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Spinal Cord Stimulation for Treating Chronic Pain: Reviewing Preclinical and Clinical Data on Paresthesia-free High Frequency Therapy

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Abstract

Background—Traditional spinal cord stimulation (SCS) requires that paresthesia overlap chronic painful areas. However, the new paradigm high-frequency SCS (HF-SCS) does not rely on paresthesia.

Study Design—A review of preclinical and clinical studies regarding the use of paresthesia-free HF-SCS for various chronic pain states.

Methods—We reviewed available literatures on high-frequency SCS, including Nevro's paresthesia free ultra high-frequency 10 kHz therapy (HF10-SCS). Data sources included relevant literature identified through searches of PubMed, MEDLINE/OVID, and SCOPUS, and manual searches of the bibliographies of known primary and review articles.

Outcome measures—The primary goal is to describe the present developing conceptions of preclinical mechanisms of HF-SCS and to review clinical efficacy on paresthesia-free HF10-SCS for various chronic pain states.

Results—HF10-SCS offers a novel pain reduction tool without paresthesia for failed back surgery syndrome and chronic axial back pain. Preclinical findings indicate that potential mechanisms of action for paresthesia-free HF-SCS differ from those of traditional SCS.

Conclusions—To fully understand and utilize paresthesia-free HF-SCS, mechanistic study and translational research will be very important, with increasing collaboration between basic science

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and clinical communities to design better trials and optimize the therapy based on mechanistic findings from effective preclinical models and approaches. Future research in these vital areas may include preclinical and clinical components conducted in parallel to optimize the potential of this technology.

Keywords

Chronic pain; paresthesia; frequency; spinal cord stimulation; dorsal horn

INTRODUCTION

Physicians in the United States have been using spinal cord stimulation (SCS) to treat chronic pain conditions since it was first developed nearly half a century ago [1]. Inspired by the seminal gate-control theory of pain proposed by Melzack and Wall [2], the conventional paradigm of SCS utilizes tonic 40–60 Hz stimulation that activates dorsal columns to elicit paresthesia over a patient's painful region. This paresthesia-based SCS has proven to be an effective treatment modality for 40–50% of patients with refractory pain conditions, including complex regional pain syndrome and failed back surgery syndrome (FBSS) [3–7]. However, conventional SCS has several limitations, such as limited clinical indications, suboptimal or inadequate pain inhibition (e.g., non-responders), and progressive reduction of treatment effects over time [8–11]. Despite technological improvements, it has been suggested, "no substantial improvement in results has occurred for more than 30 years…" [8]. Although traditional SCS is still a dominant neurostimulation therapy, with an estimated 50,000 implantations performed annually in the US to treat conditions such as low back pain and peripheral neuropathic pain [5, 12–17], there is an increasing need for new stimulation paradigms that improve short- and long-term clinical effectiveness of SCS and expand its common indications.

Several years ago, a new SCS paradigm was developed for pain treatment in which high frequency SCS (HF-SCS) was applied at low amplitudes so that the stimulation became sub-threshold for sensory activation and paresthesia-free. The most common frequency used for paresthesia-free ultra HF-SCS is 10 kHz and will be referred to as HF10-SCS. Initial findings of this new paradigm in several clinical trials have been promising, showing that HF10-SCS is highly effective and can provide pain relief after long-term use [14, 18–25]. Compared to traditional SCS, HF10-SCS had superior long-term efficacy for the treatment of back and leg pain in two randomized and controlled clinical trials [22, 23]. Notably, clinical success of HF10-SCS was not dependent on eliciting paresthesia that overlapped a patient's painful areas, which is fundamental to the clinical efficacy of traditional SCS.

METHODS SUMMARY

This review was done using searches of PubMed, MEDLINE/OVID, SCOPUS, and manual searches of the bibliographies of known primary and review articles from inception to Jan 2017. Other data included hand searches of publications driven by manuscript authors. Search terms included concepts of high frequency spinal cord stimulation with emphasis on both pre-clinical and clinical studies. Preclinical studies were assessed based on mechanisms

underlying HFSCS. Clinical studies were focused on results that included various parameters inclusive of both VAS scores as well as individual functional outcomes. Due to the limited scope of studies with meta-analysis, clinical heterogeneity, and methodological diversity we felt that a large-scale meta-analysis would have limited scope and value.

COMPARISON OF MECHANISMS FOR PAIN INHIBITION BY PARESTHESIA-FREE HF-SCS AND TRADITIONAL SCS

In recent studies, investigators have begun to determine how paresthesia-free HF-SCS affects neuropathic pain-related behavior in animal models, and to explore the underlying mechanisms. It has been suggested that SCS attenuates mechanical hypersensitivity after nerve injury in both an intensity-dependent and frequency-related fashion. Two separate investigations have shown that HF-SCS at a kHz level could suppress mechanical hypersensitivity similar to traditional 50 Hz SCS, while requiring only half of the stimulation intensity (e.g., 40% motor threshold rather than 80% motor threshold) [26, 27]. Whereas pain inhibition from traditional SCS develops quickly [8, 15, 27–29], pain relief from HF10-SCS often has an onset of hours, and sometimes requiring days in patients [18, 19, 22, 23, 36]. Intriguingly, the peak pain inhibition of sub-threshold HF-SCS also occurred later (mins) than that of traditional SCS in rats after nerve injury [27]. Recent animal studies showed that a long duration (6 hr daily for 3 months) traditional SCS (e.g., 60 Hz, 90% motor threshold) improved the decreased physical activity induced by nerve injury [31]. In addition, prolonged traditional SCS delivered daily (6 hr/day) for 4 days alleviated mechanical hyperalgesia and restored physical activity level in animals with non-inflammatory muscle pain [32]. However, the therapeutic effects and time course of continuous or prolonged sub-threshold HF-SCS (e.g., days) on animal pain behavior have not been examined. These pioneering preclinical works established basic experimental protocols (e.g., animal model, implantation, stimulation parameters, outcome measures) that may mimic certain features of clinical paresthesia-free HF-SCS and enable future investigations into mechanism(s) of action (MOA).

Several “working hypothesis” of MOA for paresthesia-free HF-SCS have been proposed, which were timely reviewed by Linderoth and Foreman and by Vallejo et al. [24, 25]. These “working hypothesis” include depolarization blockade, desynchronization of neuronal signals, membrane integration, and glial-neuronal interaction. The biological evidence for these “working hypothesis” are much needed, as the mechanistic study of paresthesia-free SCS is still in its infancy. Nevertheless, recent preclinical studies have provided the first insight into how the MOA differs between paresthesia-free HF-SCS and traditional SCS. First, unlike the activation of dorsal columns, which is essential to pain inhibition by traditional paresthesia-based SCS [28, 29, 33, 34], both computer modeling and an animal study suggested that sub-threshold HF-SCS, which mimics clinical paresthesia-free HF-SCS, neither activates nor changes the conduction properties of dorsal column fibers [27, 35]. The gracile nucleus (GN), which receives afferent inputs from dorsal column fibers from the lower body, is robustly activated during traditional SCS in nerve-injured rats. However, Song et al. [27] reported no activation of GN neurons to sub-threshold HF-SCS and no reduction of evoked responses to peripheral mechanical stimulation. These findings

are in line with clinical observations that no apparent sensory disturbance, numbness, or altered sensorimotor function occurs during HF10-SCS. This notion challenges the "differential blocking" hypothesis based on computer modeling of paresthesia-free HF-SCS [36]. According to this hypothesis, HF-SCS may induce depolarization blockade of lower-threshold large-diameter fibers in the dorsal column, which mostly carry information of vibration and pressure, and hence would avoid inducing paresthesia [38]. The same stimulation activates medium- and smaller-diameter dorsal column fibers, which leads to spinal pain inhibition through gate control mechanisms [37, 38]. However, the relevance of these findings to the MOA of clinical paresthesia-free SCS is uncertain. In particular, biphasic pulses have been used for SCS, but monophasic stimulation was employed for this computational modeling. Furthermore, a recent animal neurophysiology study, which involves recording single dorsal column axon and compound action potentials during HF-SCS, did not find evidence to support the notion of "differential blocking" induced by SCS at kHz frequencies [39]. The reasons for this discrepancy remain unclear, but additional biological studies are warranted to further test the hypothesis and predictions from computational modeling work. It is worth noting that when comparing traditional versus HFSCS both have been shown to inhibit somatosensory evoked potential in one reported case report [40].

Unlike the abrupt decrease in dorsal horn neuronal sensitization by traditional SCS [26, 41–43], HF-SCS of the same high amplitude induces much less inhibition. Wide-dynamic range (WDR) neurons are multimodal sensory neurons that play an important role in spinal nociceptive transmission. Those in deep dorsal horn have often been examined in neurophysiological studies of SCS [26, 41–43, 49]. Windup in WDR neurons is a short-term, activity-dependent neuronal sensitization that involves temporal summation of nociceptive inputs mediated by C-fibers on postsynaptic neurons. Intriguingly, inhibition of the temporal summation of pain during a trial of traditional SCS has been suggested to help in selection of patients for this treatment and in prediction of who will respond to its long-term efficacy [47]. Furthermore, activation of dorsal columns with traditional SCS parameters blocks windup [26, 42, 50]. In addition, the hyper-excitability in dorsal horn neurons after nerve injury can be normalized by traditional SCS [26, 41, 42]. Thus, tempering the spinal neuronal sensitization may contribute to traditional SCS-induced pain inhibition [26, 42, 47–50]. However, this mode of action remains to be demonstrated for paresthesia-free HF-SCS. In addition to neuronal mechanisms, traditional SCS has been shown to modulate spinal glial activation under persistent pain conditions. Astrocytes and microglia in central nervous system are important players in the pathogenesis of persistent pain. Recent studies began to reveal their roles in SCS-induced pain inhibition, such as a reduction of spinal glial reactive markers by traditional SCS in nerve-injured rats [50, 51]. Yet, it remains unclear whether non-neuronal mechanisms may contribute to pain inhibition from paresthesia-free HF-SCS, especially with longer-term treatment. Finally, traditional SCS has long been shown to activate the anterior, pretectal nucleus of the brain, whose output activates major descending pain inhibitory pathways [54]. Recent studies further revealed that activation of serotonergic neurons and the OFF-cells in rostral ventromedial medulla, and neurons in locus coeruleus may also contribute to therapeutic actions of conventional SCS [55, 56]. Direct evidence for the activation of this "spinal-brainstem-spinal

loop" mechanism by traditional SCS also includes an increase of c-fos expression in the brainstem pain modulatory circuitry [55–57]. It was estimated that up to 50% of the pain inhibitory effects from traditional SCS can be attributed to activation of supraspinal circuitry [29, 33]. Since paresthesia-free HF-SCS may not evoke neuronal activation [58], it is questionable if it can directly activate above mentioned brain and supraspinal mechanisms, such as descending pain modulatory pathways from the brainstem.

Several spinal segmental mechanisms that are known to contribute to the effect in traditional SCS have yet to be examined for paresthesia-free HF-SCS. For example, traditional SCS may induce postsynaptic potentials in dorsal horn neurons [59] and facilitate primary afferent depolarization to elicit presynaptic inhibition in the dorsal horn [60]. These actions may contribute to the inhibition of both spontaneous discharges and acutely evoked responses to peripheral test stimuli in deep lamina WDR neurons [26, 42, 43]. Furthermore, at the respective intensities that activate Aβ-fibers (supra-threshold), recent electrophysiology studies showed that 50 Hz dorsal root stimulation depressed synaptic transmission of C-fiber inputs in lamina II neurons [61, 62] and that 50 Hz SCS inhibited C-fiber-evoked local field potential in the superficial dorsal horn. Thus, traditional SCS may induce a quick onset of nociceptive transmission suppression in both the superficial and deep dorsal horn. However, no published study has inferred potential neurophysiological or neurochemical changes that may occur subtly and slowly but progressively after paresthesia-free HF-SCS. The superficial dorsal horn is in an important region for spinal nociceptive transmission that is filled with spinal projection neurons and central terminals of nociceptive afferent fibers. One potential pain-inhibiting neuronal mechanism for paresthesia-free HF-SCS may involve generation of a weak electric field that is subthreshold for evoking action potentials in dorsal column, yet changes neuronal excitability and nociceptive transmission in the superficial dorsal horn close to the electrodes. It is worth noting that (Figure 1).

SUMMARY OF PRECLINICAL FINDINGS

The lack of dorsal column activation, weak inhibition of deep WDR neurons, and slow onset of pain inhibition all suggest that sub-threshold HF-SCS may act through mechanisms distinct from those of paresthesia-based traditional SCS. A different MOA that incorporates HF10-SCS may also explain its success in rescuing some patients who have not responded to traditional SCS. For example, pain inhibition in patients treated with HF10-SCS did not correlate with paresthesia overlap from traditional SCS at the same site [63]. Traditional SCS may also alleviate certain types of nociceptive pain, such as selected ischemic pain states in vasospastic conditions and therapy-resistant angina pectoris. Traditional SCS has been shown to induce the release of multiple neurotransmitters and neuromodulators in both spinal and in supraspinal structures involved in pain modulation. However, questions about the neurophysiological and neurochemical mechanisms for paresthesia-free HF-SCS remain unanswered. We provide a summary outlining the theoretical mechanism of action for paresthesia-free HF-SCS therapy in Figure 1. Although there are limitations in translating findings from animal models to clinical treatment, it has been shown that preclinical studies can be helpful to understand how SCS works. For example, electrophysiology studies in animal models showed that traditional SCS inhibited windup in dorsal horn neurons, suggesting that inhibition of neuronal sensitization may contribute to SCS-induced pain

relief [26, 42]. These preclinical findings inspired a clinical investigation which showed that inhibition of the temporal summation of pain (e.g, windup) during an SCS trial greatly may be a biomarker for selecting appropriate patients (e.g., responders) for traditional SCS and predict who will respond to its effect long-term [47]. A recent animal study showed that low-intensity 1 kHz SCS induced greater pain inhibition than traditional SCS did [26], which provided important rationales that later helped clinicians to improve the treatment of chronic pain in patients by using paresthesia-free 1 kHz SCS for the first time [64]. Thus, these pre-clinical studies prove that animal studies can have significant medical implications and translational values. Increasing collaboration between basic science and clinical communities will promote the design of better trials based on mechanistic findings from effective preclinical approaches.

REVIEW OF CLINICAL DATA

The growing body of knowledge surrounding HF-SCS is helping investigators to better elucidate the safety and efficacy profile of this novel therapy. An important question is: whether paresthesia-free pain inhibition is a unique feature to10 kHz HF-SCS, or if it can also be produced by SCS at lower frequencies (e.g., 1, 3 kHz) or by adjusting pulse width to optimize charge delivery [65]. Some recent experimental studies comparing the efficacy of traditional SCS to sub-threshold HF-SCS have provided some insights. In a 2013 murine study, Shechter et al. [26] demonstrated that the efficacy of HF-SCS at 1 kHz and 10 kHz was superior to that of sham or 50-Hz stimulation for inhibiting the effects of mechanical hypersensitivity in a rat model of neuropathic pain. They also found no differences in efficacy between 1-kHz and 10-kHz stimulation delivered at subperception strength. After that study, North and colleagues [64] published favorable results from a randomized, 2 × 2 crossover clinical study of low frequency suprapercepti on SCS vs. subperception SCS at 1-kHz frequency. They tested whether subperception SCS at 1 kHz was sufficient to provide effective pain relief in human subjects. Indeed, 95% of the 22 patients who completed the study reported improvements in average, best, and worst pain based on numeric rating scores. The treatment effect of subperception stimulation was also significantly greater than that of paresthesia-based SCS based on Oswestry Disability Index (ODI) scores and the Patient's Global Impression of Change (PGIC) scores [64]. Furthermore, a study in 2012 by Perruchoud and colleagues revealed no significant difference between 5-kHz HF-SCS and sham stimulation in a cohort of individuals with stable chronic back pain who already were receiving traditional SCS [21]. Other data suggest significant improvement in pain sensory thresholds in chronic pain patients with frequencies as low as 1.15 kHz compared to traditional SCS [66]. Therefore, paresthesia-free SCS for pain inhibition may also be induced by SCS at a frequency that is lower than 10 kHz.

Though ambiguity may exist at these lower high-frequency stimulation parameters, a growing body of evidence supports the efficacy and therapeutic benefit of HF SCS, up to 10 kHz. A small study by Tiede et al. [67] in 2013 demonstrated that HF10-SCS was not only safe in appropriately selected patients with difficult-to-treat chronic back pain, but also effective, producing significant reductions in back and leg pain scores compared to baseline. The new HF10-SCS stimulation was actually preferred over traditional SCS parameters by 88% of the 24 individuals enrolled in this feasibility trial. A larger, prospective open-label

study produced similarly encouraging data in patients with chronic intractable back pain, the majority of whom carried a diagnosis of FBSS. In that study, 72 patients underwent permanent implantation of an HF10-SCS system after a successful trial period. Improvements were noted in visual analog scale (VAS) scores for both back and leg pain as well as other quality-of-life measures 6 months post-implantation. The mean back pain score was reduced to 2.7 at 6 months from a baseline of 8.4 ($p<0.001$); a similar mean reduction in VAS score was observed in leg pain, from 5.4 to 1.4 ($p<0.001$). A greater than 50% reduction in pain was reported in 74% of patients at 6 months. Also of note were significant improvements in ODI score, sleep disturbances, and pain medication use. Mean ODI scores decreased to 37 from 55 ($p<0.001$), and more than half of the patients achieved an improvement of more than 14 points. There was also a decrease noted in the mean number of sleep disturbances from 3.7 to 1.3 at 6-month follow-up. Additionally, opioid use, which was widespread among patients prior to the study (86%), was reduced in 62% of patients and eliminated in another 38% [20]. The investigators obtained data from this same cohort at 24 months to look at the sustainability of the initially reported results. They were able to obtain follow-up data from 65 (90%) of the original 72 patients. Improvements in mean VAS scores for back pain persisted at the 24-month mark with a mean score of 3.3±0.3 ($p<0.001$ compared to baseline). The results were similar for relief from leg pain, with a mean VAS score of 2.3±0.3 at 24 months ($p<0.001$ compared to baseline). The majority of patients (60%) reported a sustained improvement of more than 50% improvement in back pain at 24 months, and 71% reported similar improvement in leg pain. Significant improvements in ODI (40±2 vs. 55±1) and sleep disturbances (1.4±0.2 vs. 3.7±0.4) also persisted at 24 months compared to baseline (both $p<0.001$). Opioid use was reported in 57% of patients at 24 months compared to 86% at baseline. Among those who continued opioid use, the mean dose of oral morphine equivalents per patient decreased to 27 mg/day compared to 84 mg/day at baseline ($p<0.0001$). These data indicate that pain relief in these patients was not only significant, but also sustainable [68].

Similarly encouraging results were seen more recently in another prospective observational study by Kinfe and colleagues in a cohort of patients with FBSS. HF10-SCS and burst SCS were both safe and efficacious for treating intractable pain in these patients, and provided significant reduction in VAS and improvement in sleep quality as measured by the Pittsburgh Sleep Quality Index [69]. Russo et al. [70, 71] also found favorable results in a retrospective review of 256 patients who trialed HF10-SCS for chronic intractable pain of various etiologies; they reported notable improvements in both pain and ODI scores.

Results of only one randomized controlled trial comparing HF10-SCS to traditional SCS have been published to date, but the findings were similar to those of earlier open-label cohort studies. Patients in this trial had both leg and back pain. Of the 198 patients randomized, 187 (90 of the 97 individuals randomized to the HF10-SCS arm and 81 of the 92 individuals in the traditional SCS arm) underwent implantation of a permanent SCS system. At 3 months the number of leg-pain and back-pain responders was significantly greater in the HF10-SCS arm than in the traditional SCS arm ($p<0.001$). At 12 months, both back-pain and leg-pain responder rates were sustained, but responder rates were significantly higher for HF10-SCS therapy at all endpoints. Back-pain responder rates were approximately 80% throughout all 12 months in the HF10-SCS cohort compared to

approximately 50% for traditional SCS. A similar advantage for HF10-SCS therapy was seen with leg pain (~80% responder rate for HF10-SCS and 50–55% for traditional SCS). Patients who received HF10-SCS reported a greater decrease in VAS scores for both back and leg pain. Also of note was that 35.5% of individuals in the HF10-SCS arm had eliminated or decreased opioid analgesic usage at 12 months compared to 26.4% in the traditional SCS group (p=0.41). Average morphine equivalent usage over 12 months was significantly decreased with HF10-SCS therapy compared to that with traditional SCS (p=0.014) [23]. Responder rates remained higher in the HF10-SCS group than in the traditional SCS group at the 24-month follow-up for both back pain and leg pain. Data also revealed a greater decrease in the degree of both leg and back pain with HF10-SCS than with traditional SCS, suggesting significant and sustained pain relief [22, 23].

Rapcan and colleagues [72] also reported improvements with HF-SCS treatment in a small cohort of individuals with FBSS. One year after implantation of an HF10-SCS system, mean VAS score had decreased significantly from 8.7±0.88 to 4±1.5 (p<0.001). The majority (67%) of patients experienced greater than 50% pain reduction by the end of the study. Notably, 65% of patients had decreased their opioid consumption by at least 50% at 12 months. Interestingly, five participants experienced pain relief benefit with an alternating schedule of HF10-SCS and traditional SCS every 4 to 5 weeks [72].

Emerging evidence supports the utility and efficacy of HF10-SCS for treatment of refractory chronic neuropathic limb pain. A retrospective small study by Al-Kaisy et al. [19] in 2014 showed ten of 11 patients permanently implanted with an HF10-SCS system had significant improvements in pain and quality of life measures at 1, 3, and 6 months post-implantation that warrants further investigation. Similarly, case series have shown potential utility of HF10-SCS for treatment of refractory headaches and migraines. Lambru et al. [73] reported a significant reduction in headache frequency and duration in a very small case series (n=4). Arcioni et al. [74] showed similar results in a prospective open-label study of 14 patients. Given that these benefits are being observed with consistent lead placements for both cervical and lumbar SCS, the broad ranging benefits suggests that the mechanism of action is likely non-segmental and non-supratentorial. These studies also suggest that paresthesia-free cervical HF10-SCS should be further explored for use in treating refractory headache or migraine pain. It is possible that this new therapy could have potentials for other undiscovered clinical applications for neuropathic and mixed pain conditions.

ADVERSE EVENTS

None of the adverse events reported in any of the studies reviewed were found to be specific to HF-SCS. Rather, the adverse events reported have been similar to those reported with traditional SCS [75, 76]. The most common adverse events include pain at implant site, lead migration, and wound infection (Table 1).

CONCLUSIONS

Paresthesia-free HF10-SCS offers a new tool for managing FBSS and chronic axial back pain as the main clinical indications. Recent preclinical models aiming to mimic this therapy

have suggested that MOAs for its pain-relieving effect could substantially differ from those known to paresthesia-based traditional SCS, as evidenced by a lack of robust activation of dorsal columns, a weak inhibition of WDR neurons in deep dorsal horn, and a slow onset of pain inhibition. Its success in rescuing some patients who have not responded to traditional SCS further indicates a distinct MOA for HF10-SCS. The current review agrees with those by Linderoth and Foreman and by Vallejo et al., [24, 25], many unanswered questions remain to paresthesia-free HF-SCS and optimal device parameters. To truly answer these essential questions, researchers may need to 1) Design effective animal protocols and stimulation paradigms that closely mimic clinical application of HF10-SCS. In particular, continuous and long-term sub-threshold HF-SCS needs to be tested in animal models to examine potential cumulative and prolonged effects on pain behavior and activity; 2) Measure electrical field and electrochemical changes in the spinal cord following sub-threshold HF-SCS, and determine how these changes affect intrinsic membrane properties and excitability at the somata of dorsal horn neurons; 3) Examine nociceptive transmission in superficial dorsal horn, especially lamina I projection neurons, lamina II interneurons, and spinal local field potentials to C-fiber inputs, which may be under a greater influence of sub-threshold HF-SCS than deep dorsal horn neurons; 4) Measure additional behavioral readouts of neuropathic pain (e.g., ongoing pain, gait, anxiety, reduced daily activity) in animal pain models; 5) Examine the roles of spinal glial cells and glial-neuronal interaction in response to different waveforms or patterns of SCS. The benefits of answering these fundamental questions about MOA of paresthesia-free HF-SCS by preclinical study are multiple: 1) Providing rationales for parameter optimization (e.g., phase, width, frequency, duration, location); 2) Establishing a more structured framework to help standardize clinical outcomes and data; and 3) Generating a biological basis for increasing indications of paresthesia-free HF10 SCS in clinical settings.

Though the clinical findings suggest promise increased emphasis on proper controls and accountability for placebo effect will need to be done to assure that the observed improvement in analgesia is in fact a reasonable and sustained for various pain states. Results from newer studies specifically the PROCO (Effects of Pulse Rate On Clinical Outcomes in Kilohertz Frequency Spinal Cord Stimulation) randomized controlled trial, which was a multicenter, double-blind, crossover study were presented at the International Neuromodulation Society World Congress (INS; 27 May–1 June, Edinburgh, UK). These findings suggested that for back pain there were no observable differences between 1 and 10 kHz frequencies suggesting interesting clinical and basic science questions that will need to be explored and addressed. These findings are in line with previous observations by North et al. [64] and Youn et al. [66], suggesting that 10 kHz may not be the only effective frequency and is not indispensable to paresthesia-free SCS. It remains unclear what essential property of tonic paresthesia-free SCS governs the pain inhibition. New concepts such as the “high density stimulation” were proposed recently, which postulated that total charge amount delivered in a fixed time period may be viewed as an “electrical dose” which can be titrated to optimal pain relief [65]. Yet, the details remain to be parametrically examined in both preclinical and clinical settings by considering pulse amplitude, pulse width, and stimulation frequency as integrated components. Additional limitations that need to be considered with this technology are the potential for long-term tolerance. Data pending greater than two

years post implantation will be important to address whether this therapy can provide long term benefit. In addition other functional parameters such as better sleep, decrease in opiate use will need to be standardized across all studies to serve as additional biomarkers of benefit beyond VAS scores.

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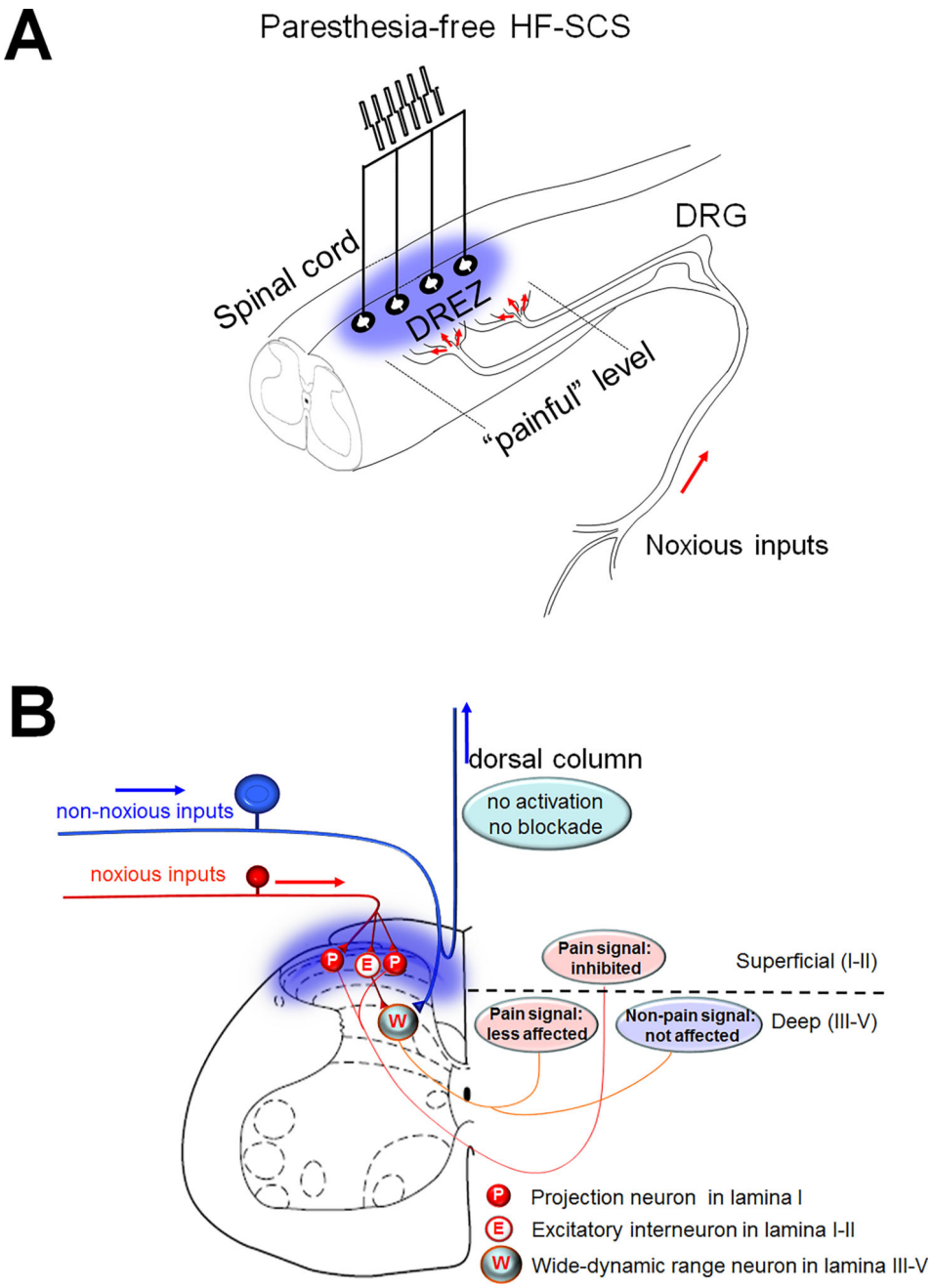

Figure 1. Schematic diagram illustrating hypothetical mechanisms for pain inhibition by paresthesia-free high-frequency (HF) spinal cord stimulation (SCS)

(A) Bipolar low-amplitude HF stimulation applied to the spinal cord surface may generate a weak, localized electric field or electrochemical disturbance (shaded area). This area may cover the superficial dorsal horn and dorsal root entry zone (DREZ) at the spinal level receiving noxious inputs (i.e., "painful" level) from dorsal root ganglion (DRG) neurons. **(B)** Nociceptive afferents (C-fibers, red) carrying noxious inputs mostly terminate in superficial dorsal horn, where they activate projection neurons (P) in lamina I. Large-diameter A-fibers (blue) mediating non-noxious inputs terminate in deeper laminae. Wide-dynamic range neurons (W) in deep dorsal horn also receive some C-fiber inputs through polysynaptic

pathways from excitatory interneurons (E) in superficial layers. Therefore, synaptic transmission and neuronal excitability in the superficial dorsal horn may be more directly affected than deeper layers by paresthesia-free HF-SCS.

Table 1

Summary of High Frequency Spinal Cord Stimulation Clinical Data

Author, Year	Study type (n)	Indication (study duration)	Stimulation parameters	Results summary
Kapural et al., 2015 and 2016	Prospective multicenter randomized controlled trial (198)	Chronic back pain with leg pain (24 months)	HF10-SCS Frequency: 10 kHz Pulse width: 30 μs Amplitude: 1.6± 1.1A (avg ± SD) vs. Traditional SCS Frequency: 39.2±15.0, 77.3±133.5 Hz Pulse width: 347±148, 591±214 μs Amplitude 3.6±2.8, 8.5±4.0 mA	At 3 months, response rates were greater in the HF10-SCS group than in the traditional SCS group for both back and leg pain (p<0.001, for both non-inferiority and superiority). At 12 months, both back pain and leg pain responder rates were sustained, and significantly higher for HF10 therapy at all endpoints. HF10-SCS group had lower VAS scores and a significantly greater decrease in average morphine equivalent usage over 12 months (p=0.014). At 24 months, the HF10-SCS group had a greater responder rate and lower back and leg pain scores.
Kinfe et al., 2016	Prospective observational study (16)	Chronic back pain, FBSS with back pain ±leg pain (3 months)	Burst Burst rate: 40 Hz Intra-burst: 500 Hz Pulse width: 1000 ms Current: 1.85–2.55 mA vs. HF10-SCS frequency Frequency: 10kHz Pulse width: 30μs Current: 1.7–3mA	Overall baseline back pain was significantly suppressed in 14 of 16 FBSS pts (8 pts with burst/6 pts with HF10-SCS). Leg pain reduction was greater in burst group than HF10-SCS group (p<0.009). Significant decreases in the Beck Depression Index were seen with both modalities.
Russo et al., 2016	Retrospective chart review (256)	Intractable chronic pain (back and leg pain, back pain only, head±neck pain, and neck±arm/shoulder pain) (6 months)	Frequency: 10 kHz Current: 0.1–3.0 mA	Of 256 pts, 189 (73%) reported a positive trial and were implanted with HF-SCS system. A mean reduction in pain of 50% was sustained up to 6 months post-implant across the entire pt population. Pts with back and leg pain saw most improvement. Sixty-eight percent of nonresponders to traditional SCS reported a positive trial and mean pain relief of 49% (p<0.001) at 6 months. Pts also reported a reduction in ODI at 6 months and improved sitting, standing, and walking tolerances.
North et al, 2016	Prospective randomized controlled trial (22)	Low-frequency supra-perception SCS: frequency 50 Hz vs. subperception SCS: frequency:1 kHz (7 weeks)	Frequency: 50 Hz vs. frequency1 kHz	Twenty-one of 22 pts (95%) reported improvements in average, best, and worst pain NPRS scores. All NPRS scores were significantly lower with subperception SCS than with paresthesia-based SCS. ODI scores and PGIC scores were significantly better after subperception SCS than after paresthesia-based SCS.
Arcioni et al., 2016	Prospective open-label study (17)	Chronic migraine (6 months)	Frequency: 10 kHz Pulse width: 30 μs Current: up to 4.0 mA	Seventeen subjects underwent a trial of cervical HF10-SCS; 14 were still implanted at 6 months (one trial failure, one trial infection, one implant site infection). Seven of the 14 subjects had >30% reduction in headache days.
Lambru et al., 2016	Retrospective case series (4)	Chronic migraine (12–42 months)	Frequency: 10 kHz Pulse width: 30 μs Current: 1.5–4.0 mA	At an average follow-up of 28 months, an improvement of at least 50% in headache frequency and/or intensity in all chronic migraine pts with HF10 cervical SCS.
Tiede et al., 2013	Prospective multicenter open-label study (24)	Chronic back pain, mostly FBSS and back pain±leg pain (4 days)	Frequency: 10 kHz Pulse width: 30 μs Current: 0.5–5.0 mA	Pts who had previously trialed traditional SCS were then trialed with HF10-SCS. Pts reported a significant improvement from baseline VAS pain scores (8.68 to 2.03, p<0.0001) during the 4-day percutaneous feasibility trial. 88% of pts preferred HF10-SCS to conventional SCS.
Van Buyten et al., 2012	Prospective multicenter open-label study (83)	Chronic back pain, mostly FBSS (6 months)	Frequency: 10 kHz Current: 1–5 mA	After a trial period, 88% of pts underwent permanent implantation of an HF-SCS system. After 6 months, mean back pain VAS score decreased from 8.4 to 2.7 (p<0.001), and mean leg pain VAS score decreased from 5.4 to 1.4 (p<0.001). A >50% reduction in pain was seen in 74% of pts at 6 months. Significant improvements

Author, Year	Study type (n)	Indication (study duration)	Stimulation parameters	Results summary
				were also seen in ODI score, sleep, and pain medication use.
Al-Kaisy, et al., 2014	Prospective multicenter open-label study (65)	Chronic back pain, mostly FBSS (24 months)	Frequency: 10 kHz Current: 1–5 mA	Improvements in mean VAS scores for back pain and leg pain persisted at the 24-month mark: back pain VAS = 3.3±0.3 (p<0.001 vs. baseline); leg pain VAS = 2.3±0.3 (p<0.001 vs. baseline). Sixty percent of pts reported a sustained improvement of >50% pain relief from back pain; 71% reported >50% pain relief from leg pain. Significant improvements in ODI score and sleep disturbances also persisted at 24 months. The number of pts on opioids decreased as did opioid consumption among pts who required it.
Perruchoud et al., 2012	Double-blind randomized two-period crossover study (40)	Chronic back pain with leg pain (2 weeks)	Frequency: 5 kHz Pulse width: 60 μs	No significant difference between HF-SCS at 5 kHz and sham stimulation in a sample of individuals who had stable control of chronic pain with traditional SCS. There were no significant differences in VAS pain scores or quality-of-life measures between the sham and HF-SCS group at the end of each 2-week study period.
Al-Kaisy, et al., 2014 (limb pain)	Retrospective chart review (198)	Chronic neuropathic limb pain (6 months)	Frequency: 10 kHz	Ten of 11 pts permanently implanted with an HF10-SCS system reported significant improvements in pain and quality-of-life measures at 1, 3, and 6 months. Mean pain score decreased from 8.2±1.7 at baseline to 3.3±1.7 at 6 months (p<0.05).
Rapcan et al., 2015	Non-randomized prospective study (21)	FBSS with predominant low back pain (12 months)	Frequency: 10 kHz	Mean VAS scores decreased from 8.7±0.88 to 4±1.5 at 12 months (p<0.001). Most pts (67%) continued to experience >50% pain reduction at the end of the study. Five pts experienced benefit in pain relief with an alternating schedule of HF10-SCS and traditional SCS. 65% of pts decreased their opioid consumption by at least 50% at 12 months.
Youn et al., 2015	Non-randomized prospective study (20)	Chronic pain with traditional SCS system in place (n/a)	Frequency: 200–1200 Hz Pulse width: 110–170ms Voltage: 3–6.5 V	Quantitative sensory testing was conducted with no stimulation, with traditional SCS, and with HF-SCS. HF-SCS significantly increased the mechanical detection threshold compared to no stimulation (p<0.001) and traditional SCS (p=0.01). Pressure pain and vibratory detection thresholds also increased significantly with HF-SCS compared to traditional SCS. Different stimulation parameters did not produce differences in thermal pain detection.

FBSS, failed back surgery syndrome; HF-SCS, high-frequency spinal cord stimulation; HF10-SCS, high-frequency spinal cord stimulation at 10 kHz; NPRS, numeric pain rating scale; ODI, Oswestry Disability Index; PGIC, patient global assessment of change; Pt, patient; SCS, spinal cord stimulation; VAS, visual analog scale.