Systematic Review

Comparison of Spinal Cord Stimulation Waveforms for Treating Chronic Low Back Pain: Systematic Review and Meta-Analysis

Jay Karri, MD[1], Vwaire Orhurhu, MD[2], Sayed Wahezi, MD[3], Tuan Tang, MD[4], Timothy Deer, MD[5], and Alaa Abd-Elsayed, MD[6]

From: [1]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX; [2]Department of Anesthesia, Critical Care and Pain Medicine, Division of Pain, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [3]Departments of Physical Medicine and Rehabilitation and Anesthesiology, Albert Einstein College of Medicine at Montefiore, Montefiore Medical Center, Bronx, NY; [4]McGovern Medical School, The University of Texas HSC, Houston, TX; [5]The Spine and Nerve Center of the Virginias, Charleston, WV; [6]Department of Anesthesia, Division of Pain Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

Address Correspondence:
Alaa Abd-Elsayed, MD
Department of Anesthesia, Division of Pain Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI
E-mail: alaaawny@hotmail.com

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Background: The treatment of chronic refractory low back pain (LBP) is challenging. Conservative and pharmacologic options have demonstrated limited efficacy. Spinal cord stimulation (SCS) has been shown to be effective in reducing chronic LBP in various contexts. With emerging SCS technologies, the collective evidence of novel waveforms relative to traditional tonic stimulation for treating chronic LBP has yet to be clearly characterized.

Objectives: To provide evidence for various SCS waveforms—tonic, burst, and high frequency (HF)—relative to each other for treating chronic LBP.

Study Design: Systematic review and meta-analysis.

Methods: PubMed, Medline, Cochrane Library, prior systematic reviews, and reference lists were screened by 2 separate authors for all randomized trials and prospective cohort studies comparing different SCS waveforms for treatment of chronic LBP.

Results: We identified 11 studies that included waveform comparisons for treating chronic LBP. Of these, 6 studies compared burst versus tonic, 2 studies compared burst versus HF, and 3 studies compared tonic versus HF. A meta-analysis of 5 studies comparing burst versus tonic was conducted and revealed pooled superiority of burst over tonic in pain reduction. One study comparing burst versus tonic was excluded given technical challenges in data extraction.

Limitations: Both randomized controlled trials and prospective cohort studies were included for meta-analysis. Several studies included a high risk of bias in at least one domain.

Conclusions: Burst stimulation is superior to tonic stimulation for treating chronic LBP. However, superiority among other waveforms has yet to be clearly established given some heterogeneity and limitations in evidence. Given the relative novelty of burst and HF SCS waveforms, evidence of longitudinal efficacy is needed.

Key words: Chronic low back pain, spinal cord stimulation, tonic, burst, high frequency

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Chronic low back pain (LBP) affects approximately 10% of the general population in the United States and is a leading contributor to disability (1,2). This high prevalence is multifaceted in etiology, but is likely in part caused by challenges in effectively treating chronic LBP (3-5). Namely, well-designed studies have found that many standard of care medications have limited efficacy and may even be inappropriate to utilize for chronic management given their risk for adverse effects (6,7).

Across the past decade, neuromodulation with spinal cord stimulation (SCS) has been utilized increasingly and with good efficacy for treating chronic LBP refractory to standard of care management (8-10). There exist numerous high-level and high-quality studies supporting the use of SCS in various chronic LBP syndromes (11-19). Many of these studies have not only demonstrated superiority of SCS over comprehensive medical management in delivering analgesia, but have also shown that SCS may confer significant improvements in function and quality of life.

Traditional SCS interventions, which utilize tonic waveforms at lower frequencies to produce paresthesia stimulation overlying areas of pain, have been shown to have variable levels of benefit (12,14,20). It has been shown that up to 50% of persons have failed to achieve and/or maintain at least 50% of analgesia (21). Additionally, there exist many limitations, including technical challenges, in capturing paresthesia production over the low back and unwanted and poorly tolerated paresthesias in a subset of the population (22,23). These collective limitations helped burgeon the second phase of SCS—paresthesia-free stimulation (24,25).

Novel waveforms with paresthesia-free stimulation, also referred to as subperception stimulation waveforms, include the increasingly popular burst and high-frequency (HF) waveforms (24,25). Most notable with these novel waveforms is that intraoperative paresthesia mapping is not needed to deliver analgesic benefit. The current evidence for the use of these novel paresthesia-free stimulation waveforms over traditional paresthesia based tonic stimulation for treating chronic LBP reveals varying levels of efficacy (11-19). Moreover, the number of studies comparing burst and HF waveforms for chronic LBP syndromes is limited (18,19). Given this paucity and variability of evidence comparing SCS waveforms, we aimed at systematically reviewing and meta-analyzing the currently available evidence for each SCS waveform for its efficacy in treating chronic LBP.

Methods

To conduct the current study, we performed a systematic review based on conventional methodology described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility Criteria

Study Types

Randomized controlled trials and prospective observational studies

Patients

Persons suffering with chronic LBP secondary to failed back surgery syndrome, axial LBP, lumbar radiculopathy, and spinal stenosis.

Interventions

Spinal Cord Stimulation.

Type of Outcome Measures

The primary outcome parameter collected was pain relief. Although functional measures were considered for collection, there existed a large variance in both scales utilized and degree of reporting.

Data Sources

All studies meeting the eligibility criteria were considered for inclusion. Multiple data sources, including PubMed, Cochrane Library, prior systematic reviews, and reference lists, were searched across a time period from 1966 through July 2019.

Search Strategy

A broad search strategy was employed across the aforementioned data sources to identify chronic LBP of various etiologies treated with SCS.

Search strategy was as follows: ((((((((((chronic low back pain) OR low back pain) OR spinal stenosis) OR disc herniation) OR lumbar radiculopathy) OR discogenic pain) OR degenerative disk disease) OR failed back surgery) OR axial low back pain) AND ((((spinal cord stimulation OR burst) OR high frequency) or tonic) OR neuromodulation).

Data Collection

All research that provided SCS interventions for treating chronic LBP and provided outcome measures of pain relief were considered. Case studies, anecdotal evidence, and book chapters were excluded from consideration.

Inclusion Criteria

Studies with patients suffering from chronic LBP, treated with SCS tonic or burst or HF waveforms in comparison, subjective pain scores (Visual Analog Scale

[VAS] or Numeric Rating Scale [NRS-11]) measured prospectively, with reported standard deviation or standard error in pain scores at various times.

Collection Process

Two review authors independently and in a standardized, unblinded fashion conducted a systematic review to identify the included studies and extract the necessary outcome measures. All disagreements were resolved by discussion or inclusion of a third author, if needed.

Data Synthesis and Analysis

For all studies, data syntheses and analyses were performed with assessments of risk of bias, quality, and outcome measures.

Outcome Measures

Subjective pain scores—either via VAS or NRS-11—were collected. Adobe Photoshop (Adobe, Inc., San Jose, CA) was utilized to extract data when data were only presented in graphs (26).

Statistical Analysis

In anticipation for heterogeneity from diverse population cohort, intervention, and diagnosis, DerSimonian and Laird random effects meta-analysis method was used. The weighted mean difference (MD) in pain scores was calculated with its 95% confidence interval (CI) at numerous time points after spinal cord stimulator therapy.

A P value of < 0.05 was considered significant for pain scores measured at numerous time points. We performed a sensitivity analysis by excluding studies one-by-one in a stepwise fashion and reassessing how the new estimate differed. Analyses were performed using STATA version 13 (StataCorp, College Station, TX).

RESULTS

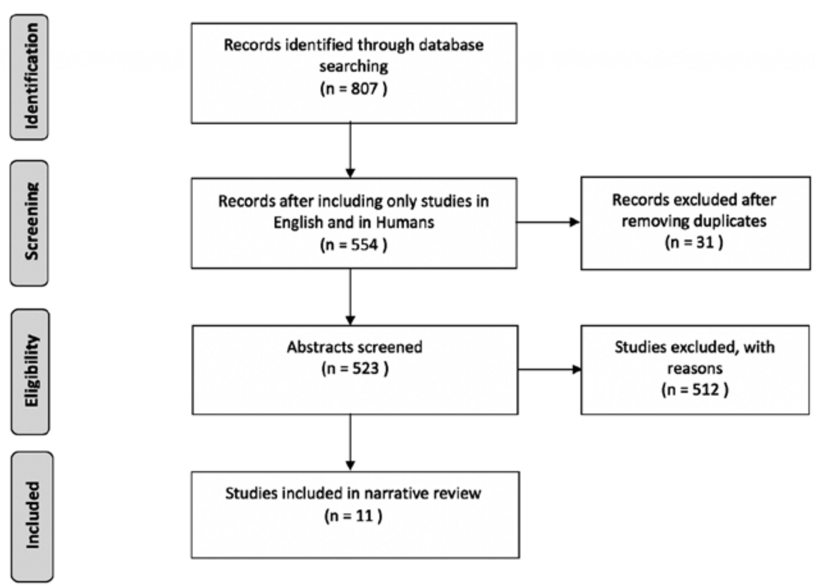
Search Results

Our systematic review identified 11 studies that included waveform comparisons for treating chronic LBP, most of which explored failed back surgery syndrome (FBSS) specifically (Fig. 1) (11–19,27,28). Of these, 6 studies compared burst versus tonic, 2 studies compared burst versus HF, and 3 studies compared tonic versus HF. Unfortunately, a burst versus HF meta-analysis was unable to be conducted as the 2 identified studies were reports from the same research study and cohort (18,19). Moreover, a tonic versus HF meta-analysis was unable to be conducted given technical challenges in extracting data of interest with certainty.

Risk of Bias Assessment

All of the included studies had undefined levels of bias across multiple domains, with 10 studies having a high level of bias in at least one domain (Fig. 2).

Fig. 1. *PRISMA flowchart of methodology utilized in systematic identification of included studies exploring explored analgesic benefit of various spinal cord stimulation waveforms, in comparison, in the treatment of chronic low back pain.*



Meta-Analysis

Burst Waveform versus Tonic Waveform

Analgesic Efficacy

Five studies reported pain scores and standard deviations for patients who received burst or tonic waveforms (Fig. 3). These studies were pooled for meta-analysis. Meta-analysis of these 5 trials revealed a significant reduction in pain scores favoring burst over tonic waveforms (MD, –1.64 points; 95% CI, –2.43 to –0.84 points; $P < 0.001$, $I^2 = 72.2\%$) (Fig. 1). Of note, the study by De Ridder et al (28) in 2013, which reported some benefit with use of burst waveform, was not included because we could not obtain variance (standard deviations) for the reported mean pain scores.

Sensitivity Analysis

A sensitivity analysis was performed on the 5 studies included for the burst versus tonic meta-analysis. The analysis was performed by sequentially removing each individual trial and evaluating how it affected the pooled estimate of the primary outcome. This process failed to find a significant difference (Fig. 4).

Publication Bias

Bias was evaluated using Begg and Egger tests (Fig. 5). The nonsignificant *P* values for both Begg and Egger tests suggest the absence of publication bias. Funnel plots are included in Fig. 5. However, because there were fewer than 10 studies, the utility of funnel plots may be questionable.

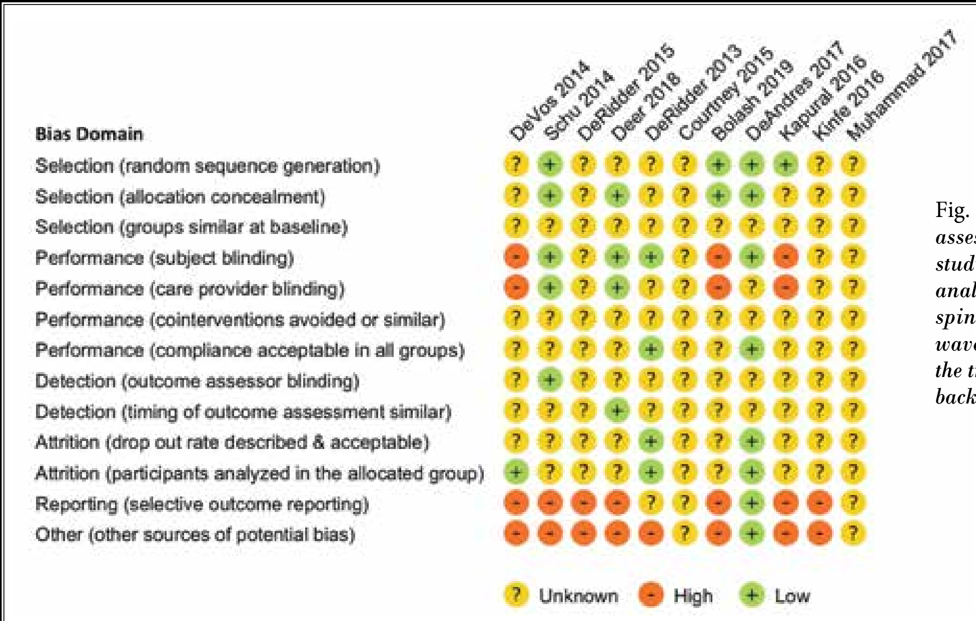
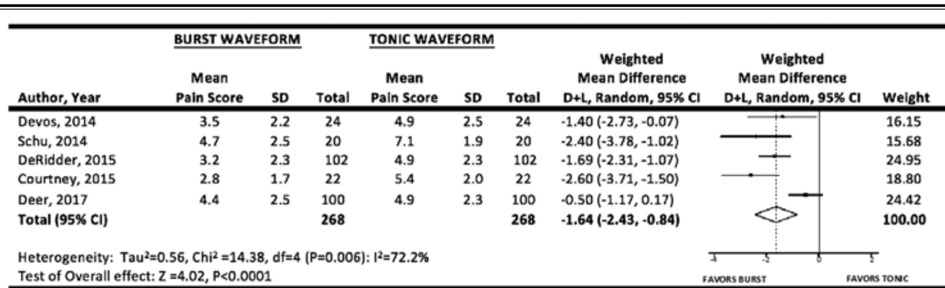


Fig. 2. *Risk of bias assessment for all included studies that explored analgesic benefit of various spinal cord stimulation waveforms, in comparison, in the treatment of chronic low back pain.*



Author, Year	BURST WAVEFORM Mean Pain Score	SD	Total	TONIC WAVEFORM Mean Pain Score	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weight
Devos, 2014	3.5	2.2	24	4.9	2.5	24	-1.40 (-2.73, -0.07)	16.15
Schu, 2014	4.7	2.5	20	7.1	1.9	20	-2.40 (-3.78, -1.02)	15.68
DeRidder, 2015	3.2	2.3	102	4.9	2.3	102	-1.69 (-2.31, -1.07)	24.95
Courtney, 2015	2.8	1.7	22	5.4	2.0	22	-2.60 (-3.71, -1.50)	18.80
Deer, 2017	4.4	2.5	100	4.9	2.3	100	-0.50 (-1.17, 0.17)	24.42
Total (95% CI)			**268**			**268**	**-1.64 (-2.43, -0.84)**	**100.00**

Heterogeneity: Tau²=0.56, Chi² =14.38, df=4 (P=0.006): I²=72.2%
Test of Overall effect: Z =4.02, P<0.0001

Fig. 3. *Meta-analysis of 5 studies comparing Burst and Tonic spinal cord stimulation in reducing pain scores of patients with chronic low back pain.*

Discussion

There high level evidence demonstrating the superiority of SCS over conventional medical management and surgery for treating chronic refractory LBP (8-10,11-19,27,28). Although much of the literature evaluates tonic stimulation for this condition we suggest that an investigation of waveform superiority may build on an already robust evidence base for SCS-treated chronic LBP. Tonic SCS may have comparative limitations when compared with other SCS waveforms, including production of paresthesias, concern for analgesic benefit, and possible loss of efficacy with chronic use (12,14,20,21). Although novel waveforms do not require paresthesia production for analgesic benefit, their overall efficacy is thought to be comparable or superior to tonic SCS (11-19,27,28). Additionally, comparisons of burst and HF interventions for chronic LBP have shown promise in reduction of leg pain results (18,19). This systematic review was performed to compare and validate the benefit of commonly programmed contemporary waveforms.

Briefly, our systematic review yielded 11 studies that were used to compare pain reduction of chronic LBP conferred by varying SCS waveforms. A risk of bias summary and statistical analysis (performed for studies included in meta-analysis) of the data revealed most included studies to have high risk of bias in at least one domain. A meta-analysis of 5 studies comparing burst versus tonic waveforms revealed, with statistical significance, the superiority of burst over tonic in producing analgesic benefit.

Burst versus Tonic

The supracerebellar mecha-

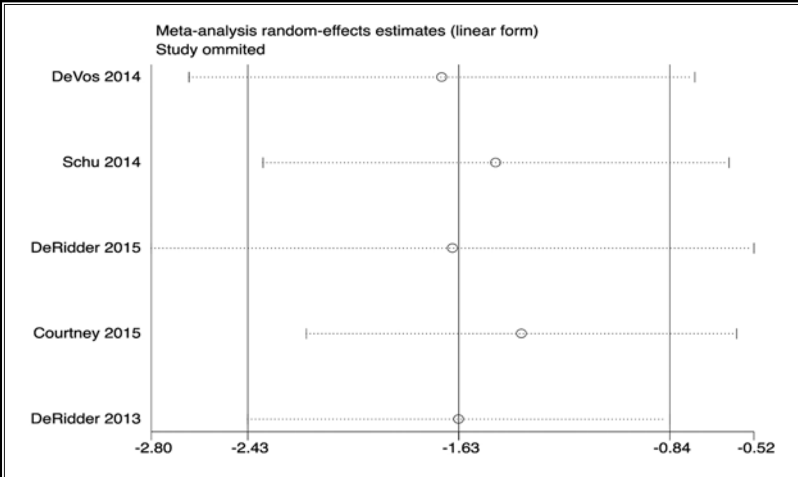


Fig. 4. *Sensitivity analysis of identified studies with omitted study to explore random effects estimates.*

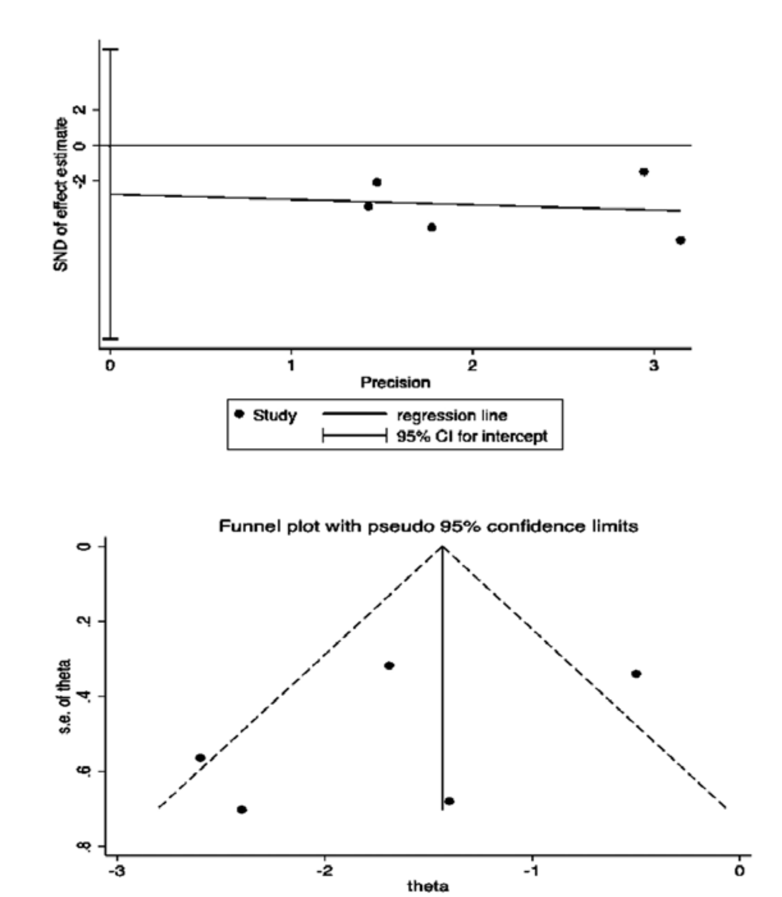


Fig. 5. Biased plotted using Beggs and Eggers Test (top)/ Funnel plots with confidence limits (bottom).

nisms underlying burst versus tonic frequency stimulation have yet to be fully or clearly elucidated. However, driving theories suggest that tonic stimulation primarily modulates the lateral thalamic pain pathways, whereas burst stimulation may modulate lateral and medial thalamic pain pathways (20,29). The medial pain pathways have synaptic connections to the anterior cingulate cortex and insula, and thereby can positively modulate the affective and emotional components of chronic pain when stimulated with burst waveforms (20). On the contrary, neuromodulation via tonic stimulation is largely limited to the lateral pain pathways, which control the somatic and discriminatory aspects of chronic pain.

Given these mechanistic differences, so too does there exist a difference in clinical outcomes. Our meta-analysis, with a pooled total of 268 patients across 5 studies, demonstrated superiority in analgesic benefit for burst stimulation over tonic stimulation (Table 1). Burst stimulation was favored over tonic and was shown to confer a mean score reduction of 1.64. Of note, the De Ridder et al (28) study from 2013 was not

Table 1. *Six studies that met inclusion criteria that compared burst and tonic SCS in reducing pain scores of patients with chronic LBP.*

Author and Year	Study Type, Evidence Level	Pain Type	Patients Type	Patient No.	Intervention	Duration	Key Findings
de Vos et al 2014 (13)	Prospective crossover I	FBSS (only group included) or PDN or FBSS-PR	> 6 months of tonic SCS	48	Tonic vs. burst	2 weeks	Burst stimulation provided additional analgesic benefit (28%) to tonic stimulation in treating FBSS. Most patients preferred burst.
Schu et al 2014 (11)	Prospective crossover randomized controlled double-blinded I	FBSS	> 3 months of tonic SCS	20	Tonic vs. burst vs. placebo	1 week	Tonic stimulation provided comparable analgesic benefit to placebo stimulus. Burst stimulation provided significant analgesic benefit relative to tonic and placebo was preferred over tonic stimulation.
De Ridder et al 2015 (12)	Prospective, crossover I	FBSS	> 6 months of tonic SCS	102	Tonic vs. burst	2 weeks	Burst was superior to both tonic and placebo stimulation. Most tonic stimulation nonresponders achieved response and meaningful benefit with burst stimulation. Those tonic stimulation responders achieved added analgesic benefit with burst stimulation.
Deer et al 2018 (15)	Prospective crossover randomized controlled unblinded I	Chronic pain of trunk and/or limbs	SCS-Naive	100	Tonic vs. burst	24, 52 weeks	Significantly more patients (70.8%) preferred burst stimulation over tonic stimulation.
De Ridder et al 2013 (28)	Prospective crossover randomized controlled double-blinded I	Limb and back pain	SCS-Naive	15	Tonic vs. burst vs. placebo	4 weeks	Burst stimulation was noninferior and superior to tonic stimulation and was preferred by most patients.
Courtney et al 2015 (14)	Prospective II	FBSS and radiculopathy in 70% of patients	> 3 months of tonic SCS	22	Tonic vs. burst	2 weeks	Overall pain scores reduced 46% from tonic to burst stimulation. Almost all patients preferred burst over tonic stimulation.

Abbreviations: FBSS, failed back surgery syndrome; PDN, painful diabetic neuropathy; PR, poor responders; SCS, spinal cord stimulation

Table 2. *Three studies that met inclusion criteria that compared burst and tonic SCS in reducing pain scores of patients with chronic LBP.*

Author and Year	Study Type, Evidence Level	Pain Type	Patients Type	Patient No.	Intervention	Duration	Key Findings
Bolash et al 2019 (17)	Prospective randomized controlled unblinded I	FBSS	SCS-Naive	72	Tonic vs. HF (wireless)	6 months	The HF waveform was noninferior to the low frequency waveforms in regard to back and leg pain at multiple time points in the first 6 months. Although some evidence exists for HF favorability, superiority was not clearly established.
De Andres et al 2017 (27)	Prospective randomized controlled double-blinded I	FBSS	SCS-Naive	55	Tonic vs. HF	12 months	Both tonic and HF stimulation caused significant pain reduction relative to baseline, as demonstrated by NRS-11 score reduction at 3 different time points in the first 12 months. However, no meaningful differences between tonic and HF waveforms were appreciated.
Kapural et al 2015 (16)	Prospective randomized controlled I	LBP	SCS-Naive	171	Tonic vs. HF	24 months	At 24 months, there was a greater response rate with HF10 therapy relative to tonic stimulation. Moreover, HF10 produced greater reduction in both back and leg pain at the 24 month time point.

Abbreviations: FBSS, failed back surgery syndrome; HF, high frequency; LBP, low back pain; NRS, numeric rating scale; SCS, spinal cord stimulation

included for meta-analysis given challenges in extracting variance and deviation data for pain scores (28). Within the included studies, burst superiority was readily demonstrated. Additionally, the SUNBURST trial also revealed that patients preferred burst stimulation over tonic waveform (15).

Tonic versus HF

While the direct mechanism of SCS neural activity modification was thought to be at the level of the dorsal columns, newer mechanistic evidence suggests varying sites of action for varying waveforms (29,30). In particular, it is thought that the effects of low frequency and burst waveforms are localized to the dorsal columns, whereas HF waveforms are thought to selectively confer neural inhibition at the level of the dorsal horns (23,31,32). Others propose that HF stimulation causes a reversible depolarization blockade or desynchronization of neural signals (23,29,33). Selective neuromodulation of the dorsal horns is also thought to possibly result in preferential excitation of second order inhibitory interneurons over excitatory interneurons or mitigate maladaptive windup in ascending circuitry. However, these working theories are simply postulated at this time and are largely based on limited rodent studies.

This selectivity for higher frequencies was clinically evidenced by Al-Kaisy et al (34) who showed in a crossover study in a small cohort of patients with FBSS, that decrement in VAS scores was achieved only with the 5,882 Hz stimulation. Interestingly, they found no meaningful dose-dependent pain reduction between the 1,200 and 3,030 Hz waveforms. A true HF waveform of 10K Hz was not explored. On the contrary, the PROCO study by Thomson et al (35), which explored benefit of various frequencies from 1K to 10K Hz in a 20 person cohort, found that all studied frequencies were equivocal in delivering analgesic benefit.

In our review, the 3 included studies all showed both meaningful pain reduction with HF waveforms relative to baseline and noninferiority of HF waveforms relative to tonic stimulation (Table 2). The study by Kapural et al (16), which was a follow-up of the SENZA study, investigated the largest cohort and across the greatest length of follow-up. It showed significant superiority of HF over tonic stimulation for both back and leg pain. Bolash et al (17) and De Andres et al (27), however, were unable to establish clear superiority of HF waveforms.

Table 3. *Two studies that met inclusion criteria that compared burst and HF SCS in reducing pain scores of patients with chronic LBP.*

Author and Year	Study Type, Evidence Level	Pain Type	Patients Type	Patient No.	Intervention	Duration	Key Findings
Kinfe et al 2016 (18)	Prospective observational II	FBSS	SCS-Naive	16	HF vs. burst	3 months	Both burst and HF waveforms produced significant reduction in back and leg pain with no differences between waveforms. However, burst was superior to HF in reducing leg pain at 3 months.
Muhammad et al 2017 (19)	Observational nonrandomized II	FBSS	SCS-Naive	16	HF vs. burst	12 months	Both burst and HF waveforms produced significant reduction in back and leg pain with no differences between waveforms. However, burst was superior to HF in reducing leg pain at 12 months.

Abbreviations: FBSS, failed back surgery syndrome; HF, high frequency; SCS, spinal cord stimulation

Burst versus HF

There exists a dearth of evidence comparing burst and HF waveforms for the treatment of chronic LBP. Both the Kinfe et al (18) and Muhammad et al (19) studies were reports of burst versus HF comparisons in the same small cohort of patients with FBSS with predominant back pain (Table 3). They found no meaningful superiority of either waveform in treating back pain but found that burst was superior to HF stimulation in reducing leg pain at the 3- and 12-month time points.

Limitations

There exist some methodologic limitations compromising our study that deserve notice. Most importantly, we included both prospective studies and placebo-controlled randomized trials in our meta-analysis. Although the inclusion of 2 different study types may draw concern for validity, this inclusion also allowed for more prospectively collected data to be included for meta-analysis. Also notable is the presence of high degree of bias in at least one domain in most studies identified for inclusion.

Second, there exists varying underlying etiologies comprising chronic LBP. Although most studies explored patients with FBSS, some studies included patient populations with unspecified diagnoses. Last, it must be noted that the novel SCS waveforms are still fairly recent and the evidence for long-term efficacy is thus lacking. Notably, our study provides a framework for understanding the limitations in evidence for the currently available SCS waveforms. This framework is especially relevant and important given the ever increasing rate of SCS-related research and technologies entering the market. Future work exploring long-term analgesic benefit, success rates, and complications with novel waveforms are needed and are likely forthcoming.

Conclusions

SCS has demonstrated efficacy in patients with chronic refractory LBP. In recent years, novel SCS waveforms with burst or HF stimulation have shown significant promise in supplanting traditional tonic waveforms. We provide a review of randomized controlled trials comparing the analgesic efficacy of various SCS waveforms in treating chronic LBP. Our meta-analysis of tonic versus burst stimulation revealed superiority of the burst waveform across data pooled from 5 separate studies. Although the largest study exploring tonic versus HF waveforms demonstrated HF superiority across a 2-year follow-up, 2 smaller and shorter studies were unable to establish HF superiority relative to tonic stimulation. Evidence comparing burst and HF stimulation is lacking, but findings from a small cohort suggest that burst and HF are equally effective in reducing back pain. However, burst demonstrated superiority to HF in reducing leg pain. Given the relative novelty of burst and HF waveforms, more longitudinal evidence for effectiveness is needed to more effectively delineate waveform superiority.

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