peripheral pain neurotransmission through pre- and postsynaptic cannabinoid (CB_1 vs. CB_2) receptors. Unlike SCS, cannabinoids decrease release of both excitatory and inhibitory neurotransmitters directly through synaptic vesicle release, and indirectly through changes in voltage-gated-channel-modulated electrochemical gradients [48, 49]. Despite its widespread physiologic mechanism of action, scant evidence of long-term efficacy and adverse events exist [38, 50, 51]. Small RCTs comparing the efficacy of cannabinoid-derived medications (e.g., Dronabinol, Nabilone, Sativex) and placebo for the treatment of neuropathic pain have yielded mixed results [51–56]. While an early trial conducted by Frank et al. found that standard opioid therapy outperforms cannabinoid therapy [57], a recent meta-analysis by Meng et al. suggests a small, significant benefit in pain symptoms using cannabinoids compared to placebo alone as well as both placebo and pharmacotherapy (opioids) [58•].

The distinct mechanism of action by which cannabinoids modulate pain make this class of medications an attractive adjuvant to existing therapies. Toth et al. and Turcotte et al. provide promising evidence for cannabinoids as an adjuvant to first-line therapy for diabetic neuropathy and multiple sclerosis-induced neuropathic pain, respectively [59, 60]. Spinal cord stimulation has shown much potential as an efficacious outpatient procedure that enhances pain relief when combined with select adjuvants [61, 62]. Between 2014 and 2016, Mondello et al. conducted the first trial comparing SCS alone and SCS with a Cannabinoid adjuvant in patients with failed back surgery syndrome. At 12-month follow-up, SCS plus cannabinoid adjuvant treatment was more effective than controls in alleviating neuropathic pain [63]. The results from this trial and excellent safety profiles of SCS and cannabinoids overall warrant further evaluation of a putative role for synergy between SCS therapy and cannabinoids.

While existing trial data supports the combination of SCS and cannabinoid adjuvants in countering chronic nociceptive and neuropathic pain, further higher quality studies are needed to determine whether they have an additive or synergistic effect. SCS targets the nociceptive signaling pathway through the generation and propagation of inhibitory signaling at multiple steps and at anatomically distinct sites along the signaling pathway [39–42]. In contrast, cannabinoids reduce neurotransmission—excitatory and inhibitory—uniformly in the central and peripheral nervous systems [48, 49]. It is possible that cannabinoid-mediated downregulation of inhibitory signals will overcome GABAergic potentiation, the proposed mechanism of SCS. On the other hand, both modalities may instead cause a cumulative decrease of excitatory glutaminergic signals in nociception. Large trials and basic preclinical inquiry into the molecular mechanisms underlying these putative therapies may lead to more efficacious and specialized treatment of nociceptive and neuropathic pain.

Chronic Pain Outcomes

Pain Relief with SCS Alone

Spinal cord stimulation therapy has been subject to multiple randomized controlled trials in an effort to understand its role in the management of chronic pain. North

et al. conducted a multicenter randomized control trial in a population of one hundred patients with predominant leg pain and radicular symptoms secondary to failed back surgery syndrome. Eligible patients were at least 18 years of age and experienced neuropathic pain radiating down the legs predominantly in dermatomal segments L4 and/or L5 and/or S1 in the setting of at least one anatomically successful surgery for herniated disc(s). The study subsequently randomized the patients in a 1:1 ratio to conventional medication management with or without SCS [64].

All patients in the study were followed for 12 months, irrespective of whether or not an implant was performed. The primary outcome was the proportion of patients with at least 50% leg pain relief at 6 months. All patients assigned to SCS therapy underwent implantable neurostimulation system (Medtronic) upon completion of a screening trial [64]. Non-SCS therapy involved an array of standard medical treatment including "oral medications, nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care". With the exception of slightly higher back pain scores in the conventional medical management group, all baseline characteristics of both groups were relatively well balanced [64].

To assess the primary outcome, the study utilized patient questionnaires recording visual analog scale (VAS) expressed as absolute values and as a proportion of patients achieving certain thresholds of pain relief on follow-up. With respect to the primary outcome measures, 24 patients in the SCS group (48%) versus 4 patients in the conventional medical management group (9%) achieved the primary outcome of 50% leg pain relief ($p < 0.001$). This pattern held true at multiple time points including 1-month, 3-month, and 6-month analyses [64]. Table 1 summarizes select studies on SCS therapy.

Pain Relief with Cannabinoid Alone

With the advent of novel cannabinoid formulations, randomized controlled studies of cannabinoids in chronic pain syndromes have been crucial in exploring efficacy of these medications as a therapeutic option for chronic pain. Serpell et al. recently conducted a double-blinded randomized placebo-controlled study of a tetrahydrocannabinol and cannabidiol oromucosal spray in peripheral neuropathic pain associated with allodynia [65]. The study used a pump action oromucosal spray that delivered 2.7 mg of THC and 2.5 mg of CBD with each 100-µL spray. Patients were instructed to self-administer the medication to an optimal dose but restricted to a maximum of 8 sprays in 3-h periods and 24 sprays in a 24-h period. The median duration of treatment with THC/CBD spray was 78.2 days, vs. 86.4 days with placebo [65].

With respect to the primary endpoint, a total of 34 patients (28%) in the THC/CBD spray group were classified as responders at the 30% preset level compared with 19 patients (16%) in the placebo group, which was statistically significant with an odds ratio of 1.97 ($p = 0.034$ 95% CI: 1.05–3.70). The co-primary endpoint of change in the PNP 0–10 NRS score was notable for a non-statistically significant mean reduction of −0.34 points ($p = 0.14$; 95% CI: −0.79 to 0.11 points) and −0.48 points ($p = 0.12$; 95% CI: −1.08 to 0.12) in favor of the THC/CBD spray treatment [65].

The authors concluded that a meaningful proportion of otherwise treatment-resistant patients had improvement in the severity of their condition with the THC/CBD. This study hints at the possibility that further dosing adjustments and treatment titration could have substantially improved observed results [65]. Table 2 summarizes select studies on cannabinoid therapy.

Pain Relief with Combined Use of Cannabinoid and SCS

Currently, trials and studies focusing on pain relief in the setting of simultaneous cannabinoid and SCS use is limited. To date, only one study by Mondello et al. has demonstrated promising results with combination therapy of cannabinoids and SCS in the setting of failed back surgery syndrome [63]. Patients were discontinued from all previous unsuccessful therapies 2 months prior to starting cannabinoid therapy, and a fixed dosage of THC/CBD was administered and increased relative to pain control response. The duration of treatment was a total of 12 months [63]. Neuropathic pain was assessed by the Douleur Neuropathique 4 (DN4) questionnaire with a total score calculated from a sum of 10 items, with a cutoff for diagnosis as a total score of 4/10. The mean pain perception calculated using the NRS (baseline numeric rating scales) suggested a decrease from 8.18 (SD 1.07) to 4.72 (SD 0.9). Their study results suggested significant analgesic improvement with combination therapy [63]. Further, high-quality explanatory randomized control trials comparing combination therapy vs. either therapy alone vs. placebo may be needed to further ascertain the role of combination SCS and cannabinoid therapy for chronic neuropathic vs. nociceptive pain.

Secondary Outcomes

Secondary Outcomes with Cannabinoid Alone

In addition to exploring the efficacy of novel cannabinoid formulations for chronic pain, several studies have highlighted the secondary benefits of these medications. Among the articles included in this review, quality of life, specifically sleep quality, was the most considered secondary

Table 1 Summary of RCTs on cannabinoids for chronic neuropathic vs. nociceptive pain

Author, year	Pain diagnosis	Cannabinoid type	Route	Pain duration	Study duration	Primary outcome	Secondary outcomes	Result	Adverse effects
Svendsen et al. 2004 [52]	Multiple sclerosis	Dronabinol	Oral	4.5 years	3 weeks	Median pain intensity in last week of treatment	QoL QST Pain relief score	Dronabinol improves central neuropathic pain in MS	Dizziness Headache Fatigue Myalgia
Rog et al. 2005 [53]	Multiple sclerosis	THC, CBD	Sprays	11.6 years	5 weeks	Mean pain intensity score	NRS PGIC PDI	Cannabis-based medicine is effective in reducing sleep disturbance in MS related central neuropathic pain	Dry mouth Dizziness Somnolence Cognitive memory loss
Lynch et al. 2014 [54]	Neuropathic, chemotherapy-related	THC, CBD	Sprays	1.4 years	4 weeks	Mean daily VAS in last week of treatment	QoL QST	NNT of 5 with average decrease of 2.6 on NRS for chemo-related neuropathic pain	Fatigue Dizziness Dry mouth Nausea
Berman et al. 2004 [55]	Neuropathic, brachial plexus injury	THC, CBD	Spray	5 years	2 weeks	Median pain severity	Sleep quality, SF-MPQ PRI, VAS PDI GHQ-12	Sleep and pain improved statistically	Dizziness, headaches, Myalgias Dysgeusia Nausea Euphoria
Selvarajah et al. 2010 [56]	Neuropathic, diabetes	THC, CBD	Sprays	0.5 years	12 weeks	NTSS	MPQ QoL	Cannabis no more efficacious than placebo for painful diabetic neuropathy	None reported
Frank et al. 2008 [57]	Neuropathic, ME	Nabilone, 2 mg	Oral	6.4 years	6 weeks	Mean VAS over last 2 weeks of treatment	QoL Mental function Sleep	Dihydrocodeine gives better pain relief than nabilone, with fewer side effects	Nausea Vomiting Fatigue
Toth et al. 2012 [59]	Neuropathic, diabetes	Nabilone	Oral	7.1 years	5 weeks	Mean daily pain in last week of treatment	Sleep quality QoL PGIC PTSS Anxiety	Flex dose nabilone was effective in reducing diabetic neuropathy symptoms, improved sleep, quality of life and overall well being	Dizziness Drowsiness

Table 1 (continued)

Author, year	Pain diagnosis	Cannabinoid type	Route	Pain duration	Study duration	Primary outcome	Secondary outcomes	Result	Adverse effects
Turcotte et al. 2015 [60]	Multiple sclerosis	Nabilone	Oral	4.5 years	9 weeks	VAS for pain intensity Impact on ADLs	PGIC	Nabilone is effective adjunct to gabapentin for MS neuropathic pain	Dizziness Dry mouth Drowsiness
Serpell et al. 2014 [65]	Neuropathic, ME	THC, CBD	Sprays	5.5 years	15 weeks	> 30% reduction in NRS baseline	Sleep Quality QoL QST BPI-SF	THC-CBD spray produced meaningful improvements in sleep, pain, and SGIC in treatment resistant patients	Disassociation Disorientation
Capano et al. 2019 [66]	Chronic pain	Cannabidiol: hemp derived (15 mg), CBD-rich soft gels containing 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidivarin (CBDV), 0.9 mg cannabidiolic acid (CBDA), 0.8 mg cannabichrome (CBC), and > 1% botanical terpene blend	Oral	3 years	8 weeks	Opioid use	Pain-related quality of life, Sleep Quality, Pain Intensity and Interference	97 completed study: - (53%) reduced or eliminated their opioids within 8 weeks after adding CBD-rich hemp extract to their regimens. Almost all CBD users (94%) reported quality of life improvements -- No significant relationship between CBD use and PHQ and PDI	No significant Adverse events reported, but a few participants reported: -Drowsiness -Nausea -Heartburn -Anxiety -Nightmares -Dry mouth
Langford et al. 2017 [69]	Multiple sclerosis	THC, CBD	Spray	5.5 years	14 weeks	> 30% reduction in NRS baseline Mean daily score last week of treatment	Anxiety QoL Sleep Quality PGIC PTSS	Equivocal response to THC/CBD spray for central neuropathic pain; but increased time to treatment failure in treatment group vs. placebo	Dizziness Drowsiness Vertigo Fatigue Dry mouth

This reflects selected studies and is not meant to be a comprehensive list of all cannabinoid studies

NTSS neuropathy total symptom score-6; *QST* quantitative sensory testing; *THC-CBD* delta-9-tetrahydrocannabinol; *NRS* numeric rating scale; *VAS* visual analog scale; *QoL* quality of life (EQ-5D); *PTSS*, *PDI* Pain Disability Index; *PGIC* Patient's Global Impression of Change; *BPI-SF* Brief Pain Inventory Short Form; *EQ-D5* European Quality of life 5 Domains

Table 2 Summary table of selected SCS studies

Author, year	Pain diagnosis	SCS parameter	Primary outcome	Secondary outcomes	Result	Adverse effects
Moens et al. [34]	FBSS, multiple sclerosis, SCI, vascular disease, cancer, occipital neuralgia, trauma, and peripheral neuropathy	-HF10 (1 study) -Conventional (6 studies)	1.Occupational status 2. Return to work	1. Types of employment after returning to work 2. Number of patients who increased working time 3. Median time of unemployment	Meta-analysis of 7 articles including 824 patients showed: - Higher prevalence of patients at work after SCS vs before -SCS treatment results in high odds to return to work	Not discussed
Verrills et al. [35]	Mixed neuropathic/nociceptive and neuropathic/radicular pain	-Traditional -DRG -HF10 -Burst frequency	Overall efficacy of SCS therapy in pain relief	1.Comparing efficacy of advanced iterations of SCS therapies among different patient populations/clinical presentations 2.Cost efficiency of SCS vs CMM	-Overall, SCS reduces pain and increases functional status in carefully selected patients with minimal side-effects -Level I evidence exists for traditional, HF10 and DRG (but not burst frequency) SCS in the treatment of specific chronic pain -Limited number of large, prospective, high-quality, randomized or controlled comparative trials in current literature -Despite high upfront cost, SCS results in decreased long-term health care costs compared with CMM	Overall minimal. Catastrophic complications are very rare, incidence of minor, reversible, complications reported at 30–40%: -5–9%: Lead fracture/disconnection -0–27%: Lead migration -1.7%: IPG failure -3–8%: Superficial infection -0.3–2%: Dural puncture -Others (unreported incidence): Allergic reaction, pain at implant site -Others (rare): epidural fibrosis, compressive phenomenon, SCI
Atkinson et al. [36]	-FBSS -CRPS -Chronic limb ischemia -RAF -Neuropathic pain -Post-operative Pain -SCI pain Phantom pain	Not specified	Develop clinical practice guide for SCS efficacy in treating different types of chronic pain	1.Indications and contraindications Benefits and complications associated with SCS	Strong indications: -FBSS -RAF -Neuropathic pain due to peripheral nerve lesion -Radicular pain after cervical spine surgery Intermediate indications: - Pain due to PVD -Intercostal Neuralgia -Peripheral neuropathic pain syndromes -CRPS Not indicated: -Avulsive brachial plexopathy -Nociceptive axial pain post-operatively -SCI pain -Postherpetic Neuralgia -Phantom pain -Central pain of non-spinal cord origin Contraindications: -Systemic/local sepsis -Uncontrolled bleeding disorder -Active anticoagulant use -Cognitive impairment -Immunosuppression -Pacemaker	Common: -11%: Electrode migration -6%: Lead fracture -5%: Infection -2.5%: Hardware malfunction -2.5% Pain at IPG site -2.5%: generator rotation -1%: insulation damage Rare: -Dural puncture (0–0.3%) -Epidural abscess -Epidural hemorrhage
Song et al. (2013) [37]	-FBSS -CRPS -Peripheral ischemic limb pain -RAF	-Traditional -PNfS -DRG -HF10	Examine current evidence supporting use of SCS for approved indications	Not examined	SCS is superior to CMM and reoperation in FBSS and has shown clinical benefit in CRPS, critical limb ischemia, and RFA	-10–30%: Lead migration/breakage -3–5% Infection -5–6%: Persistent pain -Paresthesia due to electrode mobility with position change

Table 2 (continued)

Author, year	Pain diagnosis	SCS parameter	Primary outcome	Secondary outcomes	Result	Adverse effects
Oakley et al. (2002) [39]	Not specified	Not specified	Present the current status of what is known concerning how electrical stimulation of the spinal cord may achieve pain relief	Not examined	The literature shows that the mechanism of SCS cannot be completely explained by one model. It is likely that multiple mechanisms operate sequentially or simultaneously	Not discussed
Kumar et al. 2007 [43]	Radiating neuropathic pain in FBSS	Mean (standard deviation) settings: -Amp: 3.7 V (2.0) -Pulse width: 350 µs (95.5) -Rate: 49 Hz (16.4) -45% of patients required Amp ≥ 4 V	Proportion of patients with ≥ 50% leg pain relief	-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 -Incidence of complications -Adverse effects	100 subjects: 48 (CMM) + 52 (CMM + SCS) -24 SCS patients (48%) and 4 CMM patients (9%) had ≥ 50% leg pain relief at 6 months -SCS group had increased leg and back pain relief, quality of life, functional capacity, and satisfaction, and experienced less drug adverse events -27 SCS patients (32%) had device-related complications at 12 months	- 10%: electrode migration (10%) - 8%: infection or wound breakdown - 7%: loss of paresthesia - 35% of SCS group 52% of CMM group had ≥ 1 non-device-related event (most commonly drug related)
van Beek et al. 2019 [44]	Painful diabetic peripheral neuropathy	Not specified	Treatment success rate at 24 months post-SCS implant	Not examined	- 53% of SCS group reported clinically significant improvements for pain and sleep at 24-month follow-up - 65% of SCS group reported treatment success - No significant difference was observed in treatment success rate at 6- vs 24-month follow-up	Infection (1/22 enrolled patients)
Kapural et al. 2015 [45]	Chronic leg and back pain	Average and SD of the minimum, maximum programmed parameters: frequency 39.2 ± 15.0, 77.3 ± 133.5 Hz; amplitude 3.6 ± 2.8, 8.5 ± 4.0 mA; pulse width 347 ± 148, 591 ± 214 µs)	≥ 50% back pain reduction with no SCS related neurologic deficit	- Opioid use - Disability index - Functional capacity - Satisfaction - Uncomfortable stimulation	At 3 months: - 84.5% of HF10 therapy subjects with significantly improved back pain & 83.1% for leg pain - 43.8% of traditional SCS subjects with significant improvement of back pain and 55.5% for leg pain - HF10 superiority maintained at 12 months - HF10 patients did not have paresthesias - Decreased opioid use (12 months): 35.5% (HF10) and 26.4% (traditional SCS) - Disability level (on ODI): average decrease of 16.5 (HF10) and 13 (traditional) - Satisfaction: 55.4 (HF10) and 32.3% (traditional) reported being very satisfied - Uncomfortable stimulation: 0% (HF10) and 46.5% (traditional)	- Implant site pain: 11.9% (HF10) and 10.3% (traditional SCS) - Uncomfortable paresthesia: 0% (HF10) and 11.3% (traditional SCS) - Lead migration resulting in surgical revision: 3% (HF10) and 5.2% (traditional SCS) Only 4.0% of HF10 therapy subjects had a study-related serious adverse effect compared with 7.2% of traditional SCS subjects Non-serious study-related adverse effects were reported in 27.7% of HF10 subjects and 33.0% of traditional SCS subjects

Table 2 (continued)

Author, year	Pain diagnosis	SCS parameter	Primary outcome	Secondary outcomes	Result	Adverse effects
Kapural et al. 2016 [46]	Chronic pain	HF10 therapy: 10 000 Hz, 30 µs stimulation with amplitude and stimulation location adjusted to obtain optimal analgesic response Traditional low-frequency SCS (40–60 Hz)	Compare long-term results of HF10 therapy and traditional low frequency SCS Responder rate, defined as $50% back pain reduction from baseline at 3 months	Secondary outcomes included the percentage of subjects who responded for leg pain, the percent pain relief for back and leg pain, and the disability level over the follow-up (12/24 months) period	198 subjects were randomized (101 HF10, 97 traditional) 171 (90 HF10, 81 traditional) completed a short-term trial and were implanted At 3 months: -84.5% of HF10 had primary outcome for back pain and 83.1% for leg pain - 43.8% of traditional subjects had primary outcome for back pain and 55.5% for leg pain At 24 months: more subjects met primary outcome in HF10 group than traditional (back pain: 76.5% vs 49.3%; leg pain: 72.9% vs 49.3%). - back pain decreased to a greater degree with HF10 therapy (66.9% ± 31.8%)vs traditional (41.1% ± 36.8%) -Leg pain also decreased to a greater degree with HF10 therapy (65.1% ± 36.0%) than traditional SCS (46.0% ± 40.4%) Long-term superiority of HF10 therapy compared with traditional SCS in treating both back and leg pain	5.0% in HF10, 7.2% in traditional group Most common: - Implant site pain (12.9% of HF10 group; 13.4% of traditional group) - Uncomfortable paresthesias (0% of HF10 subjects; 11.3% of traditional subjects) - Lead migration resulting in surgical revision (3% of HF10 subjects; 5.2% of traditional subjects)
Deer et al. (2017) [47]	Chronic pain of the trunk and/or limbs	Tonic (pulse 100–500 µs and freq 30–100 Hz) and burst (500 Hz)	Establish noninferiority of pain intensity after 3 months of burst compared to 3 months of tonic stimulation	1: VAS pain diary 2: Analysis of the presence of paresthesia to demonstrate the differences between the two stimulation modes 3:	121 Subjects: Burst stimulation is superior to tonic stimulation ($p < 0.001$) -VAS decrease by 30%: decrease in the overall daily VAS score from baseline by at least 30%. A total of 69/100 subjects (69.0%) responded to tonic stimulation, burst stimulation, or both. For the individual stimulation modes, 60.0% (60/100) of subjects were responders to burst stimulation and 51.0% (51/100) of subjects were responders to tonic stimulation Significantly more subjects (70.8%) preferred burst stimulation over tonic stimulation ($p < 0.001$). Preference was sustained through one year: 68.2% of subjects preferred burst stimulation, 23.9% of subjects preferred tonic, and 8.0% of subjects had no preference	A total of 158 AEs was reported during the study, 94 (59.5%) of which were considered to be non-study related. Twenty-one (21) events were considered serious adverse events (SAEs) and were reported in a total of 16 subjects (9.2%). Of all SAEs reported, only two events occurring in two subjects (1.2%) were considered study related. Both study-related SAE's occurred between the enrollment phase and activation phase of the study and included one event of persistent pain and/or numbness and one unsuccessful lead placement. Two deaths occurred during the study, both of which were un-related to the study or device [Correction added on 08 January 2018, after first online publication: the preceding sentence has been updated to correct the number of deaths.]. Non-study related SAE's occurring between enrollment and activation of the study included events such as abdominal pain, femur fracture, hip pain/hip replacement, and low potassium levels. Following activation, non-study related SAE's included 1 infection, 1 subject with a scheduled right total knee arthroplasty, 1 subject with shortness of breath, 1 infection, among others. Table 4 summarizes all the reported adverse events

Table 2 (continued)

Author, year	Pain diagnosis	SCS parameter	Primary outcome	Secondary outcomes	Result	Adverse effects
North 2005 [64]	Surgically remediable nerve root compression and concordant persistent or recurrent radicular pain (with or without lower back pain), after ≥ 1 lumbosacral spine surgery	Permanent implant (3487A-56 or 3587A Resume electrode, X-trel or ITrel pulse generator; Medtronic Inc.)	1) Crossover from randomized to alternative procedure 2) Success at last follow-up 3)Improved daily activities, neurological status, and medication use	N/A	Rate of crossover from reoperation to SCS was consistently higher than rate of crossover from SCS to reoperation ($p = 0.02$) SCS significantly more success than reoperation: 9 (47%) of 19 patients randomized to SCS and 3 (12%) of 26 patients randomized to reoperation achieved at least 50% pain relief	1 SCS patient developed infection 3 SCS patients underwent hardware revisions because of technical problems 1 reoperation patient developed wound infection
Kemler et al. 2000 [68]	Reflex sympathetic dystrophy (defined by the International Association for the Study of Pain)	Model 3487A (Medtronic) implanted and fixed with special clips; pulse generator activated (rate, 85 Hz; pulse width, 210 μsec) with use of console programmer (model 7432, Medtronic)	Pain (VAS and McGill Pain Questionnaire); global perceived effect; functional status; range of motion by goniometry	N/A	Mean reduction of 2.4 cm in the intensity of pain at 6 months, as compared with an increase of 0.2 cm in the group assigned to receive physical therapy alone	Dural puncture; infection; painful pulse generator pocket; defective lead; unsatisfactory positioning

This reflects selected studies and is not meant to be a comprehensive list of all SCS studies

HF10 high-frequency SCS; *FBSS* failed back surgery syndrome; *SCI* spinal cord injury; *IPG* implantable pulse generator; *CMM* conventional medical management; *CRPS* complex regional pain syndrome; *RAF* refractory angina pectoralis; *PVD* peripheral vascular disease; *PNfS* peripheral nerve field stimulation; *ODI* Oswestry Disability Scale

outcome. The largest study to examine sleep quality as a secondary outcome was a double-blind, randomized, placebo-controlled study of THC/CBD spray in 303 subjects with peripheral neuropathic pain. Secondary measures of sleep quality, 0–10 NRS score ($p = 0.0072$) and Subject Global Impression of Change (SGIC) ($p = 0.023$) demonstrated statistically significant differences (> 30% reduction in NRS baseline) in favor of THC/CBD spray over placebo among treatment-resistant patients [65].

A prospective cohort study by Capano et al. investigated the impact of full hemp extract cannabidiol (CBD) on opioid use (primary outcome) and quality of life (secondary outcome) indicators among 97 chronic pain patients. 94% of CBD users reported quality of life improvements after 8 weeks of use, with a significant relationship between CBD and sleep quality improvement (PSQI, $p = 0.003$), and PEG ($p = 0.006$). Interestingly, despite trends toward improvement, there was no significant relationship between CBD use and PHQ and PDI [66].

A randomized, double-blind, placebo-controlled, flexible-dose efficacy study by Toth et al. including 26 participants suggested that flex dose nabilone was effective in improving sleep quality, quality of life and overall well-being in addition to reducing diabetic neuropathy symptoms. This was also one of few studies that evaluated anxiety as a secondary outcome, demonstrating improvements from baseline for the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) [59]. In another randomized, double-blind, placebo-controlled, three period crossover study, Berman et al. examined the effect of Sativex in 48 patients with chronic neuropathic pain secondary brachial plexus root avulsion. Although the primary outcome measure (mean pain severity score during the last 7 days of treatment) failed to fall by two points as defined in the original hypothesis, secondary outcome measures of sleep showed statistically significant improvements [55]. Rog et al. performed a randomized, controlled trial showed a decrease in sleep disturbances among patients using cannabis-based medicine for central pain in multiple sclerosis [53].

Secondary Outcomes with SCS Alone

As the role of spinal cord stimulation in the management of chronic pain has continued to evolve, secondary outcome measures have demonstrated several notable findings. These primarily include decreased opioid consumption, increased functional capacity, and decreased economic costs. Several studies have also compared the efficacy of advanced iterations of SCS therapies and examined various secondary outcomes. In an RCT by Kumar et al. comparing SCS with conventional medical management (CMM), the SCS group had increased quality of life, functional capacity, and overall satisfaction, and experienced less drug adverse events [43]. Kapural et al. reported decreased opioid usage by an average of 35.5% in the HF10 group, and by 26.4% in the traditional

SCS group. They also reported that 55.4% of HF10 subjects and 32.3% traditional SCS subjects reported being very satisfied with their outcomes overall [45]. From a cost efficiency perspective, a literature review by Oakley and Prager concluded that despite high upfront cost, SCS results in decreased long-term health care costs compared with CMM [39]. However, a systematic review by Odonkor et al. suggested that a majority of studies examining benefits of SCS are of fair quality, with level 3 or 4 evidence supporting cost effectiveness of SCS over CMM [67].

In a randomized control trial comparing HF10 with traditional SCS in the treatment of chronic back and leg pain, continued pain relief at 12 and 24 months was evaluated as a secondary outcome, whereas the primary outcome was defined as ≥ 50% pain relief at 3 months. At 24 months, more subjects met the primary outcome in the HF10 group than traditional (back pain: 76.5% vs 49.3%; leg pain: 72.9% vs 49.3%). Additionally, both back and leg pain decreased to a greater degree with HF10 therapy (back: 66.9% ± 31.8%; leg: 65.1% ± 36.0%) verses traditional SCS (back: 41.1% ± 36.8%; leg: 46.0% ± 40.4%). Based on this, the authors concluded that HF10 therapy has long-term superiority compared with traditional SCS in treating both back and leg pain [45].

Several studies evaluated functional outcomes of SCS patients through a variety of different measures. Kapural et al. evaluated for disability using the Oswestry Disability Index and reported an average decrease in disability scores by 16.5 points in the HF10 group, and by 13 points in the traditional SCS group [45]. A 2018 meta-analysis by Moens et al. suggests that SCS is associated with lower median time of unemployment, and that SCS patients are more likely to increase working time [34].

Secondary Outcomes with Use of Cannabinoid and SCS Combined

In the study conducted by Mondello et al. on the combination of cannabinoids and SCS in 11 FBSS patients, the Brief Pain Inventory (BPI) was used to assess patients both at their first visit and at the end of the 12-month treatment period. Items on the questionnaire include general activities, mood, walking abilities, normal work, relations with other people, sleep, and overall enjoyment of life. The results of the study suggested a statistically significant improvement in every item on the questionnaire, most remarkably in sleep quality (11/11; $P < 0.01$) [57]. Study results are summarized in Table 3.

Adverse Effects

Adverse Effects with SCS Alone Studies

The vast majority of SCS adverse effects are considered minor in nature. Minor study-related adverse effects were

Table 3 Combination therapy of SCS and cannabinoids

Author	Pain diagnosis	Cannabinoid type	SCS therapy mode	Dose of cannabinoid	Duration of therapy	Primary outcome	Secondary outcome	Result	Adverse effect
Mondello 2018 [63]	Failed back surgery syndrome	Combination THC and CBD	N/A	Oleic suspension of THC (19%) and CBD (< 1%) 25 mg per day (PO)	12 months	Analgesia (numeric rating scale) Brief pain inventory	N/A	Mean pain perception calculated using the NRS decreased from 8.18 ± 1.07 at first visit to 4.72 ± 0.9 at the end of the observational time in all cases	Drowsiness; attention/concentration disorders; dry mouth; headache; nausea/vomiting; apathy; puffy lips; palpitations; dizziness; subjective sense of facial dysmorphism; mood disorders; forgetfulness; increased urinary retention

reported by Kapural et al. in 27.7% of HF10 subjects and 33.0% of traditional SCS subjects [45]. Overall, the incidence of minor, reversible, complications is thought to be 30–40% [31]. Among these, the most commonly cited complications in our review were superficial infection, lead migration, lead fracture, implant site pain, and uncomfortable paresthesia, respectively [35–37, 33–46, 68]. In the majority of studies, lead migration had the highest incidence of all reported complications [35–37, 43]. Other relatively minor complications for which incidence was not reported include IPG failure and allergic reaction [35]. It is worth noting that Kumar et al. reported ≥ 1 non-device-related events (most commonly drug related) in 35% of SCS group subjects compared to 52% of CMM group subjects [43].The most commonly reported adverse event is lead migration with incidence of 13%, most often seen among failed back surgery patients.

Overall, severe complications from SCS therapy are considered very rare. These include dural puncture, epidural fibrosis, spinal cord injury, and compressive phenomenon, including epidural abscess and epidural hemorrhage [35, 36, 67]. The incidence of these complications was not reported individually; however, Kapural et al. reported study-related serious adverse events in 4.0% of HF10 therapy subjects, compared with 7.2% of traditional SCS subjects [45, 46].

Adverse Effects with Cannabinoid Alone

Among the articles included in this review, the most commonly reported adverse events among subjects receiving only cannabinoid therapy were drowsiness/fatigue, dizziness, dry mouth, and nausea/vomiting, respectively [53–57, 59, 66]. Others, although less common, included heartburn, headaches, myalgias, vertigo, poor sleep quality, anxiety, nightmares, PTSS, dysgeusia, euphoria, memory loss, disassociation, and disorientation [52–57, 59, 65–69]. A study conducted by Reiman et al. did not highlight any specific adverse effects seen in cannabis users, however the study suggested that cannabis users had decreased opioid use, and thus experienced fewer side effects from opioid medications as a result [70•].

Adverse Effects with Use of Cannabinoid and SCS Combined

As can be expected by the nature of adverse effects mentioned previously in studies examining cannabinoid and SCS therapies separately, a review of the literature on the combination of both therapies does not reveal any severe adverse events. However, studies examining combination SCS and cannabinoid therapy are scant. In the study conducted by Mondello et al. on the combination of cannabinoids and SCS in 11 FBSS patients, all reported adverse events were transient, and none required medical attention or discontinuation of therapy. Reported adverse events that overlap with adverse events reported in studies examining cannabinoid and SCS therapies separately include drowsiness, attention/concentration disorders, dry mouth, headache, nausea/vomiting, palpitations, dizziness, subjective sense of facial dysmorphism, mood disorders, and forgetfulness. Interestingly, there were a few adverse effects noted in this review that were not mentioned in studies examining cannabinoid and SCS therapies separately alone. These include apathy, puffy lips, and increased urinary retention [63].

Conclusion

As research continues to develop on the role of SCS and cannabinoid therapy individually, more studies are needed to examine the efficacy of combination SCS and cannabinoid therapy. It will be instructive for future studies to consider the potential role of SCS therapy among patients with chronic cannabinoid use. Compared to SCS, data remains limited regarding the clinical efficacy of cannabinoids for pain relief. Although preliminary scant trial data supports the combination of SCS and cannabinoid adjuvants in the management of chronic nociceptive and neuropathic pain, further higher quality studies are needed to ascertain whether they work by additive or synergistic mechanisms.

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Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest None to disclose.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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