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Overview of HF10 spinal cord stimulation for the treatment of chronic pain and an introduction to the Senza Omnia™ system

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Practice points

- Spinal cord stimulation (SCS) is a well-studied and increasingly used treatment modality for chronic intractable pain states.
- The Senza SCS systems deliver high-frequency stimulation, which has proven superiority over traditional SCS systems for the treatment of back and leg pain.
- The Omnia™ implantable pulse generator is the newest offering in the Senza line and has the ability to provide high-frequency stimulation in addition to multiple other waveforms.

Chronic intractable pain affects a significant percentage of the worldwide population, and it is one of the most disabling and expensive health conditions across the globe. Spinal cord stimulation (SCS) has been used to treat chronic pain for a number of years, but high-frequency SCS was not the US FDA approved until 2015. In this review, we describe the history and development of high-frequency SCS and discuss the benefits of the Omnia™ implantable pulse generator. We also provide a thorough literature review of the published work, highlighting the efficacy and safety profiles of high-frequency SCS for the treatment of multiple chronic pain conditions. Lastly, we offer our outlook on future developments with the Omnia SCS system.

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The use of spinal cord stimulation (SCS) for the treatment of chronic pain was introduced over 50 years ago [1]. Since its inception, the technology has evolved dramatically, and this is particularly evident over the past decade. Recent years have seen the creation of new waveforms and variations in electrical dosing, but arguably the most important advancement has been the introduction of high-frequency, 10 kHz SCS (HF10). While traditional SCS (T-SCS) relies on generation of a paresthesia at the site of pain, HF10 is entirely paresthesia-free. This novel device has been shown to provide superior pain relief and outstanding patient-reported outcomes. This article provides an overview of HF10 and highlights Nevro's new Omnia™ implantable pulse generator (IPG) (Nevro Corp., CA, USA).

Nevro was founded in 2006 and introduced 10 kHz SCS with the goal of offering an effective therapy for low-back pain and other chronic pain syndromes. HF10 therapy was approved for use in Europe in 2010, Australia in 2011 and the USA in 2015. The therapy is backed by robust clinical evidence demonstrating improved and sustained pain relief versus T-SCS through rigorous level I evidence: SENZA-RCT published at 12 and 24 months [2,3].

At 24 months, the responder rate was 76% with a 2.4-cm visual analog scale (VAS) for both back and leg pain. Outcomes were further validated in a 1660-patient real-world outcomes publication in which patients reported at 74% responder rate [4]. In addition HF10 patients achieved a 68% reduction in opioid usage [5].

HF10 is a paresthesia-free therapy, which allows for numerous physician and patient benefits. For physicians, no paresthesia mapping is required during placement as leads are placed anatomically. This results in a predictable and repeatable procedure in which the patient does not need to be awakened from sedation to provide paresthesia coverage feedback. Patient benefits include the absence of paresthesias at rest, which can be perceived as uncomfortable, and the lack of suprathreshold stimulation that can often accompany positional changes with T-SCS. Additionally, paresthesia-free stimulation allows for usage while driving as well as enabling sleep without restrictions. In fact, 99% of patients report that they sleep with their device on [4].

The first widely available SCS systems from Nevro, Senza I and Senza II, were designed specifically to deliver HF10 therapy [6]. The introduction of the Omnia system allows greater programming diversity and therapeutic versatility by introducing the availability of multiple stimulation settings within a single battery.

SCS overview

Mechanism of action

There are various theories regarding the mechanism of action of how SCS provides pain relief [7]. One of the earliest theories is Melzack and Wall's gate control theory of pain, first proposed in 1965 [8]. This theory suggests that stimulating afferent low-threshold A β -fibers results in inhibition of spinal nociceptive transmission [9]. Wall and Melzack's work helped set the foundation for neuromodulation research and led to pain therapies such as SCS and transcutaneous electrical nerve stimulation [7,9]. The gate control theory has evolved into the concept of a 'neuromatrix' that involves multiple interacting neuronal pathways. In T-SCS, electrodes are placed over the dorsal columns (DCs) to deliver electrical pulses at a frequency of 30–60 Hz, which elicit paresthesias at the site of pain. Activating the DCs is thought to inhibit pain signal transmission [9].

T-SCS is associated with inhibiting neuronal activity in the dorsal horn via activation of spinal inhibitory interneurons through activity in A β -fibers [10–14]. T-SCS has been found to decrease wide dynamic range (WDR) neuronal activity in rat studies; this may play a mechanistic role in T-SCS [14–16]. Furthermore, windup is blocked by T-SCS and stabilizes long-term potentiation that occurs in WDR neurons [11,17–19]. Other potential mechanisms may involve activating descending pain-inhibitory pathways, inducing inhibitory postsynaptic potentials in dorsal horn neurons, and inhibiting presynaptic afferent inputs [20,21].

Additional studies suggest A β -fiber input activates a subset of GABAergic interneurons [22,23]. Traditional SCS stimulates the anterior pretectal nucleus activating descending pain inhibitory pathways [24]. Activation of supraspinal circuitry may contribute up to 50% of pain inhibitory effects from T-SCS [25,26]. Additionally, rat studies showed SCS-activated serotonergic cells and OFF cells in the rostral ventromedial medulla [27]. The SCS-responsive rats were found to have an increase in 5-hydroxytryptamine in the lumbar dorsal horn after SCS. SCS has been shown to increase extracellular GABA in the spinal cord and is linked to a reduction in glutamate and aspartate that lasts longer than the stimulation period [28–30].

SCS generates serotonin release into the spinal cord; this decreases neuronal excitability and pain transmission [31,32]. Serotonin may increase spinal production of dynorphin, enkephalin and GABA [33]. Moreover, SCS generates acetylcholine, adenosine and noradrenaline release [34–36]. Additionally, SCS may stimulate transcriptional and post-translational changes in neurons [9].

The exact mechanism of HF10 remains uncertain. Studies have suggested that, contrary to conventional SCS, high-frequency SCS (frequencies > 5 kHz) may not involve the DCs [37]. Multiple studies have indicated that pain inhibition at varying kilohertz levels of frequency and 50-Hz SCS appear to involve different neuronal mechanisms [38,39]. At frequencies above 5 kHz, inhibitory interneurons have been shown to be selectively activated [40]. Recently, Lee *et al.* confirmed similar results using a rodent model in which low-intensity HF10 selectively activated inhibitory interneurons in the spinal dorsal horn without activating DC fibers, thus providing paresthesia-free pain relief. A prior study suggested that HF10 stimulates the dorsal root or the dorsal root entry zone, which may suppress WDR neuronal hyperactivity [41]. Similarly, Arle *et al.* found that stimulation between 4.5 and 10 kHz preferentially recruits small and medium fibers while blocking larger fibers, ultimately resulting in pain relief by inhibiting WDR cells [42]. Additionally, it appears that only with the use of 10 kHz stimulation were pain neurons and the windup response inhibited [43].

Table 1. Omnia implantable pulse generator programming options.

Stimulation setting	Definition
High frequency (HF10)	Continuous stimulation; Frequency: 10,000 Hz, Pulse width: 30 μ s, Amplitude: 1–4 mA
Low frequency (T-SCS)	Continuous stimulation; Frequency: 2–1200 Hz, Pulse width: 100–500 μ s, Amplitude: 2–8 mA
Pulse dosing	Noncontinuous stimulation; Intermittent HF10 stimulation (i.e., 25% on and 75% off); same settings as above
Burst	Noncontinuous stimulation; Five electrical impulses with an intraburst frequency of 500 Hz; Pulse width: 1000 μ s, 2–8 mA; Burst packets repeated at frequency of 40 Hz
Burst10k™	Continuous stimulation; Burst stimulation with HF10 stimulation during interburst time periods; same settings as above
Frequency pairing	Continuous stimulation; T-SCS stimulation with HF10 stimulation between electrical impulses; same settings as above

As a whole, the theories regarding mechanism of action for high-frequency SCS vary widely and further research is needed to provide a definitive answer.

Implant procedure

The patient is positioned prone and draped in the usual sterile fashion. Antibiotics are administered 30–60 min prior to skin incision. Using fluoroscopy, the appropriate vertebral level is confirmed for the placement of the leads [44]. The midline of the epidural space is targeted with interlaminar entry between T11–T12 and L2–L3 for lumbar implants. The skin entry point is typically the medial aspect of the pedicle below the intended interlaminar entry level. Skin is incised then dissection continues to the lumbar fascia with appropriate hemostasis.

Two introducer needles are inserted through ligamentum flavum into the epidural space and the leads are advanced to the midline of the desired vertebral level with fluoroscopic guidance. For back and leg pain, the most cephalad electrode of one lead is placed at the top of the T8 vertebra and the second lead has its most cephalad electrode at the top of the T9 vertebra. The most inferior electrode is usually situated at the bottom of the T11 vertebra. There should be overlapping of the leads at the T9–T10 disc space [44]. For neck and arm pain, the electrodes are usually placed over the C2–C7 vertebra for the cervical implant [45]. The leads are then anchored to the fascia and impedances are checked to ensure the integrity of the stimulation system [44,46].

The desired IPG implant site is identified with consideration of patient comfort and infection control. The pocket should not be larger than the IPG and no deeper than 2 cm from the surface of the skin. The IPG template can be used to estimate the size of the pocket [46]. Once the pocket is created, the leads are tunneled to the pocket and connected to the IPG. The IPG is inserted into the pocket; sutures may be used to secure the IPG to the patient's soft tissue. Communication between IPG and programmer are checked, and hemostasis and irrigation are performed. Wounds are closed and dressings applied in the usual surgical manner [46].

The use of anatomical-based surgical placement eliminates 'paresthesia mapping', the process that uses stimulation from the electrodes to ensure the patient's painful areas are covered with paresthesia. As such, the patient is able to remain sedated throughout the entire procedure [45].

Introduction to Omnia

Evolution of Nevro offerings

This review article highlights on the Omnia IPG. The Senza system was the initial IPG from Nevro Corporation and was the first to offer 10 kHz, paresthesia-independent stimulation for the treatment of chronic pain [47]. The US FDA approval of the device in 2015 came with superiority labeling to T-SCS following the Senza RCT [2]. It was the only SCS therapy indicated by the FDA to deliver pain relief without paresthesias or patient restrictions on motor vehicle operation while receiving therapy [6]. It was also the only implantable SCS system approved by the FDA with labeling for 3T conditional MRI compatibility for head and extremities. The second iteration of the Senza IPG, Senza II, was smaller with potential to improve patient comfort and reduce the incidence of IPG site pain, a well-described complication of implantable SCS therapies [48–50]. The Omnia IPG, the third and current offering from Nevro Corporation, was introduced in late 2019. It maintains the size of the Senza II with the ability to deliver a wider range of therapeutic stimulation programs.

Omnia programming versatility

Programming options available on the Omnia platform include HF10, low frequency, pulse dosing, burst, Burst10k™ and frequency pairing (Table 1).

Habituation or tolerance is the subsequent loss of therapeutic effect after initial success that cannot be explained by a hardware-related issue [49,50]. The rate of this phenomenon has been noted to be 13–25.9% and is a leading cause for device explant [48–50]. While poorly understood, contributing factors may be disease progression, plasticity of central pain pathways and fibrosis around the stimulating electrodes [49,50]. As reviewed by Reddy *et al.*, there are some data to suggest that patients experiencing diminishing efficacy with their current SCS may benefit from conversion to an alternative treatment [51]. Additionally, early clinical experience demonstrates that for select difficult-to-treat pain populations, paired waveforms can provide additional opportunities for relief. In Russo *et al.*'s real-world results with Omnia from a retrospective audit of 493 patients across four Australian clinical sites, 26 patients with an average IPG duration of approximately 1.6 years were provided frequency pairing or Burst10k™ to optimize their treatment as they were not reporting adequate relief and had exhausted current therapy options. The study demonstrated that compared with baseline, at the last follow-up (72.9 $\pm$ 12.6 days), patients treated with waveform pairing showed improvements in responder rates (from 17.4 to 60%). Approximately 38% reported a decrease in their pain medication use since their previous follow-up visit [52].

The flexibility of Omnia to provide multiple alternative therapies improves the rate of durable response to SCS therapy and prevents device explant due to loss of efficacy. The pairing of waveforms across wide frequency ranges enables treatment that may utilize separate mechanisms of action. Lastly, the Omnia battery is designed with a lifespan exceeding 10 years regardless of the stimulation profile that is used, has conditional full-body MRI approval and is upgradeable to future waveforms and frequencies [6].

Clinical efficacy

The introduction of robust clinical data regarding the use of HF10 as a means of providing pain relief came by way of the SENZA series of clinical trials. The SENZA series of trials provided ample evidence that high-frequency DC SCS is safe and efficacious in the treatment of lower extremity radicular symptoms as well as axial low-back pain. There is a growing body of literature that demonstrates a broadening of the applications of HF10 including the treatment of chronic migraines, nonsurgical refractory back pain, axial neck pain and upper extremity radicular pain (Table 2). It is noteworthy that no prior clinical trials have been performed with a device that is capable of delivering energy multiple ways and this includes the Omnia IPG. Any potential benefits of enhanced programming capabilities remain to be proven.

In 2013, Van Buyten *et al.* published their work, which utilized high-frequency (up to 10 kHz) waveforms in the treatment of chronic, intractable pain of the back and/or limbs. A total of 83 patients were recruited and 82 patients took part in the study. Eighty eight percent (72 out of 82) of the patients had a successful trial period and 74% of patients who were implanted experienced at least 50% pain relief at the 6-month follow-up. At 6 months, mean back pain VAS was reduced from 8.4 to 2.7 ($p < 0.001$) and mean leg pain VAS was reduced from 5.4 to 1.4 ($p < 0.001$). There were also improvements in the Oswestry disability index (ODI) and sleep [53]. Sustained relief was demonstrated in these patients at the 24-month follow-up with a mean back pain VAS score of 3.3 ± 0.3 from 8.4 ± 0.1 at baseline and a mean leg pain VAS score of 2.3 ± 0.3 from 5.4 ± 0.4 . In all, for those implanted, 60% had $\geq 50\%$ back pain relief and 71% had $\geq 50\%$ leg pain relief after 24 months [5].

Kapural *et al.* published the SENZA-RCT randomized controlled trial across multiple US institutions in 2015. In their study, HF10 was compared with T-SCS (typically around 50 Hz) in patients with both back and leg pain. A total of 198 patients were enrolled and 171 had a successful trial (86%). At the 6-month follow-up visit, 76.4% of patients received $\geq 50\%$ back pain relief and 80.9% received this relief of their leg pain. This was in contrast to 51.9 and 54.4%, respectively, for those in the T-SCS arm. This demonstrated the superiority of high-frequency stimulation for the treatment of low back and leg pain ($p < 0.001$ for both back and leg pain) [2]. The same sustained relief that was seen in the European study was also seen in the SENZA-RCT. At 24 months, $\geq 50\%$ pain reduction of low-back pain was seen in 76.5% of high-frequency stimulation patients compared with 49.3% in the conventional arm ($p < 0.001$). Likewise, this responder rate was 72.9% in the high-frequency arm versus 49.3% in the conventional arm for leg pain ($p < 0.001$). Again, this showed the durable efficacy of this therapy that was superior to conventional means without increased incidence of adverse events (AEs) [3].

One year after SENZA-RCT was published, Arcioni *et al.* performed an open-label, exploratory study to assess the use of HF10 in the treatment of chronic, medically refractory migraines. Enrolled individuals underwent a 2–4 weeks tunneled cervical HF10 trial with subsequent implantation if they experienced a reduction in chronic migraine symptoms (pain intensity and/or migraine episodes) during the trial. Seventeen patients were trialed and 14 subjects remained implanted at 6 months (one trial failure, one trial infection, one implant site infection). At 6

Table 2. Studies evaluating high-frequency spinal cord stimulation.

Study (year)	Study type	Patients (n)	Condition investigated	Follow-up period	Results	Ref.
Van Buyten (2013); Al-Kaisy (2014)	Prospective, multicenter	83	Low back and leg pain	24 months	<ul style="list-style-type: none"> • Back pain relief >50% in 60% of patients with HF10 at 24 months • Leg pain relief >50% in 71% of patients with HF10 at 24 months 	[5,53]
Kapural (2015, 2016)	Multicenter, randomized, controlled	198	Low back and leg pain	24 months	<ul style="list-style-type: none"> • >50% back pain relief in 77% of subjects with HF10 vs 49% with T-SCS at 24 months • >50% leg pain relief in 73% of subjects with HF10 vs 49% with T-SCS at 24 months 	[2,3]
Arcioni (2016)	Prospective, single-center	17	Chronic migraine	6 months	<ul style="list-style-type: none"> • >30% reduction in overall headache days in 50% of patients at 6 months 	[54]
Al-Kaisy (2017, 2018)	Prospective, single-center	20	low-back pain without previous spine surgery	36 months	<ul style="list-style-type: none"> • Significant VAS reductions for axial back (baseline VAS 79 ± 12 to 10 ± 12 mm) and leg pain (VAS 33 ± 21 to 9 ± 13 mm) at 36 months • Reductions in ODI (baseline 53 ± 13 to 19.8 ± 13) • Decline in opioid use, 88% opioid-free at 36 months 	[55,56]
Amirdelfan (2019)	Prospective, multicenter	45	Neck and arm pain	12 months	<ul style="list-style-type: none"> • Significant VAS reductions for neck (baseline 7.6 ± 0.2 to 2.4 ± 0.4 cm) and arm pain (7.1 ± 0.3 to 1.8 ± 0.5 cm) at 3 months • Rate of neck and arm pain remitters (VAS ≤ 2.5 cm) 78.4 and 80%, respectively, at 12 months • 30% decreased/eliminated opioid use at 12 months 	[57]
Al-Kaisy (2019)	Post hoc analysis	137	Opioid usage	12 months	<ul style="list-style-type: none"> • 41% reduction in opioid use at 12 months (baseline 104.2 ± 9.0 to 61.4 ± 6.9 MME) • SENZA-EU with greater reduction (92.3 ± 15.6 to 28.1 ± 6.0 MME) compared with SENZA-RCT (112.7 ± 10.5 to 87.9 ± 10.3 MME) • High-dose subjects (>90 MME) prior to HF10 with 45.9% reduction at 12 months (196.8 ± 14.2 to 106.5 ± 14.1 MME) 	[58]
Thomson <i>et al.</i> (2018)	Randomized, controlled	20	Back and leg pain	16 weeks	<ul style="list-style-type: none"> • Mean back pain NRS scores decreased from 6.8 ± 0.3 (baseline, mean ± standard error of the mean) to 3.2 ± 0.3 (1 kHz), 3.5 ± 0.3 (4 kHz), 3.2 ± 0.3 (7 kHz) and 3.3 ± 0.4 (10 kHz). These decreases were shown to be equivalent across frequencies (p = 0.00002) • Mean leg pain NRS scores decreased from 5.5 ± 0.4 (baseline) to 2.6 ± 0.4 (1 kHz), 2.7 ± 0.4 (4 kHz), 2.7 ± 0.4 (7 kHz) and 2.9 ± 0.4 (10 kHz). Again, these results were equivalent across frequencies (p = 0.003) 	[59]

Legend: EQ-5D: EuroQuol five dimensional questionnaire; GAF: Global assessment of functioning; GIC: Global impression of change; NRS: Numeric Rating Scale; ODI: Oswestry disability index; PDI: Pain disability index; PSQI: Pittsburgh sleep quality index; SF: Short-form questionnaire; SF-MPQ: Short-form McGill pain questionnaire; T-SCS: Traditional spinal cord stimulation; VAS: Visual analogue scale.

months, 50% (7 out of 14) of implanted patients showed more than 30% reduction in headache days. Among the entire cohort, the overall reduction in headache days was 6.9 per month and among responders it was 12.9. This study provided a possible treatment option for this historically difficult patient population [54].

Al-Kaisy *et al.* were the first to publish an investigation of the efficacy of HF10 in patients with no prior history of spine surgery in 2017 [55]. This pilot study involved 21 subjects with chronic axial low-back pain who failed conventional medical management (CMM) and were not surgical candidates. All but one of the patients (20/21) had a successful HF10 trial and proceeded with implantation of the Nevro Senza system. Since this was a proof-

of-concept study, there was no single primary end point. However, back pain scores were significantly reduced at each postimplant follow-up ($p < 0.0001$), with reductions in average VAS scores of 59.9 and 72.6% at 6 and 12 months, respectively. Functional improvement as measured by ODI scores was also significantly lower at all time points, with a reduction of 47.6% compared with baseline at the 12-month follow-up.

The authors then published their results from the 36-month postimplant visit with the same cohort in 2018 [56]. Three subjects (17/20) were lost to follow-up after the preliminary study. Reductions in mean VAS scores for axial back pain were sustained at 36 months (baseline VAS 79 ± 12 to 10 ± 12 mm, $p < 0.0001$), with 80% of the subjects endorsing greater than 50% reduction. Although this study targeted patients with a predominantly back pain component, significant VAS reductions were also seen in those with leg pain (baseline VAS 33 ± 21 to 9 ± 13 mm) at 36 months. Similarly, ODI scores had sustained reductions at 36 months (baseline 53 ± 13 to 19.8 ± 13 , $p < 0.0001$) and subjects had significant improvements in health-related quality of life and mental health metrics. Opioid use also declined among subjects, with 88% being opioid free at 36 months compared with 10% at baseline. These results exhibit similar trends to the SENZA-RCT and SENZA-EU studies and demonstrate the potential utility of HF10 for ‘virgin back’ patients with refractory axial back pain who are poor surgical candidates [2,5].

In 2019, Amirdelfan *et al.* published results from a prospective, multicenter study that demonstrated the efficacy of HF10 therapy for the treatment of chronic neck and/or upper limb pain [57]. Pain etiology was heterogeneous for the patient population, with 66.7% having previously had cervical spine surgery. With a trial success rate of 89.1%, 45 patients were implanted. Eighty-six percent (39/45) of the patients achieved the primary end point, which was $\geq 50\%$ relief from baseline at 3 months follow-up. Subjects showed a significant decrease ($p < 0.001$) in mean VAS scores for both neck (baseline 7.6 ± 0.2 to 2.4 ± 0.4 cm) and arm pain (baseline 7.1 ± 0.3 to 1.8 ± 0.5 cm) at 3 months, which were sustained at the 12-month end point. Responder rates (defined as $\geq 50\%$ relief) at 12 months for neck and arm pain (89.2% for neck pain, 95% for arm pain) were also higher compared with T-SCS and dorsal nerve root stimulation (both 67%) reported from previous studies [60]. Furthermore, the rate of neck and arm pain remitters (defined as VAS scores ≤ 2.5 cm) were 78.4 and 80%, respectively, at 12 months. Additional improvements in metrics for disability/quality of life, overall satisfaction and sleep were also reported. Though opioid reduction was not actively encouraged for this study, 30% of the subjects decreased or eliminated opioid use at 12 months. It should also be noted that only 1/45 patients (2.2%) underwent device explantation, which is often an issue for patients using traditional cervical SCS devices due to positional variations in paresthesias.

As previously mentioned, the SENZA-RCT and SENZA-EU studies were critical for demonstrating the efficacy of HF10 for treating chronic low back and leg pain [2,5]. Al-Kaisy *et al.* published results from a *post hoc* analysis in 2019 on opioid usage for 137 patients taken from both SENZA studies [58]. While opioid reduction was not a primary end point for either study, mean opioid use among all patients declined by 41% at the 12-month follow-up (baseline 104.2 ± 9.0 to 61.4 ± 6.9 MME, $p < 0.001$), with the percentage of subjects who eliminated opioids also increasing (1.6–27%, $p < 0.0001$). When looking at each study separately, SENZA-EU subjects had a greater reduction (92.3 ± 15.6 to 28.1 ± 6.0 MME) compared with SENZA-RCT (112.7 ± 10.5 to 87.9 ± 10.3 MME). Subgroup analysis of patients on high-dose opioids (> 90 MME) prior to HF10 therapy demonstrated a 45.9% reduction at 12 months (196.8 ± 14.2 to 106.5 ± 14.1 MME, $p < 0.0001$). Corresponding reductions in pain scores are discussed elsewhere in this paper [2,5]. Reductions in opioid use with concomitant improvements in pain scores across both SENZA studies show the utility of HF10 therapy as a superior treatment modality and an important adjunct for reducing opioid use.

While HF10 stimulation has been shown in multiple studies to provide superior pain relief compared with traditional frequencies, other studies have found that kilohertz frequency stimulation at pulse frequencies other than 10 kHz can be equally effective [59]. A total of 34 patients underwent a paresthesia-based SCS trial and 33 patients were found to have a greater than 50% decrease in their pain. These patients were implanted with a permanent system. Next, these 33 patients underwent a ‘sweet spot’ search with 10 kHz stimulation to find the optimal stimulation location. Twenty-one patients found at least 30% pain relief during this process. Next, the 21 patients had a double-blind rate randomization phase where each patient experienced 1, 4, 7 and 10 kHz stimulation in randomized order, all at the ‘sweet spot’ location. A washout phase of a few days to 1 week was allowed between the different frequency settings. Each frequency was experienced for 4 weeks, and pulse width and amplitude were adjusted throughout the first 3 weeks to allow optimal pain relief. Twenty patients completed this portion of the study. The mean back pain NRS scores decreased from 6.8 ± 0.3 (baseline, mean $\pm$ standard error of the mean) to 3.2 ± 0.3 (1 kHz), 3.5 ± 0.3 (4 kHz), 3.2 ± 0.3 (7 kHz) and 3.3 ± 0.4 (10 kHz). These decreases

were shown to be equivalent ($p = 0.00002$). The mean leg pain NRS scores decreased from 5.5 ± 0.4 (baseline) to 2.6 ± 0.4 (1 kHz), 2.7 ± 0.4 (4 kHz), 2.7 ± 0.4 (7 kHz) and 2.9 ± 0.4 (10 kHz). Again, these results were equivalent across frequencies ($p = 0.003$).

Real-world evidence

Real-world data continue to uphold the results presented in previously published studies. In 2018, DiBenedetto *et al.* retrospectively compared 64 patients who received CMM and 32 patients who received SCS plus CMM in the treatment of chronic low-back pain, with or without radicular lower-extremity pain, to determine any difference in analgesia or perceived disability with the addition of HF10 at a single community-based interdisciplinary pain center over a 3-year period [61]. CMM included traditional interventional procedures, such as epidural steroid injections, facet joint injections, radiofrequency ablations and major joint injections. The patients who underwent SCS + CMM were followed for 12 months prior to SCS implantation as well as 12-month postimplantation. The CMM group was likewise followed for 24 months. Office visit volumes were recorded to determine the costs of healthcare utilization. The use of SCS + CMM was associated with improvements in low-back and lower-extremity pain as well as perceived disability. The addition of SCS allowed for statistically significant reductions in opioid use compared with patients undergoing CMM only. The authors postulated that this could decrease healthcare costs due to reductions in both medication utilization and number of interventional procedures. Both groups showed a decrease in modified Roland-Morris Disability Questionnaire scores, indicating a reduction in disability. These data highlight the addition of HF10 as a means of reducing opioid use, perceived disability and healthcare utilization costs.

One year later, Stauss *et al.* reviewed 1660 patients with chronic axial and/or limb pain who underwent HF10 implantation over a 4-year period across multiple international centers to assess real-world outcomes [4]. They assessed responsiveness to therapy, preferred programming of the SCS device, overall change in medication usage, change in function, change in sleep, change in quality-of-life, satisfaction of therapy, device recharge experience, frequency of therapy adjustments and device usage while sleeping and driving. Of the patients treated with HF10, more than 70% experienced at least 50% pain relief 12 months after implantation ($n = 1131$). They noted that additional HF10 optimization tools were utilized in 56.7% of patients; this included multiarea pain sequencing, bi-pole interlacing programs and pulse dosing. At their last visit, 72.3% of patients reported functional improvement and 68.0% reported improved sleep. Improvement in quality of life was reported in 90.3% of all patients. A majority of patients reported convenient recharging of the device and only 2.2% of the patients reported adjusting their therapy more often than two to three times per week. A large majority of patients reported sleeping (98.7%) and driving (98.2%) with their devices on. A decrease in medication use was reported in 32.1% of patients. Three hundred and eighty-two patients had previously failed T-SCS and of the 266 for whom there were data, 74.1% responded to therapy, 32% reported decreased medication use, 82.5% reported improved function and 70.0% reported improved sleep. The overall rate of explantation was 3.7%, due to both loss of efficacy (1.2%) and infection (1.7%). These data are in line with previously published prospective study data [62,63].

Safety & tolerability

The studies reviewed demonstrate safety profiles similar to well-accepted T-SCS safety profiles. In 2013, Van Buyten *et al.* reported that IPG site pain and lead migrations were noted to be the most common AEs [53]. Al-Kaisy *et al.* reported that these were the most common AEs and that this was in line with T-SCS. They reported no AEs directly related to stimulation effects [5]. Kapural *et al.* reported no stimulation-related neurological deficits. The authors did report comparatively low rates of lead migration and overall low incidence of study-related AEs [2]. They then extended these data to 24-month postimplantation and again demonstrated a favorable safety profile [3]. Arcioni *et al.* showed markedly less numbers of patients requiring additional surgery (24%) than a previous study utilizing occipital nerve stimulation for chronic migraine (41%) [54,64]. They reported few lead migrations ($n = 2$), infections ($n = 2$) and minimal IPG site discomfort ($n = 1$) as well. Al-Kaisy *et al.* have reported no serious AEs across several studies with the most common complications being pain at the IPG site or lead migration [55,56]. Amirdelfan *et al.* reported an improvement in neurological function in 4.4% of his patients and reported no stimulation-related neurological deficits. The authors reported two serious AEs: one extradural hematoma and one infection [57]. In real-world data, Stauss *et al.* reported that 3.7% of the patients had their devices explanted due to infection (1.7%), loss of efficacy (1.2%) and other reasons (0.8%) in the 12 months following implantation, respectively [4]. None of the studies reviewed highlighted any AEs that were outside of the accepted values consistent with T-SCS.

Conclusion

Since its seminal publication in 2015, HF10 has seen tremendous growth within the field of neuromodulation. This has been fueled by its commitment to quality research that seeks to demonstrate the efficacy and safety of HF10 in the treatment of conditions traditionally amenable to SCS, to determine the mechanism of action of their unique stimulation modality, and to expand the therapeutic indications of DC SCS. Additionally, real-world evidence continues to validate the expected patient outcomes. The Omnia IPG is the latest iteration of the Nevro Corp. Its offerings include programming frequencies from 2 to 10,000 Hz with the versatility to utilize multiple mechanisms of action, including traditional DC stimulation, paired waveforms and the direct neural inhibition that is only possible with HF10. This provides practitioners with the largest array of possible therapeutic options both in the initial and maintenance treatment of chronic pain conditions.

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