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# Intermittent Dorsal Root Ganglion Stimulation Is as Efficacious as Standard Continuous Dosing in Treating Chronic Pain: Results From a Randomized Controlled Feasibility Trial

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## ABSTRACT

**Introduction:** Dorsal root ganglion stimulation (DRG-S) is a form of neuromodulation used to treat chronic pain. A spinal cord stimulation (SCS) method with paresthesia-free waveform used in the dorsal columns, burst-SCS, recently demonstrated efficacy using intermittent stimulation, where stimulation is cycled on and off for set durations. Tonic SCS is a paresthesia-based therapy that is ineffective at sub-perception levels and when delivered in a cycled manner. DRG-S also uses a tonic waveform, yet unlike tonic SCS, it is effective at sub-perception levels. This study aimed to determine whether the cycling of stimulation at the DRG could maintain DRG-S efficacy.

**Materials and Methods:** This study followed a prospective, randomized, and balanced, double-blinded (assessor) protocol. Twenty DRG-S responders were randomized to a sequence of three programs for consecutive two-week intervals: continuous stimulation; 1 minute on:1 minute off; or 1 minute on:2 minutes off. The primary outcome of this study was change in pain ratings with the cycled programs compared with continuous stimulation. Secondary outcomes included changes in function and scores for quality of life, and stimulation program preference.

**Results:** Mean scores were similar at the end of each two-week stimulation program for Numerical Rating Scale pain (continuous = 2.9 ± 0.8, 1:1 on-off = 2.6 ± 0.7, and 1:2 on-off = 2.7 ± 0.7 cm, $p = 0.39$), disability ($p = 0.72$), and general health ($p = 0.95$). No clinically significant differences were found from the upper boundaries of the 95% confidence intervals of the mean difference in pain, disability, and general health for each intermittent stimulation program vs the continuous program. At the end of the study, the continuous stimulation, 1:1 on-off dosing, and 1:2 on-off dosing programs were preferred by a similar number of patients.

**Conclusions:** Intermittent DRG-S produces comparable results to continuous stimulation over a two-week period. Intermittent delivery may extend battery life and facilitate a smaller implantable pulse generator.

**Keywords:** Endogenous opioid system, intermittent dosing, intermittent stimulation, long-term depression, low threshold mechanoreceptors

**Conflict of Interest:** The authors reported no conflict of interest.

## INTRODUCTION

The evolution of spinal cord stimulation (SCS) therapy over the last half-century has culminated in new waveforms and treatment paradigms and improved charge delivery strategies. One such treatment, dorsal root ganglion stimulation (DRG-S), is a newer form of neuromodulation in which an electrical field is applied continuously using a tonic waveform pattern to neurons within the dorsal

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root ganglion (DRG) to relieve chronic pain. The A Prospective, Randomized, Multi-Center, Controlled Clinical Trial to Assess the Safety and Efficacy of the Spinal Modulation™ AXIUM™ Neurostimulator System in the Treatment of Chronic Pain (ACCURATE) study showed a higher treatment success rate with DRG-S than with SCS, leading to Food and Drug Administration approval to treat complex regional pain syndrome (CRPS).[1] Since then, smaller studies have demonstrated the efficacy of DRG-S in treating other neuropathic pain conditions and mixed nociceptive pain syndromes, including axial low back pain and postsurgical joint pain.[2–5]

Although DRG-S can produce paresthesia in the covered anatomy at high stimulation amplitudes, paresthesia is usually neither required nor preferred. Unlike paresthesia-dependent conventional SCS, DRG-S is typically applied at subthreshold amplitudes, which are imperceptible.[6] An accepted mechanism underlying DRG-S involves T-junction filtering at the level of the DRG itself.[7] However, evidence is accumulating that DRG-S has upstream effects within the dorsal horn of the spinal cord as well.[8,9] DRG-S modeling and mechanistic studies demonstrate modes of action separate and distinct from that of SCS.[10–14] Recent literature reviews suggest that the endogenous opioid system may be involved in these processes.[8,15]

The DRG's anatomical location within a fixed bony structure and thin surrounding cerebrospinal fluid space allows for stable and consistent electrode placement that is close in proximity to the nerve tissue with minimal variability in distance relative to body movement. Specialized membrane characteristics, condensed tissue volume, and somatic organization of pseudounipolar primary afferent neurons at the DRG also make it a unique target for neuromodulation.[11,16] These anatomical and physiological characteristics translate to a lower charge density (electric charge per unit area of a surface) required for DRG-S than for SCS.[15,17] This is reflected in the significantly lower amplitude and pulse width standard settings used for DRG-S.

With the advent of newer SCS waveforms, the concept of measuring stimulation in terms of total charge delivered per unit of time, or charge per second, was developed. It is calculated as the product of the frequency (Hz), pulse width (us), and amplitude (mA) expressed in microcoulombs per second (μC/s).[18] Burst and high-frequency spinal cord stimulation deliver a greater amount of charge per second but a lower charge per pulse (amplitude × pulse width) than tonic SCS as a means of achieving subthreshold paresthesia-free pain relief.[18,19] In contrast, DRG-S delivers a lower charge per second and a lower charge per pulse than tonic SCS.

Although the charge density and charge delivery per second of DRG-S are far lower than SCS, the implantable pulse generator (IPG) battery is nearly the same size as other non-rechargeable SCS devices on the market.[20] Electrical dosing strategies that deliver the lowest total charge for effect could reduce battery size, improve patient satisfaction, optimize battery longevity, and delay device replacement surgery.[18,20] For example, DRG-S can maintain improvements in pain, function, and quality of life at a lower stimulation frequency of 4 Hz compared with the standard 16 to 20 Hz, leading to a 65% reduction in charge delivery over time.[17] In addition, placing the active electrode in the superodorsal position reduces the required stimulator output power while maintaining equivalent analgesic efficacy compared with other electrode positions by almost four times.[21]

Beyond these strategies, an alternative or additional method to reduce mean charge delivery over time would be to use intermittent stimulation, a sequential cycling of stimulation on and off over a period of seconds to minutes (eg, 1 minute on, 1 minute off). When applied with this intermittent stimulation approach, the burst waveform (Abbott, Plano, TX) demonstrated similar efficacy to continuous delivery.[22,23] The concept of intermittent stimulation was previously explored in pain neuromodulation in 2006, when Kumar et al attempted 1 second on, 1 second off stimulation with conventional SCS. However, only 28 of 53 patients achieved pain relief.[24] Other methods of intermittent stimulation have been attempted, mostly through patient controlled device inactivation during certain activities (eg, sleep, sitting), with only anecdotal reports of its efficacy.[25–27]

Long-term depression (LTD) of the second order neuron is a process that would allow the effects of stimulation to persist longer than the stimulus application. Using very low-frequency signaling, low threshold mechanoreceptor (LTMR) fibers are responsible for fine-tuning the touch and pain processes in the dorsal horn via the endogenous opioid system, and have been shown to initiate LTD.[28–31] We previously hypothesized that DRG-S utilizes the endogenous opioid system for effect, which is supported by DRG-S efficacy at frequencies compatible with LTMR firing rates,[8,15,17] and is consistent with our anecdotal clinical observations of extended symptomatic relief after removal of DRG-S trial leads. These factors lead us to believe that DRG-S would maintain efficacy when delivered in an intermittent cycling pattern, and form the basis for this prospective, randomized, double-blinded, crossover study to test our hypothesis. Here, we report outcomes of a feasibility study comparing standard continuous DRG-S with two periodic dosing programs.

## MATERIALS AND METHODS

This is a single-center, prospective feasibility trial with a randomized, double-blinded, crossover design consisting of 20 DRG-S responders. The study was registered on clinicaltrials.gov under ID number NCT04727216. All study activities were conducted with prior authorization from the WCG Western Institutional Review Board and with participants' written informed consent. Participants who were treated with DRG-S (Abbott, Plano, TX) for a minimum of three months were eligible if their prestudy DRG-S parameters achieved ≥50% reduction from their primary pain with appropriate coverage and if DRG-S parameters remained unchanged for at least 30 days before the beginning of the study, regardless of pain diagnosis, location of pain, time since implantation, or previous history of failed SCS. Patients were excluded if their pain medication regimen changed or if they received an interventional pain procedure within 60 days before the start of the study.

Three stimulation programs were used: 1) continuous, 2) 1 minute on:1 minute off (1:1 on-off), and 3) 1 minute on:2 minutes off (1:2 on-off) (Fig. 1). Participants were blinded from each program's cycling parameters. Frequency, pulse width, and amplitude parameter settings were held constant between the three programs during the study. There were six possible sequences with the treatment programs: 123, 132, 213, 231, 312, and 321 (Fig. 1). To ensure randomization was balanced between the sequences, patients were randomly assigned in blocks to each sequential order. Outcome assessors and patients were blinded to which stimulation program was being used and the order in which the programs ran. Participants could elect to withdraw from the study at any time and be reprogrammed to their prestudy settings if they were not satisfied with their pain control.

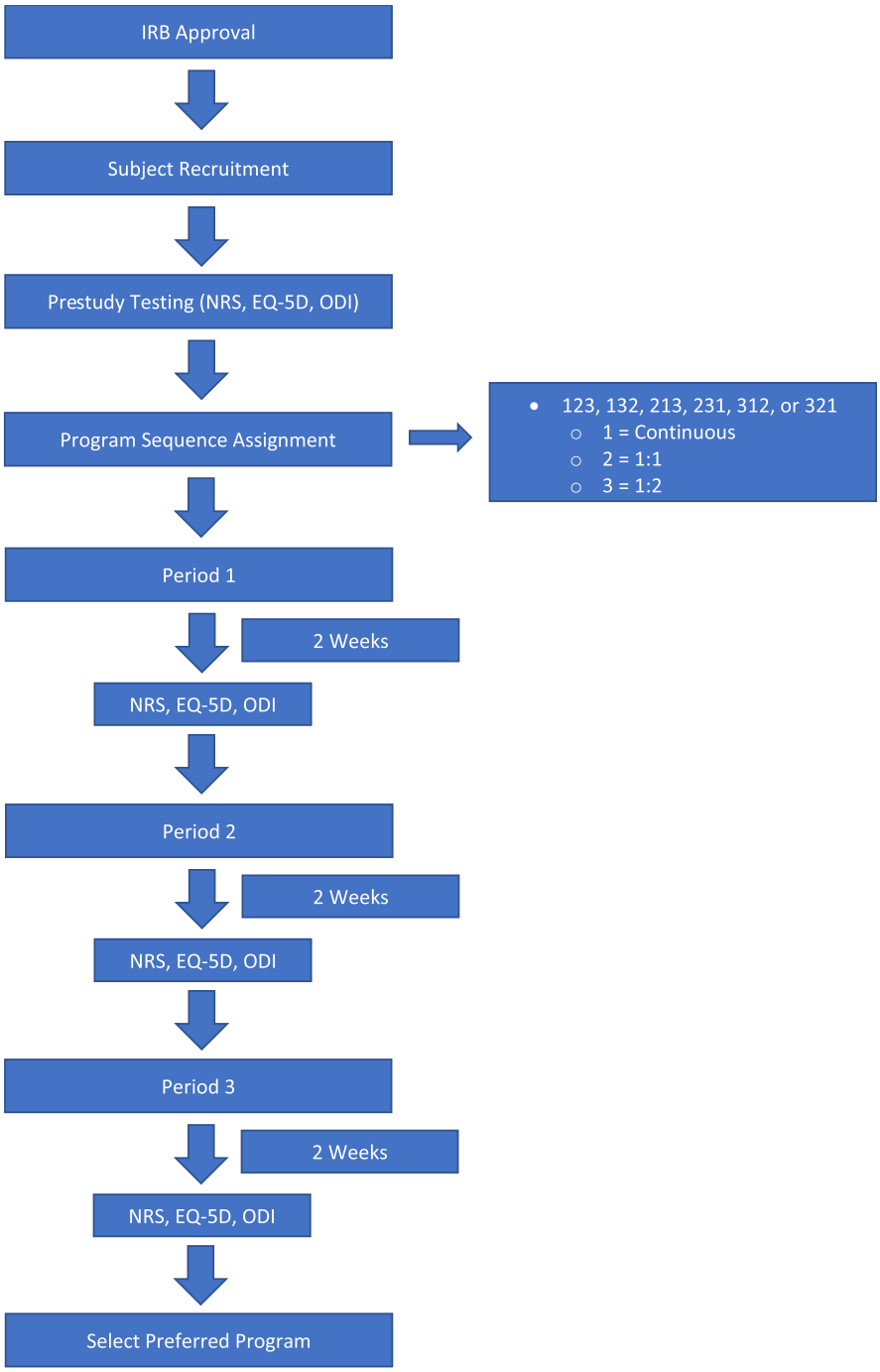


**Figure 1.** Schematic representation of study design. [Color figure can be viewed at www.neuromodulationjournal.org]

The three stimulation programs each ran for two weeks for a total study duration of six weeks. At the end of each program, patients completed pain (Numerical Rating Scale [NRS]), quality of life (EuroQol-5D [EQ-5D]),[32] and disability (Oswestry Disability Index [ODI])[33] outcome measures. In our clinical experience with neurostimulation, therapeutic effects stabilize in less than two weeks after programming changes are made. Therefore, two-week treatment periods were chosen to ensure that the observed stimulation effects at the end of the period only reflected the current stimulation program being used.[22] At the end of the study, participants selected which of the three programs they preferred and could elect to remain on their preferred study stimulation program or return to their continuous stimulation prestudy settings.

Mean pain, disability, and general health scores were compared across continuous, 1:1 on-off, and 1:2 on-off stimulation using one-way repeated-measures ANOVA with the null hypothesis of no differences rejected at $p < 0.05$. Data are presented as $n$ (%) or mean with 95% confidence interval (CI). To assess the boundaries of non-inferiority, we calculated the differences in pain, disability, and general health scores for 1:1 on-off and 1:2 on-off stimulation vs continuous stimulation and plotted the mean difference with its 95% CI. The upper limit of the 95% CI was used as a marker to assess

if a clinically relevant difference may be present between either of the intermittent stimulation paradigms vs continuous stimulation.

## RESULTS

A total of 20 patients were enrolled in this study. Patient demographics are shown in Table 1. Patients ranged from 36 to 80 years of age, with nine men and 11 women. Diagnoses of these patients included CRPS, peripheral neuropathy, and failed back surgery syndrome. Lead placements were between two to four leads per patient, with leads placed at T12 for back pain with a combination of lumbosacral leads to cover lower extremity pain, most commonly at S1. One patient had unilateral leads placed at C4, C5, and C6 for shoulder joint pain coverage. DRG-S reduced pain scores by an average of 67%, reduced disability by 54%, and improved quality of life by over 57% from pre- to postimplant before entering the study (Fig. 2). Average DRG-S parameters per lead are listed in Table 1. All enrolled participants ($n$ = 20) completed the study. Opioid medications did not change during this study, and patients did not receive any other interventions for pain.

Pain scores were similar among continuous, 1:1 on-off, and 1:2 on-off stimulation (mean ± CI: 2.9 ± 0.8, 2.6 ± 0.7, and 2.7 ± 0.7 cm, respectively, $p$ = 0.39; Fig. 2). Disability ($p$ = 0.72) and general health scores ($p$ = 0.95) were similar among stimulation paradigms as well. The upper boundaries of the 95% CI of difference between 1:1 on:off and 1:2 on:off stimulation vs continuous stimulation were not clinically relevant for pain (+0.11 and +0.24, range of NRS 0 to 10), disability (+2.36 and +1.44, range of ODI 0 to 100), and general health (+0.011 and +0.010, range of EQ-5D −0.573 to 1.000) (Fig. 3).

At the end of the study, eight patients (40%) preferred continuous stimulation, five patients (25%) selected 1:1 on-off dosing, and seven patients (35%) preferred 1:2 on-off dosing.

**Table 1.** Demographics and Baseline Characteristics of the 20 Patients in the Study.

| Baseline characteristics | Value |
|---|---|
| Demographics | |
| Age in years, mean ± CI | 61 ± 5 |
| Gender, male/female, *n* (%) | 9/11 (45/55) |
| Primary diagnosis | |
| Failed back surgery syndrome, *n* (%) | 9 (45) |
| Nonsurgical back pain, *n* (%) | 5 (25) |
| Peripheral neuropathy, *n* (%) | 1 (5) |
| CRPS, *n* (%) | 3 (15) |
| Abdominal pain, *n* (%) | 1 (5) |
| Shoulder pain, *n* (%) | 1 (5) |
| Medications | |
| Opioid medication use in mg oral morphine equivalent, mean (range) | 46 (0–126) |
| Treatment characteristics | |
| Treatment duration | |
| Duration of DRG-S prior to study in days, median (range) | 146 (95–679) |
| DRG-S lead location | |
| T12 and S1, *n* (%) | 16 (80) |
| T11 and T12, *n* (%) | 1 (5) |
| T12, L4, L5, and S1, *n* (%) | 2 (10) |
| C4, C5, and C6, *n* (%) | 1 (5) |
| DRG-S parameters | |
| Frequency in Hz, mean ± CI | 5.7 ± 0.7 |
| Pulse width in μs, mean ± CI | 264 ± 6 |
| Amplitude in mA, mean ± CI | 0.605 ± 0.12 |

## DISCUSSION

In this double-blinded randomized controlled feasibility trial, DRG-S delivered intermittently at 1:1 on-off and 1:2 on-off ratios was compared with standard continuous DRG-S. There were no clinically significant differences in pain relief, quality of life, and functional outcome measures across the three methods of delivery. It is also noteworthy that outcome measures at the end of each two-week stimulation program were similar to prestudy DRG-S outcome measures across all three programs (Fig. 2).

Fluctuations in the strength (amplitude) of the stimulation delivered to neural tissue are less common with DRG-S than tonic SCS because of a more stable target relative to body position, a closer proximity to the target tissue, and the utilization of subthreshold, paresthesia-free stimulation.[34,35] This, combined with conduction through less cerebrospinal fluid, leads to a lower impedance and a lower charge delivery requirement, reflected in lower amplitudes than required for SCS.[36,37] These factors reduce variability and increase the likelihood that intermittent stimulation programming was the primary variable affecting outcome measures.

There was no apparent program predilection for continuous, 1:1 on-off, or 1:2 on-off intermittent stimulation dosing. Patient preference was nearly equal for the 1:1 on-off, 1:2 on-off, and continuous programs, supporting the notion that there was little perceived difference between continuous and intermittent stimulation dosing. This finding was further reinforced by the similarity in outcome measures between the three programs and the pretrial DRG-S outcome measures (Fig. 2). Overall, our findings suggest that intermittent stimulation dosing of tonic DRG-S at 1:1 on-off and 1:2 on-off stimulation provides clinically equivalent results to continuous stimulation over a two-week period.

Burst-SCS, a paresthesia-free paradigm, recently demonstrated equivalent clinical efficacy to continuous stimulation at intermittent dosing ratios of up to 1:12 on-off,[23] reducing the charge delivery from 100 to 8.5 μC/s based on typically used parameter settings.[18] This reduction translates to an extension of IPG life span to up to ten years.[38] This study follows our recent publication demonstrating maintained efficacy with DRG-S at 4 Hz; the lowest possible system setting reduced the total charge delivered to 0.66 μC/s.[17] Therefore, the addition of a 1:2 on-off stimulation cycling program could lower charge output for DRG-S to 0.22 μC/s, a fraction of the charge output of tonic SCS (70 μC/s) or high-frequency spinal cord stimulation (750 μC/s)[18] (Table 2). That, in turn, should translate to a considerable extension of IPG battery longevity from a projected 6.5 years with nominal parameter settings.[39]

The results of this study demonstrate the maintained clinical efficacy of very low dose charge delivered to the DRG intermittently, a result which would not be possible without upstream effects within the dorsal horn. Our clinical findings are consistent with preclinical work showing a prolonged washout effect at very low-frequency stimulation compared with higher frequencies, and support a role of LTMRs and endogenous opioid induced LTD[29–31,40] with DRG-S. Although these LTMRs can fire and inhibit pain signaling at less than 1 Hz, they can fire synchronously with stimulation at up to 20 Hz, ranges consistent with DRG-S programming.[28] Frequencies typically used for tonic SCS may

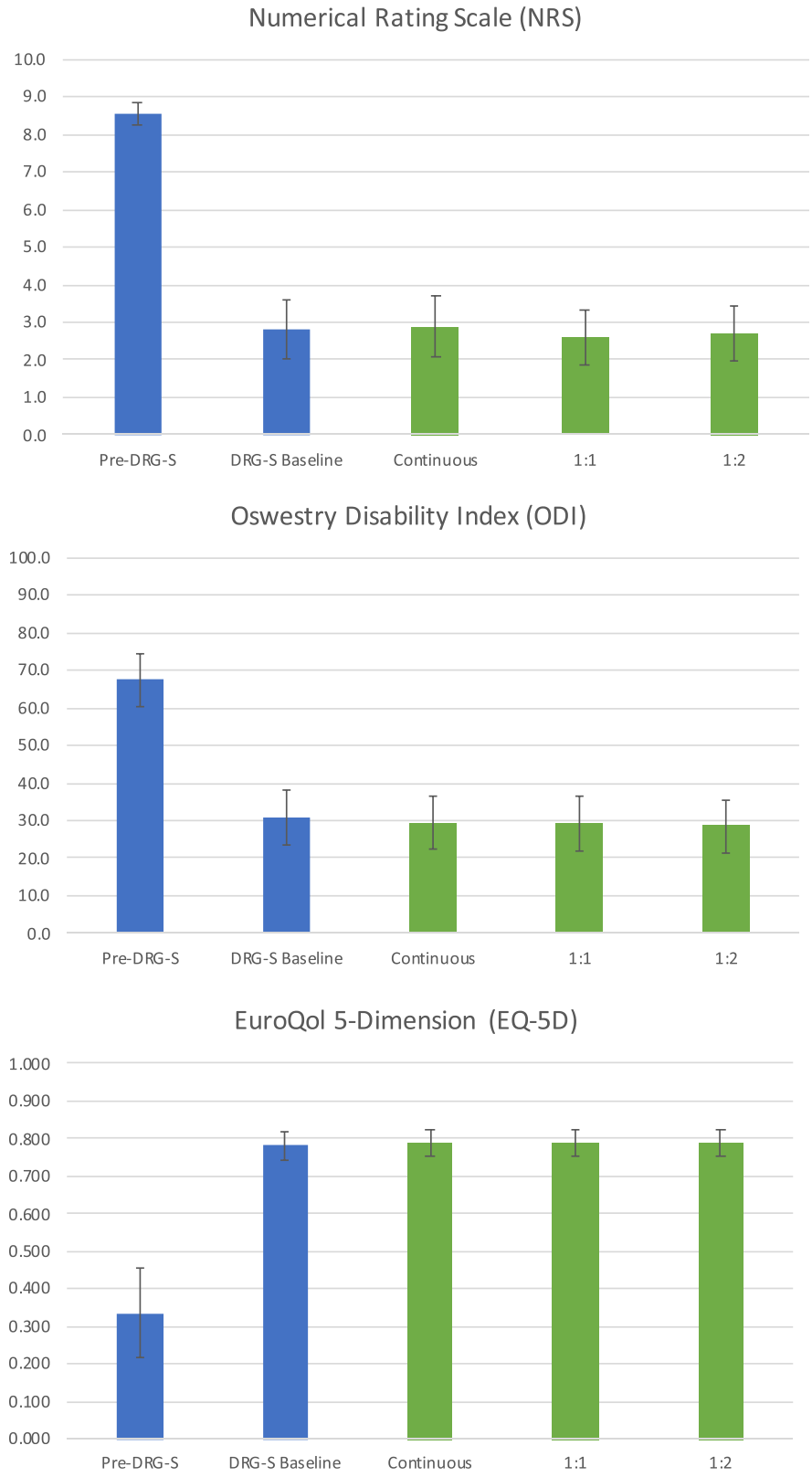


**Figure 2.** Pain (NRS), disability (ODI), and general health (EQ-5D) scores pre- and post-implant before the study (blue columns), and for each stimulation program during the study (green columns). Bars represent upper boundary of 95% CI of the mean. [Color figure can be viewed at www.neuromodulationjournal.org]

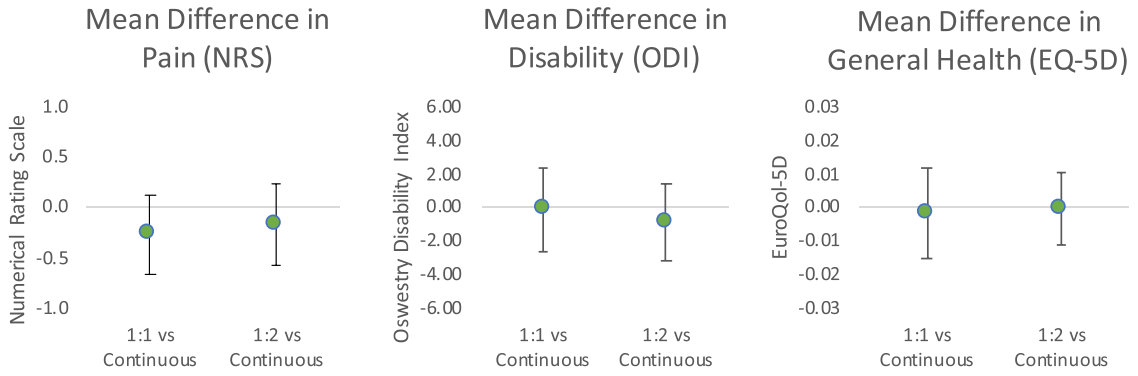


**Figure 3.** Difference in pain (NRS), disability (ODI), and general health (EQ-5D) ratings with on-off stimulation programs relative to continuous stimulation. Bars represent upper and lower boundary of 95% CI of mean. [Color figure can be viewed at www.neuromodulationjournal.org]

propagate action potentials in large diameter Aβ fibers and much less likely in Aδ or C LTMR fiber types.[11,41] These observations combined with the clinical outcomes of this study further support our hypothesis for the role of LTMRs, very low-frequency stimulation, and endogenous opioid signaling as underlying mechanisms of actions for DRG-S.[8,15] There is little evidence of the role of endogenous opioid system in tonic SCS therapy to date, and perhaps this mechanistic difference may explain why tonic SCS is ineffective when delivered in both sub-paresthesia and intermittent paradigms.

The postulation of endogenous opioid release as an underlying mechanism of pain inhibition is not new in neuromodulation. Endogenous opioid release in the deep dorsal horn has been demonstrated with 500 Hz burst stimulation[42] and has been identified as one of the possible mechanisms underlying burst-SCS.[43] Burst-SCS is a paresthesia-free form of neuromodulation with leads placed on the dorsal columns. However, it has characteristics that resemble DRG-S: effects of burst-SCS likely extend beyond stimulation of the dorsal columns, are less likely γ-aminobutyric acid mediated, cause blood oxygen level dependent response changes on fMRI,[44–46] and appear equally effective when delivered intermittently, characteristics also seen with DRG-S but not with tonic SCS.[10,47] Both burst-SCS and DRG-S improve mood, affect, and quality of life testing, domains that correlate to cortical structures in the medial pain pathway that are regulated in part by the endogenous opioid system.[48–51] Interestingly, when compared with tonic SCS in the Success Using Neuromodulation With BURST (SUNBURST) study, burst-SCS yielded similar pain scores at one-year follow-up.[52] This suggests a dissociation between the degree of improvement in affect and pain scores, which is also seen in patients taking opioid pain medications; patients consistently report "feeling better" without a corresponding reduction in pain scores.[53,54] These facts raise the question of whether endogenous opioid activity plays a more significant role in the efficacy of burst-SCS and DRG-S.

Continuous tonic SCS may have a propensity for habituation as demonstrated in rodent models,[55–58] leading to loss of efficacy and potential device explantation.[59–61] Stimulating LTMR fibers activates natural inhibitory mechanisms within the spinal cord dorsal horn via endogenous opioid release, activating opioid receptors on dorsal horn neurons orthodromically. Opioid receptors do not internalize in vivo when activated by endogenous opioids as they do with exogenous opioid administration.[62] Receptor internalization is one of the processes underlying the development of tolerance.[63] This may be one reason for the lower rate of loss of efficacy seen with DRG-S than with SCS at 12 months.[64] It is possible that intermittent dosing may further decrease these rates.

There were several limitations to this study. Only 15% or three patients in this study had the primary diagnosis of CRPS, which is the patient population that was studied in the ACCURATE trial.[1] A total of 14 patients or 70% of the participants in this study had DRG-S implanted for FBSS or non-surgical low back pain, patient populations that were not studied in the ACCURATE trial. These may be considered mixed pain syndromes rather than purely neuropathic syndromes, for which DRG-S may work through additional or alternative mechanisms of action. Therefore, this study may not be generalizable to the CRPS patient population that DRG-S is indicated for because of the very small sample size represented. The durations of the period of on vs off stimulation

**Table 2.** Charge per Second Measured in Microcoulombs per Second with DRG-S Using Continuous Programming and Intermittent Stimulation Programming Compared to Accepted Average Settings for Tonic SCS and High Frequency (10 K) SCS.

| Stimulation modality | Frequency (Hz) | Pulse width (μs)* | Amplitude (mA) | Stimulation dosing pattern | Mean charge (μC/s)* (=Hz × ms × mA) |
|---|---|---|---|---|---|
| Tonic SCS† | 50 | 400 | 3.5 | Continuous | 70 |
| High frequency SCS† | 10,000 | 30 | 2.5 | Continuous | 750 |
| DRG-S | 6 | 260 | 0.575 | Continuous | 0.9 |
| | | | | 1 on:1 off | 0.45 |
| | | | | 1 on:2 off | 0.3 |

*Pulse width requires conversion from μs ($10^{-6}$) to ms ($10^{-3}$) for calculation.
†Broadly representative parameters based on the published literature, provided for comparison/context.

(1:1 on-off, 1:2 on-off) were based on observations from a small study that demonstrated that pain suppression occurred 30 seconds from onset of stimulation, and effects carried over 90 to 120 seconds after cessation of stimulation.[65] These intervals were also within the conservative range of similar studies on periodic stimulation dosing for other neuromodulation paradigms.[22,23] However, it is unclear if the ratios and durations of on-off stimulation used with the intermittent stimulation dosing programs in this study were ideal. The maximal stimulation-off duration while maintaining efficacy is yet to be elucidated. Additionally, the observed long-term sustainability of intermittent stimulation dosing is in question. Further research is necessary to address these issues.

## CONCLUSIONS

This feasibility study demonstrated that delivering DRG-S in an intermittent cycled pattern maintains similar effects on pain relief, disability, and functional improvement to standard continuous stimulation. Maintained efficacy at a total charge per second of 0.3 μC/s through intermittent dosing further underscores the potential mechanistic differences between DRG-S and SCS and highlights the role of DRG-S in the dorsal horn. Current DRG-S IPG manufacturer battery life of around six years can likely be extended significantly with cycled stimulation. The significant improvements in pain, function, and quality of life utilizing very low-frequency stimulation and intermittent dosing with DRG-S have the potential to set a new bar for the meaning of true low energy neuromodulation.

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### Authorship Statement

Kenneth B. Chapman and Tariq Yousef designed the study. Kenneth B. Chapman, Connor Tupper, Ajax Yang, and Tariq Yousef conducted the study, including patient recruitment and data collection. Kenneth B. Chapman, Connor Tupper, Noud van Helmond, and Tariq Yousef analyzed the data. Kenneth B. Chapman prepared the manuscript draft, with important intellectual input from Connor Tupper, Ajax Yang, Noud van Helmond, and Tariq Yousef. All authors approved the final manuscript.

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## COMMENTS

I would like to congratulate the authors of the study for their work. It is a very interesting study. The authors correctly point out that this is a preliminary study and firm conclusions cannot be drawn. However, it does seem to indicate that the use of intermittent dorsal root ganglion stimulation (DRG-S) increases the battery life while still providing the same level of analgesia and life quality as the continuous stimulation. A larger study needs to be performed to confirm the findings of this orienting preliminary study. For further studies, I would like to recommend that more information regarding patient selection should be available (medication!). The influence of ongoing medication (especially the use of so-called antineuropathics or opioids) on the outcome of neuromodulation therapy is sometimes underestimated, because it is assumed that neuromodulation therapy occurs because of the failure of pharmacotherapy. However, synergistic effects cannot be ruled out when considering some of the currently discussed mechanisms of action of DRG-S (ie, endorphinergic mode of action). The differential effect of stimulation on the dorsal column and on the DRG can be explained not only by the different anatomical location but probably also by the different embryological origin of the two tissues. (Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. *Neuromodulation*. 2015;18:24-32.). The sensory elements of the peripheral nervous system (PNS) arise from a specific population of cells originating from the roof of the neural tube, namely the neural crest. These cells give rise to the neurons of the DRG, the autonomic ganglia and the paraganglia including the adrenergic neurons of the adrenal glands. Furthermore, the supportive glial Schwann cells of the PNS originate from the neural crest cells. (Catala M, Kubis N. Gross anatomy and development of the peripheral nervous system. *Handb Clin Neurol*. 2013;115:29-41.). Because of the unique pseudounipolar design of DRG neurons, the DRG is likely to act as an impediment or low-pass filter to electrical impulses traveling from the peripheral nociceptor to the spinal cord in response to electrical stimulation. (Joosten EA, Franken G. Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms. *Pain*. 2020;161:S104-S113.). The brain and spinal cord are one continuous structure comprising the CNS, arising from a common progenitor ancestry. The embryonic spinal cord contains 11 progenitor domains distributed in 11 distinct dorsoventral regions of the early embryonic neural tube and producing a small

number of primary neuronal classes. (Hochman S. Spinal cord. *Curr Biol*. 2007;17:R950-955.). Nonetheless, this work opens another window to further optimize the care of patients with regional chronic neuropathic pain using DRG-S.

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I commend the authors of this manuscript on this independent randomized controlled trial looking at optimal settings for patients being treated with dorsal root ganglion stimulation. I hope to see more research like this published as this type of work without industrial support is seldom published.

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This study makes two important contributions to the literature on DRG-S. First, at a practical level, the demonstration of the efficacy of intermittent stimulation is another step forward in the quest for minimum power consumption in neuromodulation and offers the possibility of further extending battery life. The 1:2 on/off ratio will reduce power consumption threefold; Dr Chapman's group has already shown that substantially lowering frequency from the standard 20 Hz can reduce it by approximately fourfold (Chapman KB, Yousef TA, Vissers KC, van Helmond N, Stanton-Hicks MD. Very low frequencies maintain pain relief from dorsal root ganglion stimulation: an evaluation of dorsal root ganglion neurostimulation frequency tapering. *Neuromodulation*. 2021;24:746-752.), and my own group has found that obtaining perfect superodorsal lead positioning can also have a fourfold effect. (Martin S, Hadjipavlou G, Garcia Ortega R, et al. The importance of the location of dorsal root ganglion stimulator electrodes within the nerve root exit foramen. *Neuromodulation*. 2020;23:245-251.). If all these factors operated together, the reduction could be almost 50-fold. Second, the novel finding of a tonic stimulation method that works in a cycled mode offers another piece of the jigsaw as we seek a better understanding of the mechanisms of action of neuromodulation.

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