New Programming Modes of Spinal Cord Stimulation for Chronic Pain: A Systematic Review of Outcomes with Burst and High-Frequency Technology

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Abstract

Spinal cord stimulation (SCS) is a well-established, evidence-based treatment for chronic pain. For decades, implantation of tonic SCS systems has relied on epidural electric lead placement to overlap regions of pain with paresthesias to achieve maximal postoperative pain relief. During the course of tonic SCS treatment, tolerances to the stimulation frequency may develop, leading to reduced efficacy. Recent developments in novel programming modes, such as high-frequency 10 kHz (HF10) and burst, stray from tonic SCS in their electrical stimulation delivery patterns and unique ability to deliver SCS without engendering paresthesias. To date, no review has analyzed outcomes of both HF10 SCS and burst SCS for chronic back and limb pain. This article aims to review all HF10 and burst SCS prospective observational and randomized controlled trials for chronic back and limb pain. The literature search identified 21 papers—10 HF10 SCS papers, 9 burst SCS papers, and 2 papers assessing both HF10 and burst SCS concurrently. Burst SCS and HF10 SCS have been subjected to randomized controlled studies and have used similar patient pain score reporting on a visual analog scale (VAS) and numeric rating scale (NRS). Results from these studies have reported significant reductions in axial back pain and limb pain in patients sustained for up to 20 months with burst SCS treatment and up to 36 months with HF10 SCS. Both novel programming modes show promise as viable treatments for those suffering from chronic pain and/or patients who may no longer be responders to tonic SCS.

Keywords

► spinal cord stimulation
► chronic pain
► neurostimulation

Introduction

Spinal cord stimulation (SCS) has been performed in humans for nearly a quarter century. Today, SCS is one of the most effective techniques for attenuating chronic limb and back pain—the leading cause of disability worldwide.¹ SCS as a treatment option for chronic pain increased 159% from 1997 to 2006 in the U.S. Medicare population alone and continues to increase as advancements are made in SCS technology.² The therapeutic mechanisms of SCS are not yet well understood, but evidence suggests both spinal and supraspinal effects via epidural electrical stimulation of the dorsal columns in the spinal cord are implicated in the pain-reducing properties of SCS.³ Three primary pain pathways have been identified as the principal contributors to chronic pain: (1) the lateral discriminatory pathway, and (2) medial affective pathway, which are processed in parallel but can be modified individually, and (3) descending pain inhibitory pathway.⁴ It has been suggested that traditional tonic SCS may exert its pain-alleviating effect via the lateral pain pathway, activated when pain stimuli trigger tonic firing of wide dynamic range (WDR) neurons in the spinal cord relaying information in lamina I and IV–VI of the dorsal horn, up through the lateral thalamic nuclei, and then to the primary sensory motor area, posterior insula, and secondary somatosensory cortex.⁵−⁷
The lateral pain pathway is thought to mediate the discriminatory aspects of pain such as location and duration. The medial affective/attentional pain pathway is activated concomitantly with the lateral discriminatory pathway when painful stimuli are present; triggering burst firing in nociceptive-specific neurons and relaying information from lamina I of the spinal horn up to medial thalamic nuclei; and then to the cingulate cortex, anterior insula, and amygdala. This medial pain pathway is thought to mediate the attentional and emotional “feeling” that accompanies pain stimuli.

Tonic SCS uses rhythmic, isochronous low frequencies between 40 and 60 Hz to deliver charge-balanced electrical stimulation to the dorsal spinal cord in an attempt to attenuate pain. The tonic firing pattern has been shown to decrease hyperexcitability in WDR neurons and decrease the release of glutamate, while increasing release of γ-aminobutyric acid (GABA) in the dorsal horn of the spinal cord. This constant, low-frequency conventional SCS induces a noticeable tingling sensation called stimulation-induced paresthesia, and the dogma has been to superimpose paresthesias on patient-specific region of pain for maximal pain attenuation. However, stimulation-induced paresthesias are not pleasant for some patients, and the efficacy of conventional SCS may be limited in some patients when stimulation-induced paresthesias occur outside the region of pain.

There has recently been a focus on developing new programming modes of SCS that deliver paresthesia-free stimulation such as high-frequency 10-kHz HF10 SCS and burst SCS, which stimulate the lateral pain pathway at subparesthesia thresholds. This new SCS system delivers short-duration (30 μs), high-frequency (10 kHz), low-amplitude (1–5 mA) pulses to the spinal cord. The Senza device obtained a European Conformity (CE) mark in 2010 and U.S. Food and Drug Administration (FDA) approval in 2015 for use in clinical settings. HF10 SCS has been shown most effective for chronic pain reduction when leads are placed anatomically between T8 and T11 vertebral levels. This shift from paresthesia-mapping techniques used to place conventional, low-frequency SCS leads to purely anatomical lead placement in HF10 SCS systems may provide benefits to patients and physicians, such as shorter procedure times and subsequently lower health care cost.

The mechanism of pain alleviation behind HF10 SCS remains unknown, although preclinical work has shown that HF10 SCS, such as conventional low-frequency tonic SCS, stimulates WDR neurons, which are theorized to be hyperactive in chronic pain patients. Unlike conventional SCS, HF10 SCS may impede the crucial WDR “wind-up,” or repetitive hyperexcitability, which leads to increased postdischarge response with each stimulus, thus desensitizing the WDR neurons to bring them closer to normative functional states. Results from preclinical studies of high-frequency stimulation in animal models have shown frequencies between 2 and 100 kHz suppress WDR neuronal activity, and it has since been suggested that low-kHz frequencies (1–2 kHz) may be capable of reducing neuropathic pain equally as well as HF10 SCS, while lessening charge burden and increasing battery longevity. However, open-label and RCT efficacy of low-kHz SCS (1–2 kHz) is not widely reported, and current clinical use of low-kHz frequencies is exploratory and off-label for all available SCS systems. As such, only studies reporting data for the commercially available and CE/FDA-approved HF10 system (Senza) were included in this review.

Burst Spinal Cord Stimulation

Burst SCS has been trademarked as burst DR (St. Jude Medical) named after its inventor, Dirk De Ridder. De Ridder developed burst SCS in 2010 to mimic firing patterns observed in nociceptive-specific neurons in the spinal cord and brain. The burst firing pattern is characterized by a chain of action potentials occurring during a neuron’s active phase, which is followed by a period of relative quiescence. This pattern has been observed in pain-signaling C-fibers of the medial affective pain pathway that have accrued myelination damage.

During burst SCS, a five-spike chain is delivered at 500 or 1,000 Hz at 40 times per second with 1 millisecond pulse width. The 500-Hz burst frequency (referred to simply as “burst”) is the primary programming mode used in most burst trials and is favored because results at 500 Hz burst showed maximal postsynaptic inhibition in thalamocortical and perigeniculate neurons of the brain in preclinical animal studies. Burst stimulation frequencies can be retroactively programmed into implantable pulse generators (IPGs) such as the Eon IPG and Prodigy IPG (St. Jude Medical) and are also available in the Proclaim IPG (St. Jude Medical).

Burst SCS and tonic SCS are both believed to modulate the ascending lateral discriminatory pain pathway by reducing firing rates of WDR neurons, masking the pain signal traveling to the brain.

Early clinical trials of burst SCS have shown significant paresthesia-free pain relief, though a small number of patients still experience some paresthesia (unlike fully paresthesia-free HF10 SCS) and reduced oral opioid consumption for patients with chronic pain.

Materials and Methods

Literature Search

Two separate searches were conducted with the PubMed, Medline, and Web of Science databases using the following key words and phrases: (1) spinal cord stimulation, (2) “spinal cord stimulation AND chronic pain,” (3) burst stimulation, (4) “burst stimulation AND chronic pain,” (5) high-frequency

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stimulation, (6) “high-frequency stimulation AND chronic pain,” (7) HF10 stimulation, and (8) 10 kHz stimulation. The authors also reviewed the bibliographies of relevant journal articles for additional studies. Given that HF10 and burst stimulation have only recently been developed and approved for use in humans, there was no limit to the year of publication in the literature search.

Selection of Studies
The reviewers read the abstracts of all relevant studies to determine whether the article met the following inclusion criteria: (1) HF10 or burst SCS studies in patients with primary chronic pain of the back and/or limbs; (2) the study was a randomized controlled trial (RCT); or (3) a prospective observational study or follow-up. Articles were excluded if they (1) were single-patient case reports, (2) examined preclinical animal models, or (3) only reported tonic SCS outcomes.

Results

Literature Search
The literature search identified 21 papers in total examining clinical outcomes with HF10 SCS, burst SCS, or both. Ten papers clinically assessed HF10 SCS (Table 1), nine papers clinically assessed burst SCS (Table 2), and two papers assessed both HF10 SCS and burst SCS (Table 3).

HF10 Spinal Cord Spinal Results
Tiede and colleagues published results from a short trial of HF10 stimulation in a cohort of failed back surgery.

Table 1 HF10 SCS studies included in this review in chronological order

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary region of pain</th>
<th>Previously treated with SCS?</th>
<th>Methods of study</th>
<th>Results of study</th>
<th>Stimulation programming modes used</th>
<th>Patients reporting data</th>
<th>Study design and length</th>
<th>Baseline pain score</th>
<th>Last recorded pain score with HF10 SCS</th>
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<tbody>
<tr>
<td>Tiede et al, 2013</td>
<td>Axial back pain greater than leg pain</td>
<td>SCS-naive pts</td>
<td><strong>Methods</strong>: Two trial phases with an external trial stimulator. Phase 1: tonic SCS trial (4–7 d). Phase 2: HF10 trial (4 d). Pain scores assessed at baseline (before both trials) and after day 3 of HF10 trial.</td>
<td><strong>Results</strong>: HF10 SCS trial significantly reduced pain vs. baseline and was preferred treatment option for 88% of pts vs. tonic SCS.</td>
<td>- HF10 - Tonic</td>
<td>n = 24</td>
<td>Prospective trial - 4 d</td>
<td>Global VAS pain with tonic SCS: 3.92 ± 0.90</td>
<td>Back VAS pain with tonic SCS: 2.03 ± 0.07</td>
</tr>
<tr>
<td>Van Buyten et al, 2013</td>
<td>- 87% of pts had primary axial back pain</td>
<td>- 13% of pts had primary leg pain</td>
<td>- Most pts SCS-naive</td>
<td>- 14–72 pts previously failed tonic SCS</td>
<td><strong>Methods</strong>: Pts received HF10 IPG implant and were followed for 6 mo.</td>
<td><strong>Results</strong>: HF10 SCS provided significant back pain and leg pain relief (≥ 50% pain reduction) in 74% of pts, sustained for 6 mo. Improvements in quality of sleep and disability. Pts who previously failed tonic SCS had back pain VAS reduce from 8.9 at baseline to 2.0 after 6 mo of HF10 SCS.</td>
<td>- Global VAS pain with HF10 SCS: 1.88 ± 0.85</td>
<td>Back VAS pain with HF10 SCS: 1.27 ± 0.3</td>
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<tr>
<td>Al-Kaisy et al, 2014</td>
<td>Follow-up of Van Buyten et al, 2013 (above)*</td>
<td></td>
<td><strong>Methods</strong>: Continued assessment at 12 and 24 months of pts from Van Buyten et al, 2013*</td>
<td><strong>Results</strong>: Back pain and leg pain relief with HF10 SCS was sustained for 24 mo. (60% responder rate). Sustained improvements in quality of sleep and disability. Pts who previously failed tonic SCS had back pain VAS reduce from 8.9 at baseline to 4.2 after 24 mo. of HF10 SCS. 29% of pts stopped taking oral opioids at 24 mo.</td>
<td>- HF10</td>
<td>n = 65*</td>
<td>Follow-up - 24 mo</td>
<td>Back VAS pain</td>
<td>Back VAS pain</td>
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(Continued)
Table 1 (Continued) HF10 SCS studies included in this review in chronological order

<table>
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<th>Study</th>
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<th>Baseline pain score</th>
<th>Last recorded pain score with HF10 SCS</th>
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<tbody>
<tr>
<td>Al-Kaisy et al., 2015&lt;sup&gt;15&lt;/sup&gt;</td>
<td>- Pain of the upper and lower extremities - SCS-naïve pts</td>
<td></td>
<td><strong>Methods:</strong> 11 of 15 pts proceeded to permanent of HF10/IPG implant after trial. Lower-limb pain pt. lead placement: T8–12. Upper-limb pain pt. lead placement: C2–7. Leads were placed for paresthesia overlapping here to allow for tonic SCS to be easily accessible if suboptimal results were seen with HF10 SCS.</td>
<td><strong>Results:</strong> Limb pain relief with HF10 SCS was sustained for 6 mo. in 10 of 11 pts receiving HF10 SCS.</td>
<td>- HF10</td>
<td><strong>n</strong> = 11</td>
<td>Retrospective Observational - 6 mo</td>
<td>Mean NRS score in region of pain: 8.2 ± 1.7</td>
<td>Mean NRS score in region of pain: 3.3 ± 1.7</td>
</tr>
<tr>
<td>Kapural et al., 2015&lt;sup&gt;16&lt;/sup&gt;</td>
<td>- Axial back pain and leg pain - SCS-naïve pts</td>
<td></td>
<td><strong>Methods:</strong> Pts randomized 1:1 ratio (stratified by sex and primary region of pain: limb or back) across 10 comprehensive pain treatment centers. 171 of 198 pts proceeded to permanent tonic (n = 81) or HF10 IPG (n = 90) implant.</td>
<td><strong>Results:</strong> HF10 SCS significantly reduced both back and leg pain nearly twice that of the tonic SCS treatment pain at 3, 6, and 12 mo. No paresthesia during HF10. 35% of HF10 SCS pts reduced or ceased oral opioid consumption at 12 mo.</td>
<td>- HF10 - Tonic</td>
<td><strong>n</strong> = 90</td>
<td>RCT - 12 mo</td>
<td>Prior to implant: Back VAS pain HF10 group: 7.4 ± 1.2 Tonic group: 7.8 ± 1.2 Leg VAS pain HF10 group: 7.1 ± 1.5 Tonic group: 7.6 ± 1.4</td>
<td>After 12 months: Back VAS pain HF10 group: 2.5 Tonic group: 4.3 Leg VAS pain HF10 group: 2.1 Tonic group: 3.8</td>
</tr>
<tr>
<td>Russo et al., 2016&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Axial back pain or back and leg pain - Most pts SCS-naïve - 47–189 pts previously failed tonic SCS</td>
<td></td>
<td><strong>Methods:</strong> Pts implanted with HF10 IPGs were assessed at 6 mo.</td>
<td><strong>Results:</strong> Mean pain reduction of 50% was sustained for 6 mo. Pts who previously failed tonic SCS and had a successful HF10 trial (68%) had overall pain NRS reduce from 7.2 at baseline to 3.7 after 6 mo. of HF10 SCS.</td>
<td>- HF10</td>
<td><strong>n</strong> = 186</td>
<td>Retrospective Observational - 6 mo</td>
<td>Mean NRS pain 7.5 Back NRS pain 7.4</td>
<td>Mean NRS pain 3.7 Back NRS pain 3.8</td>
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Table 1 (Continued) HF10 SCS studies included in this review in chronological order

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<tbody>
<tr>
<td>Kapural et al, 2016</td>
<td>Follow-up of Kapural et al, 2015 (above)</td>
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<td>Methods: Continued assessment at 24 mo of pts from Kapural et al, 2015. 156 pts reported data (85/90 total HF10 pts reporting, 71/81 total tonic pts reporting). Results: Pain-reducing effects of HF10 sustained for 24 mo. Back pain responders (≥ 50% reduction) were 76.5% of pts in HF10 group vs. 49.3% in tonic group. Leg pain had similar responder rate of 72.9% of pts in HF10 group vs. 49.3% in tonic group. After 24 mo, VAS pain scores in HF10 group were lower versus tonic SCS pt. group scores for both back and leg pain.</td>
<td>- HF10 - Tonic</td>
<td>n = 85*</td>
<td>Follow-up - 24 mo</td>
<td>Back VAS pain</td>
<td>Back VAS pain</td>
<td></td>
</tr>
<tr>
<td>Al-Kaisy et al, 2017a</td>
<td>Chronic low back pain with out prior spinal surgery - SCS-naïve pts</td>
<td></td>
<td>Methods: Pts implanted with HF10 IPGs were assessed up to 12 mo. Results: 20 pts reported data at 6 and 12 mo. Average reduction in back pain VAS score from baseline was −4.69 ± 2.78 at 6 mo, and −5.59 ± 1.80 at 12 mo. At 12 mo, 90% of pts were responders (VAS reductions &gt; 50% from baseline). Three pts stopped using opioids, and average intake was down 64% for all pts at 12 mo.</td>
<td>- HF10</td>
<td>n = 21</td>
<td>Prospective Observational - 12 mo</td>
<td>Back VAS: 7.9 ± 1.2</td>
<td>Back VAS: 3 ± 2</td>
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<tr>
<td>Al-Kaisy et al, 2017b</td>
<td>“Follow-up of Al-Kaisy et al, 2017a (above)</td>
<td></td>
<td>Methods: Continued assessment at 36 mo of pts from Al-Kaisy et al, 2017a. Results: 17 of 20 pts from original study reported data at the 36-mo follow-up point. 80% of these pts (16/20) reported VAS score reductions of &gt; 50% (responders) at 36 mo. The average reductions in leg VAS score was also significant at 36 mo. compared with baseline. 88% of pts had stopped using opioids at 36 mo.</td>
<td>- HF10</td>
<td>n = 17*</td>
<td>Prospective Observational - 36 mo</td>
<td>Back VAS: 7.9 ± 1.2</td>
<td>Back VAS: 1.0 ± 1.2</td>
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syndrome (FBSS) patients with primary axial back pain. Tonic stimulation was delivered for 4 to 7 days with an external trial stimulator, followed by a 4-day HF10 trial period. Significant reductions in overall pain and back pain were reported after the tonic trial and the HF10 trial, although HF10 was the preferred stimulation for 88% of patients (Table 1).

In the seminal prospective observational study of HF10 stimulation, a cohort of 72 patients with primary FBSS were followed for 6 months. Most patients were SCS-naïve (no previous SCS implantation), whereas 19% of the cohort had previously failed tonic SCS. After 6 month of HF10 therapy, reductions in back pain visual analog scale (VAS) and leg pain VAS were both statistically significant. Opioid usage was decreased in 62% of these patients and eliminated in 38% of patients at long-term follow-up.

Continued assessment occurred at 12 and 24 months in a follow-up study. Back pain VAS was sustained at 2.8 after 12 months of treatment and 3.3 after 2 years of HF10 SCS (Table 1). Leg pain relief VAS ratings remained unchanged at 2.3 after 2 years with HF10 SCS.

The first study to enroll patients with the primary indication of chronic pain of the upper and lower extremities was published by the group of Al-Kaisy et al 1 year later. Vertebral stimulation levels were identified with intraoperative paresthesia mapping and placed based on location of pain, not the purely anatomical placement between T8 and T11 pioneered by Tiede et al in 2013. Mean overall pain scores were significantly reduced at 1-month follow-up and sustained to 6-month follow-up (Table 1). Notably, zero of three patients with primary foot pain responded positively to HF10 SCS, whereas three of three patients with primary hand

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**Table 1** (Continued) HF10 SCS studies included in this review in chronological order

<table>
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<tr>
<th>Study</th>
<th>Primary region of pain</th>
<th>Methods of study</th>
<th>Stimulation programming modes used</th>
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<th>Study design and length</th>
<th>Baseline pain score</th>
<th>Last recorded pain score with HF10 SCS</th>
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</thead>
<tbody>
<tr>
<td>Thomas et al, 2018</td>
<td>Chronic low back pain with/without equal or lesser leg pain - SCS-naïve pts</td>
<td>Methods: 33 pts were enrolled in an 8-wk “sweet spot” search for optimal HF10 stimulation location. 21 pts reported ≥ 30% reduction in NRS scores during this 8-wk period, and proceeded to the randomization phase where 1, 4, 7, and 10 kHz stimulation were delivered in a randomized order for each pt. Each frequency was delivered for four consecutive weeks, with no programming changes permitted during the fourth week. 20 pts completed randomization and selected their preferred frequency for 3 mo follow-up. Results: During 16-wk randomization period, all four stimulation frequencies produced ~50% pain relief across overall pain reduction, back pain reduction and leg pain reduction scores, as reported by ED-NRS reporting. During 3-mo open-label period, 50% of pts used 1 kHz, while only 15% used HF10. Stimulation with 1 kHz produced equivalent pain reduction while using significantly less charge than 4, 7, or 10 kHz, which showed no pair-wise significant differences in charge per second.</td>
<td>- 1 kHz</td>
<td>- 4 kHz</td>
<td>- 7 kHz</td>
<td>- 10 kHz</td>
<td>n = 33</td>
</tr>
<tr>
<td>Total</td>
<td>n = 437</td>
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Abbreviations: ED-NRS, electronic diary numeric rating scale; FBSS, failed back surgery syndrome; HF10, high-frequency 10 kilohertz; IPG, implantable pulse generator; NRS, numeric rating scale; pts, patients; RCT, randomized controlled trial; SCS, spinal cord stimulation; VAS, visual analog scale.

*Included patients from previous study.
pain responded positively to HF10 SCS. Results were mixed for patients with pain of the upper limbs; one patient reported less than 10% reduction in pain, whereas another reported greater than 80% reduction with HF10 SCS.15

Results from the large SENZA-RCT comparing tonic with HF10 SCS in 198 patients with axial back and/or leg pain were published in 2015.16 Patients were randomized 1:1 to receive either tonic (n = 81) or HF10 (n = 90) system implantation. At a 12-month follow up, 84.5% of HF10 SCS patients were responders for back pain, compared with 43.8% for conventional tonic SCS.16 Back pain VAS scores for the HF10 SCS group were reduced from 7.4 prior to treatment to 2.5 at the 12-month mark (Table 1). More HF10-treated patients were responders for leg pain (83.1%) compared with tonic SCS patients (55.5%).16 A 24-month-long-term follow-up of the SENZA-RCT reported sustained analgesic efficacy of HF10 therapy for back and leg pain that was superior to tonic SCS (Table 1).15

Russo and colleagues evaluated HF10 therapy across three comprehensive Australian pain clinics in the largest patient population (n = 186) reported to date.17 Some patients in this cohort had previously undergone conventional SCS therapy, but were nonresponders. Overall mean global pain and axial back pain numeric rating scale (NRS) scores for the entire cohort were significantly reduced and sustained for 6 months. In the subpopulation of tonic SCS poor responders (PRs) who proceeded to HF10 system implantation (n = 47), significant reductions in back pain and/or leg pain were sustained through the 6-month follow-up period.17

Unlike previous studies, the 20 patients enrolled in a proof-of-concept HF10 study by Al-Kaisy and colleagues20 were considered unsuitable candidates for spinal surgery. Back pain VAS scores were reduced to an average of 59.9% and 72.9% from baseline at 6 and 12 months, respectively (Table 1). At 12 months, 80% of patients reported their condition was "much improved" or "very much improved."20

The same group later reported long-term follow-up data from 17 patients at 36 months.21 Significant reductions in back pain VAS scores were sustained at 36 months (Table 3). Importantly, 88% of patients were not taking opioids at long-term follow-up, compared with 10% at baseline.21

Thomson and colleagues22 published the first randomized, double-blind crossover study of frequencies from 1 to 10 kHz in a cohort of 33 patients. During an 8-week trial period, optimal stimulation location for HF10 was refined. Four weeks of stimulation were delivered for 1, 4, 7, and 10 kHz in a randomized order for each patient, with no adjustments permitted during the evaluation (fourth) week. All frequencies were statistically equivalent in electronic diary-reported NRS pain reduction scores throughout the 16-week trial period (Table 1). One kHz stimulation required significantly less charge compared with the other three frequencies.22 Patients were able to select their preferred frequency for a 3-month open-label phase following randomization: 50% chose 1 kHz, 10% used 4 kHz, 25% used 7 kHz, and 15% used 10 kHz. Back pain, leg pain, and overall pain reduction was sustained through the 3-month follow-up, regardless of stimulation frequency.22

**Table 1**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Back Pain VAS Reduction (%)</th>
<th>Leg Pain VAS Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kHz</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>4 kHz</td>
<td>40%</td>
<td>40%</td>
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<tr>
<td>7 kHz</td>
<td>30%</td>
<td>30%</td>
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<td>10 kHz</td>
<td>20%</td>
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**Burst Spinal Cord Stimulation Results**

De Ridder and colleagues conducted the first trial of burst SCS in 12 patients in 2010.25 Mean axial back and limb VAS scores were significantly reduced from baseline to 1-year follow-up (Table 2). Out of 12 patients, 2 (16.6%) experienced stimulation-related paresthesia.

A randomized, double-blind, placebo controlled trial comparing burst SCS, tonic SCS, and placebo in 15 SCS-naïve FBSS patients was conducted by the De Ridder group in 2013.27 Patients were assigned in a randomized order to receive burst SCS, tonic SCS, or placebo (no stimulation) each for a period of 7 days. Burst SCS, but not tonic SCS, significantly reduced global mean VAS scores but did not significantly reduce axial pain VAS scores or limb pain VAS scores compared with tonic SCS (Table 2). Tonic SCS only significantly suppressed limb pain, but not axial back pain, compared with sham stimulation.27

de Vos and colleagues28 conducted a 2-week burst SCS study of 48 patients who had already received tonic SCS treatment for a period of at least 6 months (mean = 2.5 years). Patients were classified in one of three categories: painful diabetic neuropathy (PDN) (n = 12), FBSS (n = 24), and FBSS patients who were PRs to tonic SCS (n = 12). The PDN group reported the largest VAS score reductions of the three groups, with 67% of PDN patients reporting an "extra" reduction in pain during the 2-week burst period compared with tonic SCS (Table 2). FBSS patients also experienced significant reductions in pain during tonic and burst SCS. Out of 24 FBSS patients, 14 (58%) experienced additional pain reduction during burst SCS, but 4 experienced a pain increase. For the PR group, the mean baseline VAS score decreased during tonic stimulation and was further reduced in 50% of PR patients during burst stimulation.

Schu and colleagues executed another RCT29 in 20 FBSS patients with a history of tonic SCS. All the patients reported a diminished effect of their tonic SCS treatments over time but still qualified as adequate-to-good responders. A defining feature of this study was the use of 40 and 500 Hz tonic stimulation; the latter selected to eliminate differences between burst and tonic stimulation frequency. Burst SCS significantly reduced pain scores in comparison to placebo, traditional (40 Hz) tonic SCS, and 500 Hz tonic SCS (Table 2).

In the first study examining effects of an alternative, higher-frequency (1,000 Hz) burst SCS mode on pain suppression, Van Havenbergh et al30 recruited 15 FBSS already being treated with standard burst. Patients were randomly assigned to either 1,000 Hz burst frequency or 500 Hz burst frequency each for 2 weeks. No significant difference in back pain, limb pain, or general pain scores were reported between burst frequencies (Table 2).

Courtney et al30 later report significant reductions in global, trunk, and limb pain during burst SCS compared with tonic SCS. Sixteen (76%) of 21 patients reported an overall reduction of any magnitude of pain during burst SCS, and 10 of 21 (48%) patients reported at least a 50% reduction in overall pain during burst SCS compared with tonic SCS (Table 2).

In the largest study of burst SCS to date, the De Ridder group recruited 102 patients with chronic axial back and leg...
Table 2  Burst SCS studies included in this review in chronological order

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary region of pain Previously treated with SCS?</th>
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<th>Baseline pain score</th>
<th>Last recorded pain score with burst SCS</th>
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<tbody>
<tr>
<td>De Ridder et al, 2010</td>
<td>- Axial back pain and limb pain - SCS-naïve pts</td>
<td>Methods: Pts implanted with burst IPGs after successful trial period and assessed at least 1 year later (mean follow-up time = 20.5 mo). Results: Significant reductions in both limb and back pain scores from baseline were sustained during burst SCS through the average follow-up period of 20.5 mo. Two of 11 pts experienced paresthesia during burst SCS.</td>
<td>- Burst</td>
<td>n = 11</td>
<td>Prospective Observational - 20.5 mo</td>
<td>Back VAS pain: 6.25</td>
<td>Limb VAS pain: 7.54</td>
</tr>
<tr>
<td>De Ridder et al, 2013</td>
<td>- Axial back pain and limb pain - SCS-naïve pts</td>
<td>Methods: Pts implanted with burst IPGs, assigned in a randomized order to receive tonic SCS, burst SCS, or placebo. Pt scores were assessed by a blinded clinician and then reprogrammed with the next treatment after 7 d. Results: Burst SCS significantly reduced attention paid to pain vs. placebo and vs. tonic SCS. Burst SCS significantly reduced global, back and limb pain vs. placebo. Tonic SCS did not reduce back pain vs. placebo. All pts preferred burst. Burst SCS did not generate more paresthesia than placebo.</td>
<td>- Burst - Tonic - Placebo</td>
<td>n = 15</td>
<td>RCT, placebo controlled - 7 d</td>
<td>General VAS: 8.2</td>
<td>Back VAS: 7.4</td>
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<td>De Vos et al, 2014</td>
<td>- FBSS, PDN, and &quot;PRs&quot; to SCS with back, limb, and/or feet pain - Pts received treatment with tonic SCS for at least the previous 6 mo (mean=2.5 y)</td>
<td>Methods: Pts recruited to try burst SCS for a 2-wk period: 12 pts were PDN pts. 24 pts were FBSS pts. 12 pts were FBSS pts who had exhausted all tonic SCS adjustments for pain relief (&quot;PR&quot; pts) Results: 60% of pts currently receiving tonic SCS as treatment experienced further pain reduction with burst SCS. Pain reduction in burst SCS was strongest in PDN pts, followed by FBSS pts, and last by PR pts. For the 12 PR pts, mean VAS scores decreased from 8.2 to 6.4 after 14 d of burst SCS.</td>
<td>- Burst</td>
<td>n = 48</td>
<td>Prospective Observational - 14 d</td>
<td>VAS with tonic PDN global pain: 2.8 ± 2.3 FBSS global pain: 4.9 ± 2.3 FBSS back pain: 4.4 ± 2.8 PR global pain: 7.4 ± 1.6</td>
<td>VAS with burst PDN global pain: 1.6 ± 1.8 FBSS global pain 3.5 ± 2.2 FBSS back pain: 3.1 ± 2.4 PR global pain: 6.4 ± 2.7</td>
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(Continued)
Table 2 (Continued) Burst SCS studies included in this review in chronological order

<table>
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<tr>
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<tr>
<td>Schu et al, 2014⁹</td>
<td>FBSS pts with primary leg pain - Pts received treatment with tonic SCS for at least the previous 3 mo (range: 1–1.5 y)</td>
<td><strong>Methods:</strong> Pts who still had adequate or good response to tonic SCS were randomly assigned a sequence of 1-wk 500 Hz tonic SCS, 1-wk burst SCS, and 1-wk placebo. Burst SCS at 500 and 1,000 Hz were compared in a randomized testing period of 2 wk each. Pts and evaluators were blinded to the stimulation frequency being applied and assessed. <strong>Results:</strong> Lowest mean pain scores were observed during burst SCS periods. Mean pain rating score was significantly decreased for pts only during burst SCS. Only general mean NRS scores were reported. 80% of pts preferred burst programming to 500 Hz tonic and placebo. No paresthesia during burst SCS.</td>
<td>- Burst 500 Hz tonic - Placebo</td>
<td>n = 20</td>
<td>RCT, placebo controlled - 7 d</td>
<td>General mean NRS with placebo (no stim): 8.3 ± 1.1 General mean NRS with tonic: 5.6 ± 1.7</td>
<td>General mean NRS with burst: 4.7 ± 2.5</td>
</tr>
<tr>
<td>Van Havenbergh et al, 2015²⁴</td>
<td>FBSS pts with axial back pain and limb pain - Pts received treatment with 500 Hz burst SCS for an unspecified amount of time prior to study</td>
<td><strong>Methods:</strong> 4-wk double-blind, RCT where 500 Hz burst SCS and 1,000 Hz burst SCS programming modes were each assessed for a period of 14 d. <strong>Results:</strong> No additional pain reduction during 1,000 Hz burst. No differences between the two burst SCS programming modes in general pain, back pain, limb pain, paresthesia, attention to pain, or attention to pain change.</td>
<td>- Burst - 1,000 Hz burst</td>
<td>n = 15</td>
<td>RCT - 14 d</td>
<td>No significant difference in general, axial back pain or limb pain between 500 Hz burst and 1,000 Hz burst. No difference in stimulation paresthesia or attention paid to pain</td>
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<tr>
<td>Courtney et al, 2015²⁹</td>
<td>Axial back pain and limb pain - Pts received treatment with tonic SCS for at least the previous 3 mo</td>
<td><strong>Methods:</strong> 2-wk trial of burst SCS across four investigational sites. Burst SCS was compared with the favorite tonic program pts were receiving. <strong>Results:</strong> Burst significantly reduced pain scores vs. tonic SCS. 50% of pts reported charging times of &lt; 30 min 2–3 times per week. 73% of pts reported no paresthesia during burst SCS. 20/22 pts (91%) preferred burst SCS to tonic SCS.</td>
<td>- Burst - Tonic</td>
<td>n = 22</td>
<td>Prospective Observational - 14 d</td>
<td>VAS with tonic Global: 5.4 ± 1.98 Trunk: 4.42 ± 2.75 Limb: 5.82 ± 2.12</td>
<td>VAS with burst Global: 2.83 ± 1.73 Trunk: 1.79 ± 1.98 Limb: 2.83 ± 2.28</td>
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(Continued)
Table 2 (Continued) Burst SCS studies included in this review in chronological order

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<tr>
<td>De Ridder et al., 2015</td>
<td>FBSS pts and PDN pts with axial back pain and limb pain</td>
<td>Pts received treatment with tonic SCS for at least the previous 6 mo</td>
<td>Methods: 2-wk trial of burst SCS across two investigational sites. One group of pts had previously failed tonic SCS, and one group still responded to tonic SCS.</td>
<td>Results: Pts who responded successfully to tonic SCS further improved under burst SCS. Pain suppression for this group was 50.6% during tonic SCS, improving to 73.6% during 2 wk of burst SCS. 62.5% of nonresponders to tonic SCS responded to burst SCS with an average pain suppression of 43%.</td>
<td>Burst</td>
<td>n = 102</td>
<td>Retrospective Observational</td>
<td>14 d</td>
<td>Global NRS score (no stim): 7.80 ± 1.28</td>
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<tr>
<td>Tjepkema-Cloostermans et al., 2016</td>
<td>Pain of the lower extremities</td>
<td>Pts received treatment with tonic SCS for at least the previous 6 mo</td>
<td>Methods: Pts received high (0.1–6.4 mA) and low (0.1 mA) amplitude burst SCS, for a period of 2 wk each, with a 2-wk “washout” of tonic between the high- and low-amplitude burst periods in a double-blind RCT.</td>
<td>Results: Mean VAS pain scores were significantly lower during 500 Hz burst and 1,000 Hz burst vs. tonic SCS, although no difference was found between the two novel modes of burst SCS. 58% of pts experienced a 30% further reduction in pain during high and/or low burst SCS. 72.5% of pts preferred high or low burst SCS vs. tonic SCS.</td>
<td>- High-amp. burst (0.1–6.4 mA)</td>
<td>n = 40</td>
<td>RCT</td>
<td>14 d</td>
<td>Global VAS with tonic SCS: 5.2 (CI 4.4–5.9)</td>
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<tr>
<td>Deer et al., 2018</td>
<td>Pain of the trunk and/or lower limbs (majority FBSS)</td>
<td>- SCs-naïve pts</td>
<td>Methods: Pts randomized (1:1) to 12 wk of tonic stimulation followed by 12 wk of burst SCS or 12 wk burst followed by 12 wk of tonic SCS. Assessment performed at 24 wk after randomization, and again during an open-label stimulation period of 1 y.</td>
<td>Results: 96 pts completed the 24-wk follow-up for primary endpoint analysis. Superiority of burst over tonic stimulation for overall VAS, trunk VAS, and limb VAS was observed (mean difference in VAS score between burst and tonic was −5.1 mm). At 1-y follow-up, significant reductions in overall VAS scores were sustained in 80 pts. Of these pts, 68% indicated that burst was the preferred stimulation mode compared with 24% of pts preferring tonic SCS.</td>
<td>Burst</td>
<td>n = 100</td>
<td>RCT</td>
<td>24-wk crossover: 12 wk tonic and 12 wk burst</td>
<td>1-y open-label follow-up</td>
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Total: n = 373

Abbreviations: FBSS, failed back surgery syndrome; IPG, implantable pulse generator; NRS, numeric rating scale; pts, patients; PDN, painful diabetic neuropathy; PR, poor responder; RCT, randomized controlled trial; SCS, spinal cord stimulation; VAS, visual analog scale.
pain who had been using tonic SCS for at least 6 months. Burst SCS resulted in significant reduction in both limb and back pain from baseline compared with tonic SCS. For patients who did not respond to tonic SCS, 62.5% responded to burst SCS after the 2-week period (Table 2).

In a subsequent study, 40 patients with FBSS who had been receiving tonic SCS therapy for pain of the lower extremities were recruited for an RCT comparing high amplitude (0.1–6.4 mA) and low amplitude (0.1 mA) burst SCS to tonic SCS (0.4–19 mA). Average VAS pain scores for the most affected body parts were reduced during periods of both high- and low-amplitude burst compared with tonic SCS (Table 2). Twenty-three (58%) of 40 patients had additional clinically relevant pain reduction with both forms of burst stimulation compared with tonic.

Results from the long-awaited Success Using Neurumodulation with BURST (SUNBURST) study were published in 2018. In the largest multicenter RCT of burst stimulation to date, 100 un-blinded patients were randomized to receive 12 weeks of both tonic and burst stimulations. A post hoc analysis revealed that burst SCS provided superior pain relief for trunk pain and limb pain, with 70.8% of patients preferring burst stimulation at the end of the 24-week study period (Table 2). At 1-year follow-up, 68% of patients were receiving burst SCS as their “preferred treatment” during an open-label phase. Significant reductions in daily overall VAS score from baseline in all patients were sustained at 1-year, regardless of stimulation paradigm (Table 2).

Comparison of HF10 and Burst Spinal Cord Stimulation
To date, only a single observational study and a long-term follow-up have compared outcomes with both burst SCS and HF10 SCS. Kinfe et al selected 16 SCS-eligible FBSS patients to receive either burst or HF10 SCS. Two of eight patients assigned to HF10 SCS failed the trial period. At 3 months, significant decreases in the mean back pain VAS score was observed in both burst and HF10 groups compared with baseline, with no differences between the modalities (Table 3). However, patients being treated with burst SCS, but not HF10, reported a significant reduction in leg pain VAS scores (Table 3). Five of eight burst SCS patients were responders for leg pain, whereas no HF10 SCS patients were responders (Table 3).

A follow-up of 14 patients the following year revealed significant and sustained back pain analgesia at long-term follow-up for both burst and HF10 patients. Burst pain intensity was lower than HF10 pain intensity but not statistically different (Table 3). A mean increase in leg pain VAS was reported with HF10 at long-term follow-up, and two HF10 patients were explanted due to lack of efficacy after 10 months, meaning 4 of 8 (50%) of HF10 patients failed to achieve a good response.

Discussion
The goal of this review is to analyze the best current evidence behind two new programming modes of SCS for chronic intractable pain: HF10 and burst SCS. To date, 21 studies examining clinical outcomes of these novel programming modes in patients with chronic axial back pain and/or limb pain have been identified in the literature. RCTs of HF10 SCS have demonstrated superiority to tonic SCS in reducing primary axial back and leg pain in SCS-naïve FBSS patients for a period of 2 years. Burst stimulation RCTs have demonstrated superiority to tonic SCS in reducing axial and limb pain in SCS-naïve patients and PRs to tonic SCS for periods of 7 to 14 days. In two published studies directly comparing outcomes with HF10 and burst SCS, results suggest that both novel SCS modes provided equivalent and significant back pain relief at 15 months.

Significant analgesic efficacy has been demonstrated with both novel forms of SCS without engendering paresthesias. There is growing evidence that these newer, paresthesia-free modes of SCS may be preferred over traditional tonic SCS by most patients and may also provide an SCS salvage strategy for tonic SCS patients experiencing loss of efficacy over time. The importance of paresthesias aside, the efficacy of tonic SCS has been supported by high-level class I evidence. Comparison of tonic SCS to best medical management and repeat lumbar surgery in RCTs remain among the strongest evidence studies in neuromodulation. Moreover, although the loss of efficacy of tonic SCS has become an impetus for designing new modes of SCS, the durability of tonic SCS for some patients has been reported with very long follow-ups (8 years), and it will therefore take many more years for newer modes to have comparative long-term follow up data. Tonic SCS has also been shown to be a cost-effective method of reducing opioid consumption, which will need to be investigated using the new modes of SCS.

Despite the lack of long-term follow up in burst SCS and HF10 SCS, it is laudable that data behind these new modes are being accumulated at a higher evidence level than was seen in the early years of tonic SCS. Much of the tonic SCS literature is lower evidence comprising case series reports with relatively short follow-up periods. Both burst and HF10 SCS have commonly used similar pain score outcomes, which may facilitate better data pooling and meta-analysis, particularly for small cohort studies. Although small sample sizes do not preclude observing a true difference in a well-powered RCT, they may be especially prone to publication bias and inflated effect size estimates.

Another major limitation of study design for burst SCS has been the overwhelming number of articles published by its inventor (De Ridder). Likewise, nearly all HF10 studies have been sponsored by its parent company (Neuro). It is imperative that independent RCTs be performed in the future; the paresthesia-free nature of burst SCS and HF10 SCS makes placebo-controlled studies possible, which was never feasible for tonic SCS.

The short duration of burst SCS treatment in these studies is also a concern; no burst RCT had a treatment arm exceeding 12 weeks. This is a significant limitation with burst SCS as compared with HF10 SCS, in which pain alleviation in a RCT has been demonstrated up to 12 months. Given the fact that durability is one of the major problems with tonic SCS in patients, it is important that future studies provide long-term outcomes with the new paresthesia-free modes before declaring that “superiority” has been achieved over tonic SCS.
With explantation rates due to loss of efficacy remaining high for patients with tonic SCS—around 9.2% in one U.S. nationwide study of 8,727 tonic SCS patients—44 the potential for SCS salvage in these patients is promising. Rates of tolerance are relatively high with traditional tonic SCS for the treatment of chronic pain, with one 10-year study reporting a 29% tolerance rate. All forms of neuromodulation are likely to be associated with some level of tolerance, which may be secondary to plasticity in the nervous system. This will likely remain a challenge for all forms of electrical neuromodulation and is likely

### Table 3 Combined HF10 and burst SCS studies included in this review in chronological order

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<tbody>
<tr>
<td>Kinfe et al, 201611</td>
<td>- FBSS pts with at least 70% of their overall pain being axial back pain - SCS-naïve pts</td>
<td>Methods: Pts were nonrandomly assigned to either burst SCS or HF10 SCS implant, stratified by baseline back pain VAS scores and gender. Pts with successful trial proceeded to permanent implant of their respective assigned SCS system and assessed at 3 mo. Results: Two HF10 pts failed trial. Zero burst pts failed trial. Overall baseline VAS was significantly reduced in all pts regardless of programming mode. Significant VAS back pain reductions were found in all six HF10 SCS pts with permanent HF10 IPG, and all eight burst SCS pts after 3 mo. Burst pts experienced significantly larger limb VAS score reductions from baseline compared with HF10 pts. Disability and sleep quality scores were significantly reduced from baseline and sustained for 3 mo in both treatment groups.</td>
<td>- HF10 Burst</td>
<td>n = 16</td>
<td>Prospective Observational - 3 mos.</td>
<td>Back VAS pain (no stim.): 7.9 ± 0.7 Leg VAS pain (no stim.): 3.1 ± 1.5</td>
<td>Back VAS for both the HF10 and burst SCS groups: 2.3 ± 1.0 Back VAS with HF10 SCS: 2.2 ± 1.0 with burst SCS: 1.8 ± 0.7</td>
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<td>Muhammed et al, 201735 (above)</td>
<td>- Follow-up of Kinfe et al, 201611</td>
<td>Methods: Continued assessment at 15 mo of pts from Kinfe et al, 201611 Results: Back pain was significantly reduced in both HF10 and burst SCS pts at 15 mo follow-up. No significant difference in back pain intensity between HF10 and burst therapy between groups at 15 mo. Burst SCS resulted in significant sustained reductions in leg pain at long-term follow-up, whereas HF10 pts averaged an increase in leg pain of 18% (±99.1). Two HF10 pts explanted after long-term follow-up due to lack of efficacy (4/8 total pts failed to respond to HF10 SCS during study).</td>
<td>- HF10 Burst</td>
<td>n = 14</td>
<td>Follow-Up - 15 mo</td>
<td>Report above</td>
<td>Back VAS with HF10 SCS: 3.5 ± 3.27 with burst SCS: 1 ± 1.41 Leg VAS with HF10 SCS: N/A (increase from baseline)† with burst SCS: 1.5 ± 1.06</td>
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<td>Total</td>
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<td>n = 16</td>
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Abbreviations: FBSS, failed back surgery syndrome; HF10, high-frequency 10 kilohertz; NRS, numeric rating scale; pts, patients; SCS, spinal cord stimulation; VAS, visual analog scale.† Included patients from previous study.
engendered by scar tissue formation at the electrode-nervous system interface, which is also a contributor to loss of stimulation efficacy. It is possible that maintaining pain control with SCS will require chronic toggling between multiple modes of programming to prevent tolerance. Because access to permanent SCS implant has typically required a successful SCS trial period, it may be ideal if the SCS trials of the future allowed patients to sample different modes of SCS programming from different companies during a single trial.

Conclusion

Tonic SCS has become a well-established surgical intervention for chronic pain. HF10 and burst SCS are novel paresthesia-free programming modes of SCS, with promise for pain management in patients naïve to SCS, and in patients currently undergoing tonic SCS. There is short-term evidence that these newer modes may provide superior pain relief over traditional tonic SCS for both axial back pain and/or limb pain; however, there remains a lack of long-term evidence. Independently funded longitudinal studies with larger patient populations, randomization, blinding, and placebo control are needed to further elucidate the efficacy and patient selection for these novel technologies.

Conflict of Interest

Nestor D. Tomycz has served as a consultant for St. Jude Medical and is a member of the Medtronic Global Advisory Panel. Jeffrey Bergman and Derrick Dupré declare no conflicts of interest.

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