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Application and future trends of spinal cord stimulation

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ABSTRACT

Neuropathic pain impacts 7-10% of the general population and seriously undermines quality of life despite available medications. Although initially approved to treat chronic neuropathic pain as an alternative to conventional medical management, spinal cord stimulation (SCS) is expanding its application prospect to the treatment for an assortment of indications including ischemic pain and neurodegenerative disorders, with new stimulation modalities, techniques, and electrode materials emerging every year. Despite its proven efficacy and cost-effectiveness when compared with the long-term application of insufficiently effective and potentially harmful medications, SCS is still largely neglected by pain physicians and neurosurgeons worldwide because of the exorbitant cost of the devices and possible complications. The mechanism of action, constituents and clinical applications, and performance of SCS are here reviewed, with a special focus on five indications amenable to SCS treatment, including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), painful diabetic neuropathy (PDN), critical limb ischemia (CLI) and Parkinson's disease (PD). Among all the indications, only FBSS and CRPS have a mature application scenario, and SCS treatment for PDN has just recently been approved by FDA. The clinical study of more conditions that may benefit from SCS treatment, such as CLI and PD, is still underway. Market expectations and recent developments of SCS are further discussed to provide an outlook for the future trends of spinal cord stimulation.

Keywords: spinal cord stimulation, constituent and mechanism, clinical applications

1. INTRODUCTION

Spinal cord stimulation (SCS) is an interventional therapy initially approved by the Food and Drug Administration (FDA) as a treatment for chronic neuropathic pain, which is pain induced by a disease or lesion of the somatosensory system and impacts 7-10% of the general population [1]. Neuropathic pain severely undermines quality of life and increases the burden on society. However, conventional medical management (CMM) of neuropathic pain such as antidepressants and opioids only has very limited effectiveness and may be associated with a wide range of adverse effects [2]. As a relatively new treatment for neuropathic pain refractory to CMM, SCS entered clinical application as a direct derivative of Melzack and Wall's gate control theory (GCT) of pain [3]. Since then, SCS has gained a foothold as an efficacious treatment for chronic pain resulting from many etiologies, improving mental health and quality of life [4].

SCS has produced positive clinical outcomes in the treatment for chronic pain of various origins. Its primary indication, however, is neuropathic pain. The pathology of neuropathic pain, although still not fully understood, predominantly involves a disease or lesion of the myelinated Aβ and Aδ fibers and the small unmyelinated C fibers [1]. As shown in (Fig. 1), the mechanism underlying SCS therapy was first explained through GCT [3], which proposed that electrical stimulation of the projections of non-nociceptive Aβ fibers inside the dorsal horn could inhibit signals transmitted by nociceptive Aδ and C fibers. However, recent studies have proven this traditional theory insufficient to fully elucidate the mechanisms through which SCS modulates and alleviates neuropathic pain, suggesting the involvement of both spinal pathways and supraspinal centers of the neuromatrix [5]. According to the neuromatrix theory of pain, pain is generated through the output of a broadly distributed neural network spread across the brain, of which the somatic sensory input caused by injury or disease is only one part [6]. In other words, the brain does not just passively receive and process afferent pain signals from the body, but it may give rise to pain feelings on its own without any incoming nociceptive signals, a fact that is particularly related to some types of chronic pain. As a result, there is little understanding of why

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SCS works in some patients but has very poor effects on others.

Although the pain-generating mechanism is convoluted and constitutes an enormous obstacle to the widespread use of SCS, numerous advances in SCS have been made in recent years, which include novel stimulation modalities such as high-frequency burst spinal cord stimulation (Burst-SCS) and high-frequency SCS (HF-SCS) [7], novel techniques such as dorsal root ganglion stimulation (DRG-SCS) [5] and closed-loop evoked compound action potential SCS (ECAP-SCS) [8], and technological development such as wireless power transfer [9] and emerging electrode materials [10]. As deeper rules of pain inhibition are revealed and new stimulation technologies are developed and approved, SCS no doubt has a bright prospect.

In this review, first of all, we introduce the constituent of a conventional SCS system. Then we mainly talk about the application of SCS treatment in various types of chronic conditions, explaining the definition and background of each condition and how SCS devices work on it. We discuss the validated research data and draw some comparisons between different types of SCS and conventional treatment methods such as medications and physical therapy. In the end, by summarizing clinical data and conclusions from other reviews, we discuss the pros and cons of current SCS technology, describe recent developments, and provide our perspectives on the future trends of SCS.

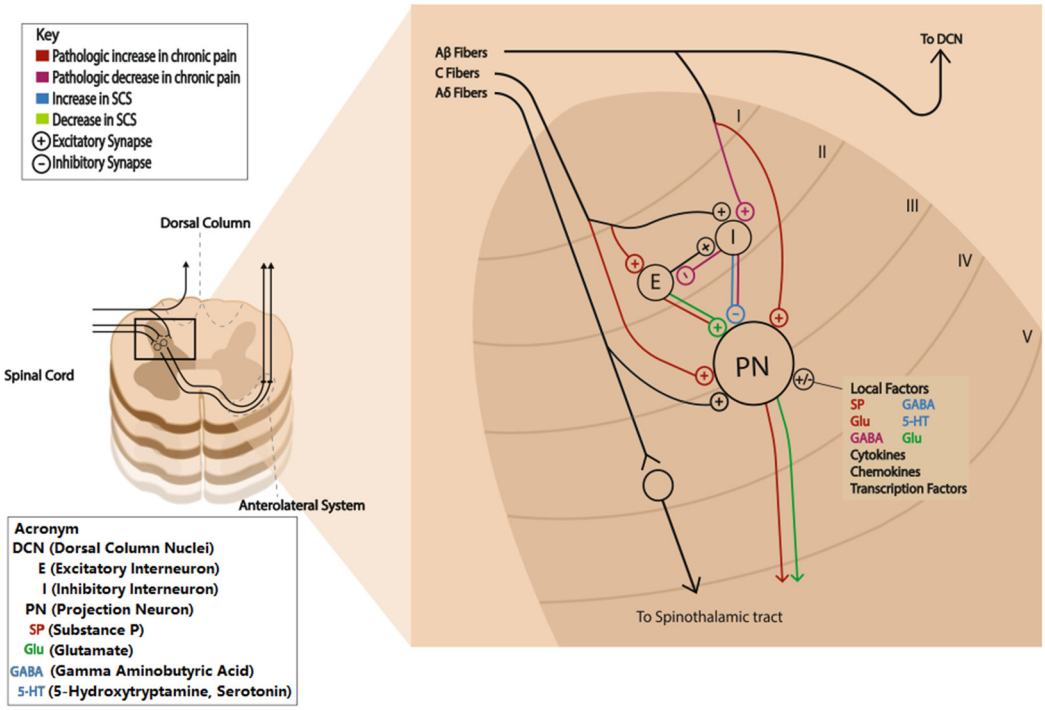

Figure 1. Changes in the Dorsal Horn Circuitry resulting from chronic pain or SCS. When chronic pain develops, the neural circuitry undergoes abnormal reconfiguration in which reinforcement of excitatory pathways and attenuation of inhibitory pathways combined with local factors destabilize the normal input equilibrium of the projection neuron, resulting in nociceptive responses to sub-threshold stimuli. SCS helps restore balance through the activation of local segmental as well as descending supraspinal mechanisms. Image modified from [8].

2. CONSTITUENT OF A SPINAL CORD STIMULATOR

An implantable and a wearable component make up a conventional spinal cord stimulator. The implantable portion, as illustrated in (Fig.2), consists of electrodes that are placed in the dorsal column and lead wires that connect the electrodes to an implantable pulse generator (IPG) with a battery. The wearable part usually comprises a remote control to adjust the IPG and a battery recharger to wirelessly recharge the IPG battery.

IPG dictates the waveform of the spinal cord stimulator, which can be conventional (tonic), HF or Burst. In conventional tonic SCS, IPG generates very simple square waves, which lead to paresthesias in patients, an undesirable adverse effect. With the advent of HF-SCS and Burst-SCS, there is a significant improvement in user experience and stimulation effects.

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After the electrical pulses are generated by IPG, they travel to the electrodes through the lead wire and then stimulate the nerve fibers within the dorsal horn, resulting in inhibition of the pain signal pathway as illustrated in (Fig.1).

Electrodes also play an essential role in SCS, since their material directly determines the bio-compatibility of an SCS device, and the placement of electrodes has a direct impact on pain relief. As the electrodes' functional part directly contacts the spinal cord and stimulates it electrically, the material needs to be bio-compatible and carefully selected to avoid voltage overshoot, otherwise, tissue damage, impaired stimulation performance, and paresthesias may occur. Appropriate placement of electrodes is as important as choosing the right material for the electrodes [11], and there is an optimal position to place the electrodes in each patient. To achieve the desired position of the electrodes, patients are usually required to keep awake and constantly interact with the surgeon in the implanting surgery session.

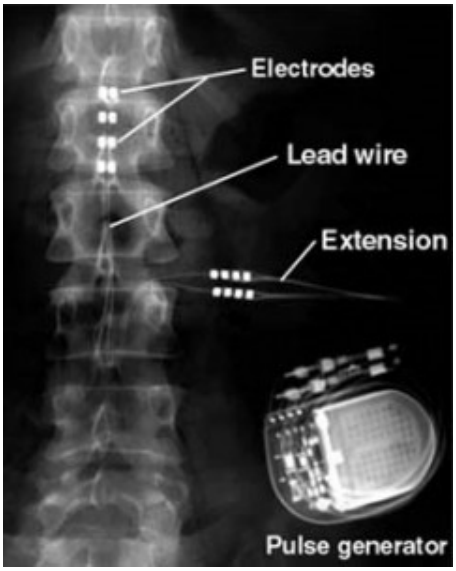

Figure 2. Placement and constituent of a spinal cord stimulator. Image modified from Spine Institute Northwest. (https://www.fixmypain.ca/treatments/spinal-cord-stimulators/)

3. CLINICAL APPLICATIONS

SCS has been applied in the treatment for a wide range of chronic intractable conditions, but there is an obvious scarcity of randomized controlled trials (RCTs). The primary indication of SCS, neuropathic pain, mainly includes failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and painful diabetic neuropathy (PDN). In addition, there is mounting evidence to suggest the use of SCS in ischemic pain such as critical limb ischemia (CLI) and neurodegenerative disorders such as Parkinson's disease (PD). Among all the indications amenable for SCS, only FBSS and CRPS have a mature application scenario, and the first SCS device to treat PDN has just been approved by FDA in 2022. The clinical study of more conditions that may benefit from SCS treatment is still underway.

3.1 Failed Back Surgery Syndrome (FBSS)

FBSS is defined as out of expectation of patients or surgeons after a spine surgery, which leads to chronic low back pain. Spine surgeries are likely to fail with an incidence of 10-40%. Due to the increasing number of spine surgeries each year, the number of FBSS patients also shows a year-on-year growth. Research on FBSS dates back hundreds of years, and before the appearance of SCS, CMM was the main approach to suppressing low back pain. Because of its long-term efficacy and complete absence of addiction, SCS has emerged as one of the surgical options for FBSS patients. Enough clinical evidence has been put forward to advocate SCS treatment for FBSS patients, and presently there have been plenty of trials carried out to compare paresthesia-based conventional SCS therapy with paresthesia-free SCS modalities such as HF and Burst [12]. A lot of research has proven that most patients will have a prominent preference for paresthesia-free SCS.

Kallewaard et.al found that HF-SCS took effect on nearly 90% of FBSS patients in their trial. Sixty patients received SCS implantation and after 12 months, 80% of them reported that their pain feeling had a reduction by more than 50%

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[13]. Nissen et.al analyzed more than 20 years of data collected from 224 patients implanted with SCS and focused on the comparison between CMM and SCS [14]. They demonstrated that higher opioid use before implantation may lead to a higher probability of implantation failure. And for those SCS-incompatible patients, they would rapidly have to increase the dose of opioid drugs after the explantation of SCS. On the contrary, some of the opioid users with successful implantation would rely less on opioid drugs or completely abstain from them. For different kinds of paresthesia-free SCS methods, the rate of successful abstinence ranges from 30% to 40%, whereas the success rate of conventional SCS is nearly 20%. Interaction between SCS and CMM is complicated, but most clinicians have to consider it since patients normally receive multiple therapies. Drugs research also indicates that SCS surgery failure is highly related to medication history.

3.2 Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS) is characterized by excruciating pain quite disproportional to the inciting event, in association with motor, sensory, autonomic, and trophic abnormalities [15]. There is a distinction between CRPS type I, in which a nerve lesion is not present, and CRPS type II, in which it is. Although our understanding of CRPS has increased substantially over the past few decades, with the discovery of multiple mechanisms, the pathophysiology of CRPS remains elusive and there is as yet no scientifically-validated cure for CRPS [15].

The consensus opinion of experts suggests that SCS should be considered in the treatment plan after CMM has failed to relieve chronic pain induced by CRPS. Moreover, SCS has been proven to successfully improve blood flow and alleviate endothelial dysfunction in CRPS patients by attenuating T-cell activation, improving peripheral tissue oxygenation, and suppressing anti-angiogenetic activity [16].

Kemler et al. were the first to carry out a prospective RCT in patients suffering from CRPS type I, which found that in patients receiving SCS treatment combined with physical therapy (PT), the average pain intensity was greatly diminished and the global perceived effect was much more improved, compared with the control group who only received PT [17]. Harke et al. studied the long-term impact of SCS on improving the functional status in CRPS type I patients and found that, after SCS therapy, there was a permanent reduction from 10 to 0-2 in both pain and allodynia on a 10 cm visual analog scale (VAS) [18]. Geurts et al. conducted a prospective cohort study which showed that, during 12 years of follow-up, SCS provided efficacious long-term pain relief for 63% of patients implanted with SCS and 41% of them had more than 30% pain reduction after the end of the study [4]. As for new stimulation modalities and techniques, Goebel et al. found that DRG-SCS could be promising in some CRPS cases where conventional SCS treatment has failed [19]; Gill et al. suggested that HF-SCS at 10 kHz might be a feasible therapy for CRPS patients with chronic pain, even including those who received unsatisfying outcomes from conventional SCS treatment [20].

3.3 Painful Diabetic Neuropathy (PDN)

About one in every three diabetic patients is affected by painful diabetic neuropathy (PDN) [21], which is defined as pain arising from peripheral somatosensory system abnormalities in diabetic people. PDN is characterized by various sorts of pain feelings occurring with paresthesias or allodynia and significantly impairs quality of life. Available medications for PDN such as anticonvulsants have poor long-term adherence, inadequate pain relief, and several adverse effects including confusion, fatigue, and dizziness, which are more severe among elderly patients [22].

SCS offers a novel and effective approach to alleviating chronic PDN and thus should be considered for patients who do not respond to CMM. However, further research is required to clarify the potential mechanisms, which may involve increased cutaneous blood perfusion in the periphery, improved central or peripheral sensory processing, and changes in the density of intraepidermal nerve fibers [23].

SCS treatment for PDN was first reported by Tesfaye et al. in 1996, suggesting statistically significant pain relief at 3, 6, and 14 months and improvement of exercise tolerance at 3 and 6 months [24]. Later, conventional SCS was contrasted with CMM in patients experiencing PDN in a prospective RCT with 6-month follow-up, which proved the superiority of SCS over CMM, as 59% of patients in the SCS-treated group met the success criteria at 6 months, but only 7% of patients in the control group did [25]. A 5-year follow-up of another prospective clinical study by van Beek et al. found that, after 5 years, treatment success of SCS was seen in 55% of all patients, and 80% of those who had received a permanent SCS implant continued using their device [26]. Additionally, the more severe the neuropathy was, the more likely long-term SCS treatment would fail during the 5-year follow-up. Recently, Petersen et al. conducted a prospective, multicenter RCT using a Senza system (Nevro Corp.), which showed that HF-SCS at 10 kHz could achieve the best results, as 79% of patients in the HF-SCS combined with CMM group experienced at least 50% pain reduction at 3

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months, with merely 5% in the CMM group; at 6 months, neurological examination results improved in 3% of the CMM group and 62% of the HF-SCS combined with CMM group [27].

3.4 Critical Limb Ischemia (CLI)

The definition of critical limb ischemia (CLI) is severe claudication, ischemic rest pain, tissue loss, or gangrene when peripheral artery disease and hypoperfusion of the lower extremities are present [28]. CLI results from a long-term shortage of blood supply, triggering a series of pathophysiological events which in the end give rise to rest pain or trophic lesions in the legs. Patients with non-reconstructible CLI have a poor prognosis, with amputations continuing to be performed despite recent advancements in revascularization.

CLI patients who are unsuitable for endovascular intervention or surgery or who have undergone revascularization but still suffer even after proper medical treatment are identified as potential candidates for SCS treatment [29]. SCS activates cellular signaling molecules which then cause an array of events, including the release of vasodilatory molecules, drops in vascular resistance, and the relaxation of smooth muscle cells. Moreover, SCS inhibits pain transmission and sympathetic vasoconstriction and mitigates microvascular perfusion deficiency. As a consequence, SCS provides relief of rest pain, avoids or delays amputation, and improves the patient's quality of life [30].

Cook et al. were the pioneers to propose that SCS treatment might avoid the necessity for amputation in a certain number of CLI patients [31]. Ubbink et al. assessed 6 clinical studies comprised of nearly 450 patients and concluded that pain relief and limb salvage after 12 months were significantly higher in the SCS-treated group, with far more patients reaching a better stage than in the control group receiving conservative medical treatment [32]. Klinkova et al. evaluated the long-term clinical results in CLI patients receiving SCS treatment and found that one year after SCS, 74% of patients reported optimistic clinical outcomes, with pain intensity in VAS considerably decreased from 8 to 2 cm and brachial-ankle index (ABI) improved from 0.27 to 0.51 [33]. However, adverse clinical results were observed in 16.7% of the total cases, which might be ascribed to low peripheral tissue metabolism values and impaired functional status of the microvasculature. Nevertheless, CLI patients treated with SCS experienced significantly improved quality of life, including drops in pain severity and increases in walking and sleep quality.

3.5 Parkinson's disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disorder with a 0.1-0.2% incidence above the age of 40. Notably, in North America, over 1 million people are affected by PD. The most usual PD symptoms include tremors, pain, and postural instability, profoundly impacting quality of life and even mortality rates [34]. Current treatment for PD includes dopamine therapy as well as deep brain stimulation (DBS), but these methods are faced with challenges such as reduced efficacy and protracted use time. Recently, however, there is mounting evidence suggesting that for PD patients, SCS can be utilized both as an independent treatment and as a salvage therapy after DBS has lost its effectiveness.

The mechanisms of SCS treatment for PD are still inadequately explained. One of the possibilities is that electrical stimulation of the spinal cord transmits signals to basal ganglia circuits. After that, the release of stored dopamine is promoted, a process similar to DBS. A neuroprotective component caused by SCS may also delay the progression of dopaminergic neuron loss in the brain. Furthermore, using SCS, only 1/5 of the original dose of levodopa would be sufficient to bring equivalent improvements in locomotion compared with levodopa alone in the rat model [34]. Increased understanding of how dopamine replacement therapy can be optimally combined with SCS is one of the further goals in relieving motor symptoms in PD patients.

Thevathasan et al. found that SCS was unsuccessful in relieving akinesia or restoring locomotion in PD patients with leads placed in the high cervical position [35]. However, another study by Fénelon et al. demonstrated that SCS improved gait disorders and abnormal posture with leads placed at the T9-T10 level [36]. Moreover, little information is available on the possible synergistic combination of SCS and DBS in PD patients regarding improved gait and postural instability. Indeed, all levels of the nervous system are involved in the neuroanatomy of gait function. Thus, it is hard to point out a specific area that would receive the most benefits from SCS in the improvement of gait function. Nevertheless, the combination of DBS and SCS offers a novel method capable of stimulating several complementary neuronal areas at the same time, improving postural function and optimizing transmission in spinal locomotor tracts. Recently, Mazzone et al. compared conventional SCS with Burst-SCS in the high cervical region (C1-2 or C2-3) and found that patients treated with Burst-SCS reported faster improvement in motor functions and needed fewer adjustments to programming in 3 months [37]. However, more work is still required to achieve optimal effectiveness at specific spinal levels and with the best stimulation modalities.

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4. DISCUSSION

Among the five indications discussed above amenable to SCS treatment, the safety and high performance of SCS treatment for FBSS and CRPS have already been demonstrated by adequate clinical evidence. Therefore, researches mainly focus on the improvement of SCS efficacy and cost-effectiveness as well as alleviation of adverse effects. In recent years, SCS treatment for FBSS and CRPS patients has significantly benefitted from innovations in electrode material and stimulation modalities and techniques, resulting in an average of more than 60% pain reduction. The clinical trials of SCS for PDN also came to fruition, leading to FDA approval of the first commercial SCS device for PDN in 2022. More possibilities remain to be explored for SCS in various pain-related fields. As more profound rules of pain relief and neuromodulation are revealed, it is hopeful that SCS may soon be approved to treat CLI and PD, where there is already plenty of research. However, the interaction between SCS and CMM must be considered for practical SCS products because both synergy and incompatibility may occur when CMM and SCS are applied to a patient simultaneously.

Typical SCS indications such as FBSS or CRPS already enjoy a mature market. However, at the present stage, CMM is still the mainstream approach to treating neuropathic pain even though SCS has been available for decades and the performance of SCS therapy overwhelms some of the conventional ones [13]. Although it is not possible for SCS treatment to completely replace CMM due to the intrinsic drawbacks of SCS such as invasiveness and potential failures and complications, it is highly likely for SCS to replace some of the low-efficacy CMM treatments. Meanwhile, it is worthwhile to popularize SCS treatment for FBSS and CRPS patients in developing countries, which is currently hampered by the exorbitant cost of the SCS device and lack of knowledge of SCS.

On the other hand, for SCS to be extended to new fields, it is crucial to utilize novel stimulation technologies combined with other therapies. For some complicated diseases like PD, ongoing research and explorations into conventional tonic SCS in cervical and thoracic positions and Burst-DRG spinal cord stimulation have yielded positive outcomes. However, it is not feasible to stop using drugs since the underlying pathology is still unclear. Different stimulation patterns and frequencies should also be considered to optimize efficacy. With advances in clinical research and big data, it is very hopeful that before long, each patient's preferences for stimulation modality, technique, or system could be taken into account to customize individual stimulation approaches [7].

For practical uses of SCS, electrode selection and placement are as vital as stimulation modalities. Inappropriate placement of the electrodes could result in inadequate pain reduction and more severe adverse effects. Therefore, a cautious assessment should be conducted to find the best placement of electrodes before SCS implantation. One of the most common problems causing low efficacy is voltage overshoot, which could be resolved with the help of emerging electrode materials. Lithium iron phosphate (LFP) has been widely studied as a promising material since it offers many advantages, including comparatively high capacity, a long plateau at 3.45V, and low cost. LiCoPO4 (LCP) is another substrate material prevalently used to isolate bio-tissues from the implants. Clinical trials have confirmed the effectiveness of pain inhibition and decreased voltage overshoot brought by LCP-based SCS, opening new avenues for developing a smaller spinal cord stimulator with equivalent performance [10].

An assortment of things must also be considered in legal and ethical aspects. Legal considerations are more about human safety. In the US, an SCS device is required to provide proof of safety and effectiveness before it could be approved by the FDA and commercialized. Because most patients hesitate about spine implants, SCS is regarded as a device that treats rare disorders (< 4000 patients a year). This pathway can obtain a Humanitarian Device Exemption, a more flexible standard allowing for faster approval. Meanwhile, defined demands and ethical principles should be met for animal experiments. The main parameter in this context is 3Rs, which are efforts to replace, reduce, and refine experiments [38]. It is also necessary to consider the ethical aspect. For health care, the problems can be allocated into four types of conflicts (1) freedom and health, (2) supervision and anonymity, (3) self-determination and heteronomy, and (4) security/privacy and safety/effectiveness [39]. For example, when choosing a type of SCS therapy, the safety and efficacy of the SCS device are sometimes in conflict with the cost.

There are still other considerations concerning the application of SCS. For instance, most literature does not mention the commercial effects of SCS, such as the cost, on patients' quality of life. Moreover, insufficient evidence exists to demonstrate the benefit of permanent SCS implantation after 2 years since most long-term researches last no more than 24 months [40]. Last but not least, concerning SCS application in FBSS and CRPS patients, existing research appears to be biased based on funding sources, and results focus mainly on FBSS leg pain and CRPS type I, which means that SCS patients are sometimes unable to obtain information from a neutral party.

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Nevertheless, SCS has displayed great growth potential. Each year, new and more advanced SCS products are emerging and the market size is expanding rapidly, bringing more possibilities for patients. However, research on spinal cord stimulation always requires abundant clinical experience, multidisciplinary technology, and close interaction with patients. The future directions of SCS include: (1) a decrease in SCS device costs to achieve popularization, particularly in developing countries, (2) more clinical trials to gather evidence for the long-term effectiveness and safety of SCS to treat a more expansive range of indications, (3) advances in SCS technology to reduce device size, invasiveness, and complications and improve long-term efficacy and (4) personalized SCS treatment for each patient.

5. CONCLUSION

SCS has displayed a tremendously promising prospect not only in the commercial market for the management of neuropathic pain but also in the academic field for other indications like ischemic pain and neurodegenerative disorders. However, as a relatively novel therapy, its mechanism and compatibility with other therapies are poorly understood, necessitating considerably more work in this field. Apart from that, as a surgery-based permanent pain relief solution, SCS is too expensive for an ordinary family in developing countries. Some other aspects of the limitation of SCS are also illustrated in this review. Nevertheless, SCS is gradually occupying the market and breaking through limitations thanks to technological advances. With a deeper comprehension of pain relief, SCS is sure to have a wider application in the future.

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