HHS Public Access

Author manuscript

Neuromodulation. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Neuromodulation. 2020 July ; 23(5): 562–571. doi:10.1111/ner.13067.

A Review of Clinical Data on Salvage Therapy in Spinal Cord Stimulation

Rajiv D. Reddy, MD[1], **Roya Moheimani, MD**[2], **Gregory G. Yu, MD, PharmD**[3], **Krishnan V. Chakravarthy, MD, PhD**[1,4]

[1]Department of Anesthesiology and Pain Medicine, University of California San Diego Health Sciences, La Jolla, CA, USA.

[2]VA Greater LA Health Care System/UCLA, Los Angeles, CA, United States.

[3]Georgetown University Hospital/Washington Hospital Center Emergency Medicine Residency Program, Washington, DC, USA

[4]VA San Diego Healthcare System, San Diego, CA, USA.

Abstract

Background: Since its introduction in 1967, neuromodulation through spinal cord stimulation (SCS) or dorsal root ganglion stimulation (DRGs) has advanced significantly in both the technology and indications for use[1].There are now over 14,000 SCS implants performed worldwide every year[2]. This review focuses on mechanisms behind the loss of efficacy in neuromodulation and current data on salvage therapy, defined as the conversion of a neuromodulation device to an alternative SCS or DRG stimulation, in the event of loss of efficacy or failure of a trial.

Study Design: A narrative review of clinical studies regarding habituation, explant data, and salvage therapy with SCS.

Methods: Available literature was reviewed on spinal cord stimulation technology and salvage therapy. Data sources included relevant literature identified through searches of PubMed, MEDLINE/OVID, SCOPUS, and manual searches of the bibliographies of known primary and review articles.

Outcome measures: The primary outcome measures were to understand the mechanisms of loss of efficacy, provide a review of explants due to failure in treatment, and summarize the data on current salvage therapy in SCS.

Results—A total of 8 studies and 4 abstracts/poster presentations were identified and reviewed. Of the 8 studies, only one was a randomized controlled trial.

Corresponding Author: Krishnan Chakravarthy MD, PhD, Department of Anesthesia, Pain Medicine, UC San Diego Health Center, San Diego, CA, kvchakravarthy@ucsd.edu, Phone: 716-908-2392, Fax: 858-249-1239.

Authorship Statement: Krishnan Chakravarthy is a consultant to Abbott, Medincell and Bioness.

Conflict of Interest Statement: Krishnan Chakravarthy is a consultant to Abbott, Bioness, Medincell. He is a founder of Newrom Biomedical, Douleur Therapeutics. All other authors report no financial conflicts of interest.

Conclusions: There is limited evidence for the appropriate treatment alternatives, but from data currently available the conversion from conventional tonic stimulation to burst, high frequency (10kHz), multiple wave forms, and/or DRGs may be appropriate in select patients and will require further research to determine the most appropriate first line salvage in the context of the underlying pain pathology.

Keywords

neuromodulation; spinal cord stimulation; salvage therapy; dorsal root ganglion stimulation

INTRODUCTION:

Since its introduction in 1967, neuromodulation via spinal cord stimulation (SCS) or dorsal root ganglion stimulation (DRGs) has advanced significantly in both the technology and pain conditions able to be treated[1]. There are now over 14,000 SCS implants performed worldwide every year[2]. Currently there are randomized control trials supporting SCS in the treatment of failed spinal surgery, complex regional pain syndrome, critical limb ischemia, refractory angina; there is less robust research supporting their use in peripheral neuropathy, phantom limb pain, abdominal pain, pelvic pain, postherpetic neuralgia and other neuropathic syndromes[3].

SCS has posited itself as treatment option for those who fail traditional management, as well as a means to potentially reduce use of opioids[4–6]. While the precise mechanism of action for SCS and DRGs remains unclear, there are numerous proposed theories, as well as on-going studies[5,7–11]. Initially conceived as involving the Gate Control Theory as proposed by Melzack and Wall, current research has indicated is much more complex[12]. Among the difficulties in studying this technology is the inherent complexity of the pain pathways within the human nervous system and determining the downstream effect in the overall sensory processing. Additionally, the multiple ways in which the technology can be applied for treatment (tonic, high frequency, multiple waveform, burst) fragments the overall clarity of its mechanism of action. Proposed mechanism of action includes altering the firing patterns of wide dynamic range neurons (“wind-up” mechanism of chronic pain), reducing glial cell activation, neuronal firing blockade, altering supraspinal pain pathways, and upregulating the inhibitory neurotransmitters [5,7–11].

While evidence for the efficacy SCS and DRGs has been favorable, the most common reason for failure over the long-term period has been shown to be lack or loss of efficacy (LoE) or a decline in the device’s ability to relieve pain[13–15]. Additional reasons for failure include complications from the device migrating leading to change in stimulations or pain from mass effect, implantable pulse generator (IPG) pocket pain, and infection[13,16]. Furthermore, the literature suggests that most explanation of stimulator devices occur 12 months or more after the device is placed[13,16]. Evaluation of the reasons for explant and suboptimal success of SCS is crucial, as the initial upfront costs of the device are high with the goal to reduce overall cost over the long-term. The 30-month point post-SCS implant has been previously suggested to be the point where there is a break-even on conservative medical management and cost effectiveness[17].Mechanisms underlying LoE can be grouped

into 1) operation or mechanical issues related to the IPG, leads, or granuloma/scar tissue, 2) patient specific changes such as psychological changes or new injury, and 3) physiologic tolerance or habituation to the treatment itself [18]. The most challenging to study, but perhaps most important mechanism is the development of tolerance to the treatment. There is currently limited evidence as to the underlying mechanisms that may lead to LoE of SCS, but several proposed theories include habituation, neuronal fatigue, plasticity, and cortical reorganization[19].

Due to the emergence of multiple SCS device manufacturers, technological advances, and waveform algorithms, providers have the ability to offer patients a conversion to alternative SCS devices in the event of LoE, coined as 'salvage therapy'. While the stimulator implant-to-trial percentage was shown to be high in previously published literature, a recent national survey found the rates to be much lower (~41%) [20]. While not well described in the literature, converting to more than one device during the trial period could be done to optimize resources (as most insurances only cover one trial period) and further delineate responders. This similarly has been described as a 'salvage' during trial, as opposed to after implantation. Additionally, in some cases salvage treatment can be done by changing the IPG only and delivering a novel therapy via the existing implanted leads.

Limited data for the application of salvage treatment has thus far been presented, and at the time of writing, no review has been published on the topic. Salvage therapy has been examined via intrathecal baclofen in patients with failed with some success, however, still requires further study[21]. The focus of this review is to provide practitioners with the most recent research and evidence for salvage therapy through the use of SCS and DRGs, as well as to understand the mechanisms of LoE, and review of the explant data due to treatment failure.

METHODS:

A comprehensive literature search was conducted from 1966 through January 2019 in the English language. Databases included in the search were Medline, PubMed, Cochrane Review Database, and Google Scholar. The search strategy emphasized neuromodulation, spinal cord stimulator, dorsal ganglion stimulation, and terms; explant, conversion, loss-of-efficacy, salvage therapy, burst, high-frequency, high density, tonic, paresthesia, and paresthesia-free stimulation. The search terms explant was individually paired with each type of SCS or DRGs, and then paired individually with conversion, loss-of-efficacy, and salvage therapy. Additionally, conversion, loss-of-efficacy, and salvage therapy were themselves individually paired with each type of SCS or DRGs. The reference lists of all publications found were also examined for further studies. Non–English-language articles were excluded.

RESULTS:

Clinical Data on Loss of Efficacy- Explant Data Summary

Van Buyten and colleagues performed a retrospective chart review of SCS systems implanted from 2010–2013 in three European countries[22]. There were 955 implants,

including conventional non-rechargeable, conventional re-chargeable, and high frequency (10 kHz) rechargeable SCS were evaluated with 2259 total years of follow up. The overall explant rate was 8.0% per year and 52% of explants were for inadequate pain relief, with cumulative rate of explant increasing as time progressed. The yearly explant rates specifically due to inadequate pain relief were 2.8% (conventional non-rechargeable), 5.5% (conventional rechargeable), and 5.0% (high-frequency). A survival curve showed a total rate of explant for inadequate pain relief was 19% at 5 years post implant. Other reasons for explant were pain at the pocket site, infections/wound complications, IPG problems, MRI requirements, lead problems, resolution of pain, and 'no specific reason'. There was no statistically significant difference between conventional rechargeable and high frequency devices. There was, however, a significant difference between non-rechargeable and rechargeable systems (p=0.011). Additional risk factors for explant due to inadequate pain relief, found to be significant in multivariable regression analysis, were female gender (increased hazard ratio (HR), p=0.011) and peripheral neuropathy as a pain diagnosis (decreased HR, p=0.039). The authors' concluded that there are higher explant rates for conventional rechargeable and high frequency SCS than non-rechargeable systems.

Pope and colleagues performed a retrospective chart review in 18 US centers with data from 352 patients with explant performed between 2011 to 2016[16]. The reasons for explantation in sequential order were LoE (43.9%), complications (20.2%), need for MRI (19.4%), remission of pain (6.1%), other (5.8%), device malfunction (4.6%). They type of SCS therapy delivered is not specified. The overall five-year explant rate reported by the medical centers involved was 7.2%.Rechargeable therapies were explanted at a median timepoint of 15 months, and non-rechargeable median at 36 months. Rechargeable devices were explanted significantly faster (2.4 times) than non-rechargeable devices (2.4 times) (p=<0.001). They found 71.8% of implants were removed prior to 30 months, which is close to the breakeven point for conservative medical management, an important point of consideration for cost-effectiveness. There was no statistically significant association in explant and lead type, pain diagnosis, opioid use, or duration of pain prior to implant. A notable finding was that roughly 20% of explants were done by a different provider than the implanting one. This raises the concern that failure of devices in general may be underestimated by providers, as well as show reliable patient reported pain scores are, particularly when given to the implanting physician. The authors concluded that the loss or lack of efficacy was the most frequent reason for explant, and with rechargeable devices requiring earlier explant.

Hayek and colleagues performed a retrospective chart review in one US center with 345 patients and 56 explants[13]. They type of SCS therapy delivered and IPG type is not specified. The reasons for explantation in sequential order were loss of therapeutic effect (39%), infections (17.9%), IPG discomfort/migration (14.3%), paresthesias/dysethesias (10.7%), need for MRI (7.1%) lead migration (3.6%), lead fracture/malfunction (3.6%), IPG malfunction (3.6%), wound dehiscence/seroma (1.8%), patient request (1.8%), required for surgery (1.8%). Of note, further analysis found that CRPS as the pain diagnosis had a statistically significant higher explant rate for all reasons combined (p=<0.05), however, this result must be interpreted in the context of a small sample size. . The median time until an explant due to loss of therapeutic effect was 19.62 months. Loss of therapeutic effect

occurred in 13.7% of all patients and accounted for 39.0% of explants. The median time until explant due to loss of therapeutic effect was roughly 19months. They concluded that the incidence of loss of therapeutic effect of SCS was the most common reason for explant, and most often occurred after 12 months.

Dupré and colleagues performed a retrospective chart review in one US center with 165 conventional SCS paddle lead explants[23]. The reasons for explantation in sequential order were inadequate pain control (IPC) (73%), hardware discomfort (22%), need for MRI (10%), infection (9%), painful dysesthesias (9%), electrical arcing (4%), resolution of inciting symptoms (4%), weakness (2%), pseudomeningocele (1%) and muscle spasms (1%). They further analyzed the patients with IPC and were able to separate them in 3 groups: 1) 41.8% had IPC from the time of surgical completion until explantation, despite adequate paresthesia distribution, 2) 39.1% stated that the pain coverage was initially satisfactory (at least 1 month of coverage), but was gradually lost over time despite adequate paresthesias in the areas of interest, 3) 19.1% stated that pain control was inadequate in addition to loss of paresthesia coverage over areas of interest. The authors concluded that the most common reason for explant was inadequate pain control despite most patients continuing to have paresthesia coverage.

In conclusion, these studies show that the majority of explants are due to LoE followed by infections, hardware malfunction/discomfort, and/or a need for MRI with the earlier systems (Table 1). LoE was not further defined in any of the studies reviewed, past describing it as inadequate control or increased pain for the patient. Overall, the studies support that conventional rechargeable and high frequency SCS systems were explanted more frequently and at earlier time points than non-rechargeable systems.

Data on Salvage Studies

Using the search criteria outlined above, a total of 8 studies were identified. The studies were comprised of 1 case report, 2 case series, 1 retrospective observational study, 1 retrospective comparative study, 1 prospective single-arm open-label study, 1 open-label prospective multi-arm comparative study, and 1 randomized controlled trial[24–30].One poster abstract presented the frame work for a large multi-center prospective observational study (the RENEW study). The salvage data below is presented in this review based on each individual waveform and individual anatomical target with their respective level of evidence (Table 2).

Dorsal Root Ganglion: Goebel et. al presented a case of a veteran patient with severe single limb complex regional pain syndrome(CRPS) that resulted in such severe pain the patient had undergone trans-tibial amputation[28]. The patient was refractory to surgical implant of a paddle lead spinal cord stimulator under general anesthesia due to incomplete coverage of his pain. After continued issues with pain and function, the authors proceeded with a percutaneous trial of conventional spinal cord stimulation which was unsuccessful. He then underwent a trial DRGs of the left L4 dorsal root ganglion with >75% improvement. He subsequently had surgical implant of DRG stimulator. This patient was still reporting

benefit from this procedure 17 months later, with increased functionality and was able to be fitted with a definitive prosthesis.

Yang and colleagues reported a case series of 2 CRPS patients with failed tonic SCS therapy that were offered DRG stimulation for salvage treatment[25]. Patient 1 reported a 90% pain reduction with significant gait improvement during DRG stimulation trial and subsequently explanted t-SCS. Patient 2 underwent a surgical revision of her existing system whereby a DRG-SCS system was added to the existing t-SCS system to create a hybrid system. Patient 2 reported an immediate pain reduction with sustained pain improvement and functional gains at 8 months follow up. Authors concluded that DRG-SCS was a reasonable salvage therapy in patients who failed t-SCS in CRPS.

Multiple Waveforms: Haider and colleagues performed a retrospective cohort analysis on 22 patients who had failed high frequency (10kHz) SCS trial with subsequent conversion to a separate system with multiple waveforms[27]. Multiple waveforms is a description of the different stimulation options from the patient's new device; conventional, burst, and 1 kHz sub-perception, as well as anode intensification (altering field shape to recruit more and deeper nerve fibers). These patients thereby had multiple types of therapy SCS programming with one IPG. Within this cohort of 22, only16 had either a numerical rating scale, visual analog scale, or percent pain relief scores available. In this study, 42% of the patients had the primary diagnosis of failed back surgery syndrome (FBSS). Of the 16, 10 (63%) reported >50% relief with multiple waveform SCS. Of those within the 16 who had experienced no relief with the 10kHz trial, 80% had >50% improvement with the multiple waveform trial. Among the 16 patients analyzed, 68% preferred multiple waveform SCS and none preferred 10 kHz SCS.

Burst Stimulation: De Ridder and colleagues performed a retrospective comparative analysis on 102 patients from Belgium and Netherlands[26]. This study consisted of 2 groups, patients who failed tonic stimulation and patients who still responded to tonic stimulation. The breakdown of patient diagnosis is not provided, but they do state the all patients had neuropathic pain, mostly from FBSS. All patients were switched from tonic to burst stimulation, and the number of responders as well as pain reduction were all evaluated. No changes were made to the generators or electrode placement. On the pain numeric rating scale (NRS), the average pain improved from a baseline of 7.8 to 4.9 with tonic and to 3.2 with burst stimulation. Of note, 62.5% of non-responders to tonic stimulation responded to burst stimulation. Responders to tonic stimulation also had a pain reduction from 50.6% to 73.6%. The authors concluded that burst stimulation was overall significantly better than tonic stimulation, and this programming change can rescue some non-responders to tonic stimulation and further improve pain relief in responders.

Courtney and colleagues examined a cohort of 22 subjects from 4 different sites who had been previously implanted with a SCS device and were then subsequently trialed on burst stimulation for 14 days[24]. The primary diagnosis of patients was radiculopathy (36%) followed by FBSS (32%). They were assessed at 7 and 14 days, and the authors found that average overall VAS reduced from 53.5 (±20.2) during tonic SCS to 28.5 (±18.1) during burst (46%, $p < 0.001$). Additionally, the trunk and limb VAS scores were also reduced by

33% and 51%, respectively. As compared to tonic stimulation, with burst stimulation 16 subjects (73%) reported no paresthesia, 5 (23%) reported a reduction, and 1 (4%) reported increased paresthesia. Burst was preferred by 91% of the patients in the cohort with pain relief. Again, this study focused on programming changes as opposed to hardware modifications or changes.

De Vos and colleagues studied burst stimulation in 48 patients with at least 6 months of conventional tonic stimulation therapy[30]. These patients were separated into 3 different groups, which included patients with painful diabetic neuropathy (PDN), FBSS, and FBSS patients who were poor responders to tonic SCS (PR). Pain scores were assessed prior to implementation, with tonic stimulation and after 2 weeks of burst stimulation. Burst stimulation reduced pain significantly in almost all patients. Although PDN and FBSS patients benefitted the most with burst stimulation on average, burst stimulation reduced pain in PR group by 23% (10% reduction w/ tonic stimulation). Authors concluded that about 60% of patients with tonic SCS experienced further pain reduction upon application of burst stimulation. While the average pain reduction was limited in the PR group, 3 patients (25%) benefited significantly from switching to burst therapy. Hunter and colleagues performed a retrospective review of 307 patients from 7 pain practices who failed conventional tonic or high frequency SCS had their therapy converted to burst either through surgical revision (generator IPG was changed), or in cases where their current system was already burst capable, simply activated[31]. At follow-up the cohort reported statistically significant reductions in NRS, percentage of pain relief and opioid consumption. The follow-up for the surgical revision group extended to ~302 days and showed a 2.54 NRS reduction. No changes were made to hardware in these studies, only programming changes.

Subperception/Subthreshold: North and colleagues performed a crossover study on 22 patients with ineffective treatment with conventional paresthesia-based SCS[29]. The 22 subjects were randomly assigned to two groups, one group receiving paresthesia-based stimulation, and the other groupreceiving1 kHz sub-perception stimulation. The most common diagnosis was FBSS at 45%. Each group received treatment for three weeks followed by a 7–10-day washout period prior to being crossed over to the other type of stimulation. They found that numerical rating scale (NRS) were significantly lower with sub-perception stimulation compared to paresthesia-based stimulation ($p<0.01$, $p< 0.05$, and $p<0.05$, respectively). Additionally, treatment with sub-perception stimulation had significantly greater improvement than that of paresthesia-based stimulation on Oswestry Disability Index (ODI) scores ($p=3.9737\times10^{-5}$) and Patient Global Impression of Change (PGIC) scores ($p=3.0396\times10^{-5}$). A notable limitation is the inability to blind the patient to treatment, due to the sensation difference between paresthesia and sub-perception.

Kapural and colleagues performed a retrospective case series from 95 patients with unsatisfactory pain relief or unpleasant paresthesias with implanted conventional paresthesia-based SCS, who were then trialed with 1–1.2 kHz sub-threshold stimulation[32]. The most common pain diagnosis was FBSS (38%). The patients were able to revert to the original traditional stimulation at their choosing, however, follow-up on patients was a minimum of 12 months. Primary outcome assessment was via patient-reported NRS and change in daily morphine equivalent. The length of time before loss of effect for the

traditional SCS for each patient was not given. The authors found no significant difference in pain scores or medication usage after switching to sub-threshold stimulation. Roughly one-third of the subjects had no benefit with the change to sub-threshold stimulation and returned to traditional SCS within 1 week. Only 13 subjects continued using 1–1.2 kHz subthreshold SCS for 3 months, and 2/95 of subjects continued using it at 12 months. Of note, patients reported that with the change to the higher frequency they had difficulty with the increased charging demand for the IPG. The authors concluded that based on this case series, there was no clinical benefit of 1–1.2 kHz sub-threshold stimulation for patients who had ineffective relief with traditional SCS. These studies were accomplished by delivering a new waveform through the existing implanted device.

High Frequency (10kHz): Russo and colleagues performed a retrospective chart review on their clinical experience with HF10 SCS over a 6-month period involving 256 patients with neck, arm, leg, and/or back pain who were not candidates for, or responders to, traditional SCS[33]. Of the 256 patients trialed, 189 were implanted (73%) with a resulting overall mean reduction in pain by about 50% on the NRS ($p=0.001$) across all groups. Most, notably, a subset of patients who had previously failed tonic stimulation (n=76) responded to HF10 trial (68%). Of the 47 of those patients who proceeded to implant, an overall mean reduction on the NRS was seen from 7.2 to 3.7 ($p=0.001$) at 6-months. Of note, the authors do not indicate if failure of tonic SCS was determined via a failed trial or LoE post-implant. Additionally, no standardized definition was provided for “failure” of the previous tonic stimulation. In this study all patients were trialed and/or implanted with new leads and IPG.

Van Buyten and colleagues completed a prospective open-label multicenter study examining the use of HF10 SCS in 83 patients with predominate low back pain over a 6-month period[34]. The most common listed diagnosis was FBSS (81%). Of the 83 patients, 72 proceed with implant after successful trial (88%). At the 6-month time point, back and leg pain was found to have a statistically significant reduction (78% and 80% respectively, $p< 0.001$), with 74% of patients with greater than 50% pain relief and 47% of the patients with greater than 80% pain relief. A small subset of patients (n=14) enrolled in the study had previously failed conventional SCS. Of the 14, 11 had a positive trial and proceeded to implant (79%) For this group, at the 6-month time point mean VAS for back pain was reduced from 8.9 to 2.0, and leg pain was reduced from 7.7 to 1.9 (no significance or p-value provided). In this subset of patients, the authors do not indicate if failure of conventional SCS was determined via a failed trial or LoE post-implant. Again, no standardized definition was provided for “failure” of the previous conventional stimulation. In this study all patients were trialed and/or implanted with new leads and IPG.

Tiede and colleagues performed a prospective comparative multicenter open-label trial comparing conventional SCS to HF10 therapy in a group of 25 patients with predominate low back pain. The patients started the SCS trial with the conventional system and after a period of 4–7 days were then switched to HF10 therapy via use of the implanted trial leads. The most common listed diagnosis was FBSS (88%). Following the conventional stimulation trial period there was a 55% mean reduction in pain from baseline on the VAS ($p =0.001$). Following the HF10 stimulation trial there was a 77% mean reduction in pain from baseline on the VAS ($p =0.001$). Using a responder analysis (threshold of 50% or greater

pain relief), 58% was observed with conventional stimulation trial, and 83% with HF10 stimulation trial. The study was not powered to compare the two types of therapy, and so no statistical analysis was done between groups.

Ghosh and colleagues examined high frequency SCS as salvage for failed traditional tonic stimulation in 32 patients in a retrospective chart review[35]. The patients were grouped into three categories: failed trial, inadequate response at ≤6-month post-implant, and inadequate response at >6 months post-implant. The patient's diagnoses were mixed with failed back surgery syndrome (FBSS) being the most common (56.3%). At a minimum follow-up of 6 months, overall 75% of patients were moderate or excellent responders, set at 25% and 50% reduction of pain on the NRS, respectively. In a subset analysis 70.6% of patient with FBSS, and 75% of patients with CRPS, were moderate or excellent responders to 10 KHz SCS.

Verrills and colleagues performed a prospective comparative study period of 86 patients with chronic low back with or without leg pain who had failed conventional SCS or peripheral nerve field stimulation (PNFS)[36]. The patients were then trialed with high frequency (10kHz) SCS and if successful (>50% pain relief), subsequently implanted. Of the 53 patients who previously failed conventional SCS, 36 had successful trials proceeding to implant. Of the 33 patients who had failed PNFS, 24 had successful trials. At the 6-month follow-up period pain reductions of 3.0 ± 2.5 ($p = 0.006$) and 2.4 ± 2.9 ($p = 0.012$) NRS were seen in the failed PNS and failed conventional SCS groups, respectively.

DISCUSSION:

In this review we have aimed to outline landmark studies that show both explant data as well reviewed the currently available salvage data, with salvage defined as the conversion of a neuromodulation device to an alternative SCS or DRG stimulation, in the event of loss of efficacy or failure of a trial. While the review of explant and salvage data is vital, preclinical data is important to include in order to propel future thinking in regards to mechanisms for loss of efficacy and salvage treatments. From preclinical work in animal models, there are several major hurdles that may explain the loss and lack of efficacy of spinal cord stimulation. First, with chronic pain and allodynia there are phenotypic changes that occur in the population of Aδ and Aα,β fibers, which are usually involved in detecting mechanical stimuli. These fibers begin releasing pain mediating neuropeptides, specifically substance P[37,38]. Substance P is typically thought to be released by c-fibers, the main nociceptor not by Aδ and Aα,β fibers [39]. These fibers have different thresholds of response to certain frequencies than the main nociceptive c-fibers. This learning, or neuroplasticity, that occurs in the Aδ, and Aα,β fibers may occur over the lifetime of placement of SCSs. More translational studies are warranted to further evaluate this phenomenon and specifically address the concepts of constant versus intermittent stimulation in propagating neuroplasticity in the spinal cord.

Habituation, which occurs after repeated stimulation, may present clinically as patient developing a loss or lack of efficacy to neuromodulation and is a potential hurdle for the placement of SCSs over the long term[40]. Habituation can be defined as synaptic suppression when a constant stimulation is detected by sensory neurons. This suppression of signal can

possibly be circumvented, as described by burst dependent protection (BDP), by providing intense stimuli[40,41]. The concept of burst dependent protection still needs to be translated into a clinically meaningful programming output based on pulse width, amplitude, frequency, and duty cycle. Tonic stimulation may facilitate habituation based on this concept and would support the use of intermittent pulse frequencies at certain frequencies. This theory is well supported in studies conducted in the animal model for neuropathic pain[42].

The pre-selection of candidates undergoing SCS appears to play a hurdle in animal models as well[43]. In the rat model, differing levels of pre-implantation allodynia plays a role in success of the SCS. This may be explained by the phenotypic changes or neuroplasticity of the sensory fibers to detect noxious stimuli. Studies both in humans and in rats selecting and stratifying candidates for implantation of SCSs seems to suggest the importance of personalizing therapy to each individual patient. Increased emphasis on genetic, immunological, and neurophysiological markers in creating personalized therapy may be warranted in the future[50].

In regard to patient specific factors, multiple studies have examined the relationship between psychologic components and outcome of SCS. Block and colleagues found that higher pre-implant Minnesota Multiphasic Personality Inventory–2–Restructured Form (MMPI-2-RF) scores in the domains of emotional dysfunction, somatic/cognitive complaints, and interpersonal problems were associated with worse SCS outcomes at 5 months[44]. Bendinger and colleagues found that Hospital Anxiety and Depression Score (HADS), Pain Self-Efficacy Questionnaire (PSEQ), and sleep interference are risk factors for failure (>50% fall in pain relief) of SCS treatment at a 1-year follow-up[45]. Psychologic factors are already a consideration pre-implant, however, these results suggest that further study into their relation to LoE, device explanation, and candidacy for salvage therapy is warranted.

Understanding the underlying cause for explant, as well as the rates at which occurs, is crucial to furthering salvage treatment. Based on the clinical studies reviewed, the most common reason for explant was overwhelming inadequate pain control or LoE, followed by infections, hardware malfunction/discomfort, and/or a need for MRI. The underlying mechanistic causes of LoE cannot be distinguished within these clinical studies. The preclinical data presented may have a role, conjecture and warrants further study. Non-rechargeable systems were less likely to be explanted than conventional rechargeable and high frequency SCS systems. Additionally, rechargeable systems were explanted earlier in the devices lifespan as compared to non-rechargeable. This was thought to be possibly related to device ‘fatigue’ with the increased need for maintenance due to charging. Overall, the studies found the timing of most explants occurred after 1 year from implant, indicating that the mechanistic process of LoE occurring is likely gradual, requiring studies to evaluate patients for at least one year from time of implantation. Further complicating the study of explants, as well as provider perception of SCS success, is the finding by Pope and colleagues that 20% of explants are not performed by the one who implant the device. This would potentially cause practitioners to underestimate their explant data, or have unreliable patient reported outcomes. Despite the number of patients and explants reviewed, there is a significant challenge in identifying unique characteristics of those patients who fail treatment versus those who continue to get relief. Van Buyten and colleagues found that for

explants (all indications), females had a HR that was higher than males, and that peripheral neuropathy as the pain diagnosis had lower HR. The authors note that despite these statistically significant findings, it is difficult to translate them to clinical relevance. Hayek and colleagues did find that patients with CRPs had an overall (all indications) higher rate of explant, however, the strength of their findings were limited by small sample size of the sub analysis. They postulated that CRPS can have a dynamic disease state which could lead to inadequate coverage or poor control of the pain overtime. Furthermore, establishing clinical criteria that could be universally used to define LoE is needed. None of the studies reviewed provided any in-depth review of what LoE meant for the patients in the clinical setting. For example, LoE or inadequate pain control could mean a patient has had minimal increase in pain, a complete return to baseline level of pain, more pain, change in distribution, or a new type of pain. Notably, Dupré and colleagues found that after subgroup analysis of explants due to IPC, most patients continued to have adequate paresthesia coverage of their pain regions despite having poor pain control. This finding, while somewhat surprising, is an important consideration in understanding possible mechanisms of LoE. Further categorizing and standardizing the clinical criteria of LoE or IPC is essential to maximize the consistency in how it is reported in the literature, studied mechanistically, and managed clinically. A translational study examining the subset of patients who fail treatment for any predictive or neurophysiological explanatory factors for their LoE is greatly needed. In the meantime, continuing to pool data on those who have failed treatment is warranted and may provide insight for future analysis.

The use of salvage therapy for diminished efficacy from SCS treatment or during failed trial is a technique used by many practitioners, however, as demonstrated by this review, is not well reported. The studies presented and reviewed are level III-V with no large scale randomized and/or placebo-controlled trials. Notably, there are no long-term prospective studies, albeit from a case report at 17-months follow-up (28). In fact, all of the other prospective studies reported a follow-up time of 6 months or less. This is a significant limitation in determining the efficacy of salvage treatment, as review of explant data has demonstrated that average time until LoE is after 12 months. It may be that if these patients are followed for more than 12 months, they will subsequently develop tolerance to their new rescue therapy. The summation of the literature reviewed does suggest that there is a subset of patients failing or having diminishing efficacy with their current SCS treatment that may benefit from conversion to alternative treatment. Although analysis was limited by small sample sizes and missing patient information, the most common diagnosis observed was clearly FBSS. While the fact that FBSS was the most commonly reported does not confirm that they would be more likely to respond than other diagnoses, given their representation in almost all studies reviewed suggest that those patients may be responsive to salvage therapy. Salvage treatment with burst stimulation and HF10 were the most commonly studied and reported, followed by DRG, subperception/subthreshold, and multiple waveforms (Table 1). Notably, Kapural and colleagues demonstrated no significant improvement with subthreshold stimulation (1–1.2 kHz) as a salvage for traditional stimulation. The study was limited by being retrospective, with the omission of important patient information, such as length of treatment prior to LoE for each patient. Its strengths include the number or patients included and the follow-up period of 12 months. This is in contrast to the study performed

by North and colleagues, which did show improvement, but with a length of follow-up of just 3 weeks raises the possibility those patients would similarly have diminished efficacy. This study also highlights the importance of distinguishing between subperception (1.2 kHz) and high frequency (10 kHz) when discussing paresthesia-free treatment paradigms. Additionally, the authors noted that using the IPG that was implanted to deliver higher frequencies led to increased charge burden, device maintenance, and decreased patient satisfaction. This is a crucial factor to consider when deciding to salvage a patient's treatment, as treatment is limited to the capabilities of the current IPG, which may not be optimized to deliver a different type of therapy. It is important to note the presentation of the studies reviewed does not signify definitive efficacy or utility of one over another, but rather what has been currently reported, and further study needed to draw any substantial conclusions.

The use of salvage therapy during a SCS trial is especially intriguing, as many of the percutaneous leads used are compatible with different devices allowing for more than one type of treatment within a single trial period. With its high cost and the potential restriction on number of trials for a patient covered by insurance, the ability to offer alternative treatments in the setting of a failure with the originally planned therapy could better conserve resources, as well as positively impact patient outcomes. Given the variability and regulations on approved duration of trial period in both the US, Europe, and internationally we need to examine whether we should be extending the length of the SCS trial period and consider different devices, washout of therapy duration, and risk/benefits with regards to infections.

The myriad of options within the technology in combination with complex pain pathways and various pain states that can be treated, make developing a salvage therapy study with SCSs logistically difficult. It may be that certain pain conditions may be physiologically more amenable to salvage treatment, however, without further study of the conditions treated in salvage treatment, it makes the external validity unclear and problematic for a practitioner to know what therapy to utilize and for which diagnosis.

Future Areas of Research

Understanding the mechanisms of LoE will continue to be paramount for the field of neuromodulation and SCSs. This has been challenging thus far due to the complexity of pain neurophysiology coupled with the multiple mechanisms of action for each treatment to be studied. Development of standardized clinical criteria for loss of therapy to spinal cord stimulation that examines pain distribution changes and levels, both pre-implant and post-implant, are needed. To solidify the utility of salvage treatment, long-term studies are needed to demonstrate no subsequent LoE. As found in the review of the available literature, the median time from implant to explant due to LoE is over 12 months, and so future studies would ideally have an endpoint time of 12–24 months.

With the rapidly advancing SCS technology and further advancement of its understanding, patients who have failed or have reduced efficacy with their current treatment may benefit from salvage therapy with a new device or algorithm/waveform. There is currently limited evidence for the appropriate treatment alternatives, but as this current review has shown,

conversion from conventional tonic stimulation to burst, high frequency (10kHz), multiple wave forms, and/or DRGs may be appropriate in select patients. Further study of both the reasons for SCS explant and use of salvage therapy is warranted, providing an exciting area for future development in the neuromodulation space.

Acknowledgments

Financial Support Disclosure: The authors declare no financial support with regards to this body of work.

REFERENCES:

1. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46(4):489–491. doi:10.1002/app.1991.070431113 [PubMed: 4952225]
2. Gharibo C, Laux G, Forzani BR, Sellars C, Kim E, Zou S. State of the Field Survey: Spinal Cord Stimulator Use by Academic Pain Medicine Practices. Pain Med. 2014;15(2):188–195. doi:10.1111/pme.12264 [PubMed: 24138612]
3. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The neuromodulation appropriateness consensus committee. Neuromodulation. 2014;17(6):515–550. doi:10.1111/ner.12208 [PubMed: 25112889]
4. Falowski S, Pope JE, Raza A. Early US Experience With Stimulation of the Dorsal Root Ganglia for the Treatment of Peripheral Neuropathy in the Lower Extremities: A Multicenter Retrospective Case Series. Neuromodulation. 2018;2018. doi:10.1111/ner.12860
5. Chakravarthy K, Richter H, Christo PJ, Williams K, Guan Y. Spinal Cord Stimulation for Treating Chronic Pain: Reviewing Preclinical and Clinical Data on Paresthesia-Free High-Frequency Therapy. Neuromodulation. 2018;21(1):10–18. doi:10.1111/ner.12721 [PubMed: 29105244]
6. Sharan AD, Riley J, Falowski S, et al. Association of Opioid Usage with Spinal Cord Stimulation Outcomes. Pain Med. 2018;19(4):699–707. doi:10.1093/pm/pnx262 [PubMed: 29244102]
7. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. Brain Res. 2014;1569:19–31. doi:10.1016/j.brainres.2014.04.039 [PubMed: 24802658]
8. Sato KL, Johanek LM, Sanada LS, Sluka KA. Spinal cord stimulation reduces mechanical hyperalgesia and glial cell activation in animals with neuropathic pain. Anesth Analg. 2014;118(2):464–472. doi:10.1213/ANE.0000000000000047 [PubMed: 24361846]
9. Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation. 2014;17(3):226–234. doi:10.1111/ner.12161 [PubMed: 24612269]
10. Shechter R, Yang F, Ph D, et al. dependent Inhibition of Mechanical Hypersensitivity in a Rat Model of Neuropathic Pain. Pain Med. 2015;119(2):422–432.
11. Barchini J, Tchachaghian S, Shamaa F, et al. Spinal segmental and supraspinal mechanisms underlying the pain-relieving effects of spinal cord stimulation: An experimental study in a rat model of neuropathy. Neuroscience. 2012;215:196–208. doi:10.1016/j.neuroscience.2012.04.057 [PubMed: 22548781]
12. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–979. http://www.ncbi.nlm.nih.gov/pubmed/5320816. Accessed January 4, 2019. [PubMed: 5320816]
13. Hayek SM, Veizi E, Hanes M. Treatment-limiting complications of percutaneous spinal cord stimulator implants: A review of eight years of experience from an academic center database. Neuromodulation. 2015;18(7):603–608. doi:10.1111/ner.12312 [PubMed: 26053499]
14. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain. Anesthesiology. 2015;123(4):851–860. doi:10.1097/ALN.0000000000000774 [PubMed: 26218762]

15. Manca A, Kumar K, Taylor RS, et al. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). Eur J Pain. 2008;12(8):1047–1058. doi:10.1016/j.ejpain.2008.01.014 [PubMed: 18359255]

16. Pope JE, Deer TR, Falowski S, et al. Multicenter Retrospective Study of Neurostimulation With Exit of Therapy by Explant. Neuromodulation. 2017;20(6):543–552. doi:10.1111/ner.12634 [PubMed: 28714533]

17. Kumar K, Rizvi S. Cost-Effectiveness of Spinal Cord Stimulation Therapy in Management of Chronic Pain. Pain Med. 2013;14(11):1631–1649. doi:10.1111/pme.12146 [PubMed: 23710759]

18. Mann SA, Sparkes E, Duarte R V., Raphael JH. Attrition with spinal cord stimulation. Br J Neurosurg. 2015;29(6):823–828. doi:10.3109/02688697.2015.1054352 [PubMed: 26087397]

19. Kumar K, Hunter G, Demeria D. Spinal Cord Stimulation in Treatment of Chronic Benign Pain: Challenges in Treatment Planning and Present Status, a 22-Year Experience. Neurosurgery. 2006;58(3):481–496. doi:10.1227/01.NEU.0000192162.99567.96 [PubMed: 16528188]

20. Huang KT, Martin J, Marky A, et al. A national survey of spinal cord stimulation trial-to-permanent conversion rates. Neuromodulation. 2015;18(2):133–139. doi:10.1111/ner.12199 [PubMed: 24930992]

21. Lind G, Meyerson BA, Winter J, Linderoth B. Intrathecal baclofen as adjuvant therapy to enhance the effect of spinal cord stimulation in neuropathic pain: a pilot study. Eur J Pain. 2004;8(4):377–383. doi:10.1016/j.ejpain.2003.11.002 [PubMed: 15207519]

22. Van Buyten JP, Wille F, Smet I, et al. Therapy-Related Explants After Spinal Cord Stimulation: Results of an International Retrospective Chart Review Study. Neuromodulation. 2017;20(7):642–649. doi:10.1111/ner.12642 [PubMed: 28834092]

23. Dupré DA, Tomycz N, Whiting D, Oh M. Spinal Cord Stimulator Explantation: Motives for Removal of Surgically Placed Paddle Systems. Pain Pract. 2018;18(4):500–504. doi:10.1111/papr.12639 [PubMed: 28875558]

24. Courtney P, Espinet A, Mitchell B, et al. Improved Pain Relief With Burst Spinal Cord Stimulation for Two Weeks in Patients Using Tonic Stimulation: Results From a Small Clinical Study. Neuromodulation. 2015;18(5):361–366. doi:10.1111/ner.12294 [PubMed: 25879884]

25. Yang A, Hunter CW. Dorsal Root Ganglion Stimulation as a Salvage Treatment for Complex Regional Pain Syndrome Refractory to Dorsal Column Spinal Cord Stimulation: A Case Series. Neuromodulation. 2017. doi:10.1111/ner.12622

26. De Ridder D, Lenders MWPMPM, De Vos CC, et al. A 2-center comparative study on tonic versus burst spinal cord stimulation: Amount of responders and amount of pain suppression. Clin J Pain. 2015;31(5):433–437. doi:10.1097/AJP.0000000000000129 [PubMed: 24977394]

27. Haider N, Ligham D, Quave B, et al. Spinal Cord Stimulation (SCS) Trial Outcomes After Conversion to a Multiple Waveform SCS System. Neuromodulation. 2018;21(5):504–507. doi:10.1111/ner.12783 [PubMed: 29889356]

28. Goebel A, Lewis S, Phillip R, Sharma M. Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome (CRPS) Recurrence after Amputation for CRPS, and Failure of Conventional Spinal Cord Stimulation. Pain Pract. 2018;18(1):104–108. doi:10.1111/papr.12582 [PubMed: 28422399]

29. North JM, Hong KSJ, Cho PY. Clinical Outcomes of 1 kHz Subperception Spinal Cord Stimulation in Implanted Patients With Failed Paresthesia-Based Stimulation: Results of a Prospective Randomized Controlled Trial. Neuromodulation. 2016;19(7):731–737. doi:10.1111/ner.12441 [PubMed: 27186822]

30. De Vos CC, Bom MJ, Vanneste S, Lenders MWPM, De Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation. 2014;17(2):152–158. doi:10.1111/ner.12116 [PubMed: 24655043]

31. Hunter CW, Yang A, Carlson J, et al. BURST (able) - A Retrospective , Multicenter Study Examining the Impact of Burst-DR on Pain and Opioid Consumption in the Setting of Salvage Treatment and “ Upgrade .” 2018;21(1):2018. doi:10.1016/j.wneu.2013.01.040.

32. Kapural L, Harandi S. Long-term efficacy of 1–1.2 kHz subthreshold spinal cord stimulation following failed traditional spinal cord stimulation: a retrospective case series. Reg Anesth Pain Med. 2019;44(1):107–110. doi:10.1136/rapm-2018-000003 [PubMed: 30640661]
33. Russo M, Verrills P, Mitchell B, Salmon J, Barnard A, Santarelli D. High frequency spinal cord stimulation at 10 khz for the treatment of chronic pain: 6-month australian clinical experience. Pain Physician. 2016;19(4):267–280. [PubMed: 27228514]
34. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: Results of a prospective multicenter European clinical study. Neuromodulation. 2013;16(1):59–65. doi:10.1111/ner.12006 [PubMed: 23199157]
35. Ghosh P, Simopoulos T. High Frequency Spinal Cord Stimulation (HF-SCS) at 10 kHz as Salvage Therapy for Unsuccessful Traditional Spinal Cord Stimulator Trials and Implants. 2019:40.
36. Verrills P, Fafmm M, Fipp M, et al. Salvaging Failed Neuromodulation Implants with Nevro High Frequency Spinal Cord System : 6 Month Outcomes All patients in mean pain compared with baseline values (Baseline vs . End of trial. :80.
37. Santiago S, Ferrer T, Espinosa ML. Neurophysiological studies of thin myelinated (A delta) and unmyelinated (C) fibers: application to peripheral neuropathies. Neurophysiol Clin Neurophysiol. 2000;30(1):27–42. doi:10.1016/S0987-7053(00)88865-6
38. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. J Pain Symptom Manage. 2000;19(1 Suppl):S2–6. [PubMed: 10687331]
39. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413(6852):203–210. doi:10.1038/35093019 [PubMed: 11557989]
40. Gover TD, Abrams TW. Insights into a molecular switch that gates sensory neuron synapses during habituation in Aplysia. Neurobiol Learn Mem. 2009;92(2):155–165. doi:10.1016/j.nlm.2009.03.006 [PubMed: 19345275]
41. Wan Q, Jiang X-YY, Negroiu AM, Lu S- GG, McKay KS, Abrams TW. Protein kinase C acts as a molecular detector of firing patterns to mediate sensory gating in Aplysia. Nat Neurosci. 2012;15(8):1144–1152. doi:10.1038/nn.3158 [PubMed: 22772333]
42. Gong W-Y, Johanek LM, Sluka KA. A Comparison of the Effects of Burst and Tonic Spinal Cord Stimulation on Hyperalgesia and Physical Activity in an Animal Model of Neuropathic Pain. Anesth Analg. 2016;122(4):1178–1185. doi:10.1213/ANE.0000000000001161 [PubMed: 26859873]
43. Smits H, Ultenius C, Deumens R, et al. Effect of spinal cord stimulation in an animal model of neuropathic pain relates to degree of tactile “allodynia.” Neuroscience. 2006;143(2):541–546. doi:10.1016/j.neuroscience.2006.08.007 [PubMed: 16978792]
44. Block AR, Marek RJ, Ben-Porath YS, Kukal D. Associations Between Pre-Implant Psychosocial Factors and Spinal Cord Stimulation Outcome: Evaluation Using the MMPI-2-RF. Assessment. 2015;24(1):60–70. doi:10.1177/1073191115601518 [PubMed: 26318387]
45. Bendinger T, Plunkett N, Poole D, Turnbull D. Psychological Factors as Outcome Predictors for Spinal Cord Stimulation. Neuromodulation. 2015;18(6):465–471. doi:10.1111/ner.12321 [PubMed: 26095096]

Table 1.

Explant Data Summary

Year	Author	Methods/Population	Reasons for Explant	Discussion
2017	Van Buyten, et al	Implant centers in 3 European Countries Retrospective chart review 8,720 patients, 955 explants	Inadequate pain relief (per year) - Nonrechareable (2.8%), Rechargeable (5.5%), High-frequency (5.0%) Inadequate pain relief (total) - 94/180 (52.2%) Other reasons for explant (no data) - pain at pocket, infection/wound, IPG problem, MRI required, lead problem, free of pain, no specific reason	Study found higher explant rates for conventional rechargeable and high frequency SCS than non-rechargeable systems. Data only included explants due to “inadequate pain relief”.
2017	Pope, et al	18 centers in US Retrospective chart review 352 explants	Percentage of total explants Efficacy (43.9%), complications (20.2%), need for MRI (19.4%), remission of pain (6.1%), other (5.8%), device malfunction (4.6%)	Loss or lack of efficacy and complications most frequently were reasons for explant. Rechargeable devices required earlier explants.
2017	Dupre et al	1 US academic center Retrospective review 165 explants	Percentage of total explants Inadequate pain control 73%), hardware discomfort (22%),need for MRI (10%), infection (9%), painful dysesthesias (9%), electrical arcing (4%), resolution of inciting symptoms (4%), weakness (2%), pseudomeningocele (1%) and muscle spasms (1%)	Most common reason for explant is inadequate pain control. Need SCS improvement in quality and duration of pain control. Also need MRI compatible systems.
2015	Hayek, et al	1 US academic center Retrospective study 345 patients, 56 explants	Percentage of total explants Loss of therapeutic effect (39%), infections (17.9%), IPG discomfort/migration (14.3%), paresthesia/ dysethesia (10.7%), need for MRI (7.1%) lead migration (3.6%), lead fracture/malfunction (3.6%), IPG malfunction (3.6%), wound dehiscence/seroma (1.8%), patient request (1.8%), required for surgery (1.8%)	Incidence of SCS implants requiring surgical revision or explant is 34.6% w/ majority of complications due to hardware-related issues and most revisions/ explants occuring within the first 12 months.

Table 2.

Salvage Data Summary

Authors	Year	Study Design	Study Population	Intervention	Results	Conclusion	Level of Evidence
Goebel et al	2018	Case Report	A veteran with CRPS with severe phantom limb pain	DRG Stimulation	17 months 60% pain relief	DRG stimulation was successful for a patient who failed surgical paddle placement and tonic percutaneous trial	Level V
Yang et al	2017	Case Series	2 CRPS pts who failed t-SCS	DRG Stimulation	Pt 1: 90% pain reduction Pt 2: 44% pain reduction (DRG-only)	DRG stimulation is a reasonable salvage therapy in patients who fail t-SCS in CRPS	Level V
Haider et al	2018	Retrospective Case Series	16 patients who failed 10kHz trial	Trial converted to multiple waveform SCS	10(63%) reported >50% relief with multiple waveform SCS	Multiple waveform SCS should be considered as either first line or as an alternative option for patients who failed 10kHz trial	Level IV
De Ridder et al	2015	Retrospective Comparative	102 pts total Group 1: failed t-SCS Group 2: t-SCS responders	Burst stimulation x 2 weeks	Average Pain Scale: baseline (7.8), tonic (4.9), burst (3.2) 62.5% of nonresponders to tonic stimulation responded to burst.	Burst stimulation may be significantly better than tonic. It can rescue some non-responders to tonic stimulation and further improve pain reduction in responders.	Level IV
Courtney et al	2015	Prospective Case Series	22 patients receiving conventional tonic stimulation	Trial of 14 days with burst stimulation	Overall VAS reduced from 53.5 (±20.2)during tonic SCS to 28.5 (±18.1)during burst (46%, $p < 0.001$)	A majority of subjects had improved pain relief using burst compared with tonic stimulation and 91% preferred it. Burst stimulation should be considered in patients with tonic SCS.	Level IV
De Vos et al	2014	Prospective Comparative	PDN- 12 pts FBSS- 24 pts Poor responder- 12 pts All conventional tonic stimulation	Burst stimulation x 2 weeks	Pain Reduction (compared to baseline) Burst - PDN 77%, FBSS 57%, PR 23% Tonic - PDN 58%, FBSS 41%, PR 10%	~60% of patients w/ t-SCS experienced further pain reduction w/ burst stimulation	Level IV
Hunter et al	2018	Retrospective review ***Abstract**	307 patients who failed tonic or high frequency SCS	Therapy converted to burst either through surgical revision or turning on burst capable device	Cohort reported statistically significant reductions in NRS, percentage of pain relief and opioid consumption.	Implementing burst stimulation in patients who have failed tonic or 10kHz therapy may provide superior relief and reduce opioid consumption	Level IV
North et al	2016	Prospective Randomized Crossover Trial	22 patients with ineffective relief with paresthesia stimulation	Crossover study of paresthesia-based versus subperception 1kHz SCS. 3 weeks of treatment A, 7–10 washout, followed by 3 weeks of treatment B	NRS (average, best, and worst) significantly lower with subperception stimulation ($p<0.01$, $p< 0.05$, and $p<0.05$, respectively), and improved ODI scores ($p=3.9737\times10^{-5}$) and PGIC scores ($p=3.0396\times10^{-5}$).	1 kHz subperception stimulation is an effective alternative for subjects with failed paresthesia-based stimulation.	Level III

Authors	Year	Study Design	Study Population	Intervention	Results	Conclusion	Level of Evidence
Kapural et al	2019	Retrospective Case Series	95 patients with ineffective treatment with conventional SCS	Trialed with 1–1.2 kHz subthreshold stimulation using patient's current device	Patient-reported NRS and change daily opioid-consumption. No significant difference in pain scores or medication usage and most patients (~66%) switched back to conventional SCS after 1 week	No clinical benefit of 1–1.2 kHz subthreshold stimulation for patients who had ineffective relief with traditional SCS	Level IV
Russo et al	2016	Retrospective Chart Review	256 patients who were not candidates for, or responders to, t-SCS	Trialed with HF10 SCS and if successful, subsequently implanted	Of patient's that had failed t-SCS - reported NRS mean reduction was 7.2 to 3.7 (p=0.001) at 6-months	HF10 SCS is a viable alternative therapy, and can be used as salvage treatment for patients who have previously failed t-SCS	Level IV
Van Buyten et al	2013	Prospective Case Series Open-Label	83 patients with predominate low back pain over a 6-month period. Subset (n=14) had previously failed t-SCS	Trialed with HF10 SCS and if successful, subsequently implanted	For group that failed t-SCS, at 6-months VAS, back pain was reduced from 8.9 to 2.0, and leg pain was reduced from 7.7 to 1.9 (no significance or p-value provided)	HF10 SCS provided significant relief in back and leg pain, and may be used as salvage treatment for patients who have previously failed t-SCS	Level IV
Tiede et al		Prospective Comparative Open-Label	25 patients with predominate low back pain over a trial period (4–7 days)	Patients started with t-SCS trial and after 4–7 days switched to HF10 therapy trial	t-SCS provided a mean reduction of 55% (p =0.001), and for HF10 77% reduction (p =0.001) on the VAS. The study was not powered to compare the two types of therapy	Patients with predominant back pain trailed with HF10 had significant pain relief	Level IV
Ghosh et al	2018	Retrospective Review *Abstract	32 patients who failed tonic stimulation, 3 groups: failed trial, failure at ≤6, and at >6 months post-implant	Therapy converted to high frequency (10kHz) SCS	At minimum follow-up of 6 months, 75% of patients were moderate or excellent responders, set at 25% and 50% reduction of pain on the NRS, respectively	Based on the short-term data, conversion from failed tonic stimulation to high frequency may be of benefit, particularly in failure 6 months-post implant	Level IV
Verrills at al	2018	Prospective Comparative Study *Abstract	86 patients who had failed conventional SCS or peripheral nerve stimulation (PNFS)	Trialed with high frequency (10kHz) SCS and if successful (>50% pain relief), subsequently implanted	6-month follow-up period pain reductions of 3.0 ± 2.5 (p = 0.006) and 2.4 ± 2.9 (p = 0.012) NRS were seen in the failed PNS and failed conventional SCS groups, respectively	In patients who have failed conventional paresthesia-based SCS of PNFS, treatment with 10kHz can be a successful treatment option	Level IV