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Ultra-Low Energy Cycled Burst Spinal Cord Stimulation Yields Robust Outcomes in Pain, Function, and Affective Domains: A Subanalysis From Two Prospective, Multicenter, International Clinical Trials

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ABSTRACT

Introduction: DeRidder's burst stimulation design has become a key spinal cord stimulation (SCS) waveform because it reduces the intensity of pain as well as its associated emotional distress. The brain pathways underlying these outcomes may also allow for the effects of stimulation to carry over after stimulation is turned off, making it amenable to intermittent application. Here, the utility of intermittently cycled burst was evaluated using data from two large real-world prospective studies (TRIUMPH, REALITY).

Materials and Methods: Subjects used intermittent dosing in a 1:3 ratio (30 sec on, 90 sec off; $N = 100$) in TRIUMPH and 1:12 ratio in REALITY (30-sec on, 360-sec off; $N = 95$) for six months. Pain intensity (0–10 numeric rating scale), pain-related emotions on the pain catastrophizing scale (PCS), and physical function on PROMIS questionnaires were compared with preimplant baseline ratings and by group.

Results: In both groups, mean pain intensity decreased by nearly 50% relative to baseline, PCS scores significantly decreased, and physical function improved. Importantly, no differences between the 1:3 and 1:12 groups were identified. A high proportion, 80% and 77% of the 1:3 and 1:12 groups, respectively, were considered responders on a multiple measures. No adverse events were associated with intermittent stimulation.

Discussion: Intermittent cycling of burst SCS lowers the overall electric charge delivered to the spinal cord and preserves battery consumption, without compromising pain relief and associated symptoms.

Keywords: burst, duty cycling, intermittent stimulation, microdosing, spinal cord stimulation

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INTRODUCTION

Spinal cord stimulation (SCS) is an established intervention for the treatment of chronic neuropathic pain, with tens of thousands of implants per year worldwide (1,2). As a drug-free, minimally invasive, and reversible option, SCS is emerging as a powerful, nonpharmacological tool among the available pain management treatment options (3). As such, SCS, once considered a treatment of last resort, is moving up the analgesic ladder and is an orthodox entry into pain management algorithms (4–7). Successful SCS therapy is often characterized by improvements in pain intensity as measured on a visual analog scale or numerical rating scale (NRS). Recently, there has been an increased interest in evaluating functional and quality of life domains, along with reduction of opioid dependency (8–11).

The burst waveform developed by Dirk DeRidder, MD, PhD, has been in clinical use for the last decade (12). It has been shown to be superior to tonic stimulation, and its effect on alleviating pain, improving function, and reducing emotional distress have been consistently supported in clinical studies (9,13,14). Uniquely, burst attenuates the emotional aspects of chronic pain such as catastrophizing, depression, anxiety, and attention to pain (9,13,14), likely through preferential recruitment of the medial pain pathway in the brain that project to the dorsal anterior cingulate cortex and anterior insula (15–18). The burst waveform may be especially amenable to intermittent stimulation because of an extended carry-over effect. The carry-over effect, demonstrated in animals (19,20), may be due to recruitment of medial brain pathways through non-GABAergic mechanisms (19,21). Other tonic based waveforms (22) may wash out too quickly to allow for seamless clinical effects. A number of other SCS manufacturers offer burst waveforms with characteristics that differ from DeRidder's burst, such as charge balancing strategies, that may have consequences for neural functioning and pain management (23–25).

Compared with tonic stimulation, burst pulses are longer (~50 μsec for tonic vs. 1000 μsec for burst) and more frequent (single pulses for tonic vs. packets of five pulses for burst), but of lower amplitude (100–200% of paresthesia threshold for tonic vs. ~20–60% of paresthesia threshold for burst). Although some fundamental differences exist between different manufacturers' approaches to burst-style stimulation, DeRidder's burst delivers an overall electric dose (mA per second) that is nearly three times higher than tonic-based SCS (12,23,24).

To optimize treatment with any waveform, SCS stimulation parameters must be titrated to the correct dose for the patient. This approach is common with pharmaceuticals and pain pumps: using the lowest effective dose increases safety and decreases tolerance to treatment (26,27). By reducing the overall electric charge delivered to the spinal cord, SCS clinicians may take the simple approach of reducing amplitude and/or frequency parameters. In tonic SCS, it appears necessary to maintain amplitudes that generate paresthesia (28,29), while waveforms that can be operated without paresthesia such as clustered tonic and higher frequencies may use lower amplitudes (30,31). Keeping burst amplitudes low appears to optimize clinical outcomes (32). In addition, intermittent stimulation has been utilized to further reduce the overall dose specific to burst. Two previous reports have shown that, when applied in a regular on–off cycle, burst has the same effectiveness as continuously applied stimulation (33,34) while reducing the average charge over time by a factor of 2–12 times. This has the added benefit of reducing the draw on the device battery, potentially increasing its longevity.

The previous studies of intermittent burst stimulation were small pilot feasibility trials, with short-term testing rigorously controlled in a blinded environment (33,34). A six-month continuation of therapy with patients' preferred program parameters gave clear indications that there was clinical utility in intermittent stimulation, as nearly half of the subjects chose to use the least-intense intermittent cycle (1:12 ratio, corresponding to 30 sec on followed by 360 sec off) (34). These findings established the legitimacy of intermittent stimulation in burst and represented a critical step in the research cadence but shed limited light on its utility in real-world conditions across larger groups of participants. For this, the current report describes an analysis comparing clinical outcomes from two clinical study cohorts with burst SCS applied in an intermittently cycling fashion.

MATERIALS AND METHODS

Data were extracted from two prospective studies with the acronyms TRIUMPH (registered with ClinicalTrials.gov at NCT03082261) and REALITY (NCT03876054). Prior to initiating both studies, institutional review board or ethics committee approval was received at each site. Inclusion criteria for this analysis were a baseline pain score ≥ 6 on a 0–10 NRS, receipt of a permanent burst capable SCS system (BurstDR waveform, Proclaim, Prodigy, Abbott, Plano, TX, USA), utilization of intermittent cycling, and completion of data collection for the six-month follow-up visit. The majority of subjects included in the TRIUMPH study used 1:3 intermittent cycling with 30 sec of ON time and 90 sec OFF time (a total of six hours of stimulation in a day), while the majority in the REALITY study used a 1:12 intermittent cycling with 30 sec ON and 360 sec OFF (a total of 1.8 hours of stimulation in a day). The initial amplitude was set at 60% of perception threshold and tailored for each patient.

At preimplant baseline and again after six months of treatment, subjects completed NRS pain intensity ratings, pain-related emotional distress assessed on the pain catastrophizing scale (PCS) (35), and physical function measured using PROMIS questionnaires (PROMIS-8 for TRIUMPH and PROMIS-29 for REALITY) (36). Device settings for intermittent cycling were also collected in the

TRIUMPH study at six-month follow-up. Settings were collected at implant and follow-up in the REALITY study.

Data analysis included NRS mean changes from baseline, as well as the responder rates at the typically reported 50% pain relief relative to baseline as well as 30%, which is considered a clinically significant reduction (13). Because the PROMIS-8 and PROMIS-29 questionnaires have four physical-function questions in common (''Are you able to do chores such as vacuuming or yard work?''; ''Are you able to go up and down stairs at a normal pace?''; ''Are you able to go for a walk of at least 15 minutes?''; and ''Are you able to run errands and shop?''), responses for these four items were extracted from the complete questionnaires and scored per questionnaire instructions. Additionally, a multidimensional responder index was calculated using a tiered approach that evaluates response rates on NRS, PCS, and physical function on PROMIS. A subject was considered a responder if they 1) reported a 2-point decrease on NRS, 2) a 1-point decrease on NRS and clinical meaningful improvement on both PCS and PROMIS-PF (2-point improvement), or 3) a clinical meaningful improvement in both PCS and PROMIS-PF but no change on NRS. A clinical meaningful improvement on PCS was defined as a 40% decrease from baseline (37), or a follow-up score < 30 when ≥30 was reported at baseline (38). The latter identifies subjects clinically catastrophizing at baseline that are no longer considered catastrophizing at follow-up. A 2-point reduction in *t*-score on PROMIS-PF defined a clinically meaningful improvement in function (39). A similar composite approach has been described previously (40). Finally, activity level and impact of pain on life were collected for subjects on both intermittent cycles. This was assessed by asking ''What impact does pain have on your life'' and ''indicate the frequency of exercise.'' Subjects reported which category best reflected the impact on their lives and frequency of exercise.

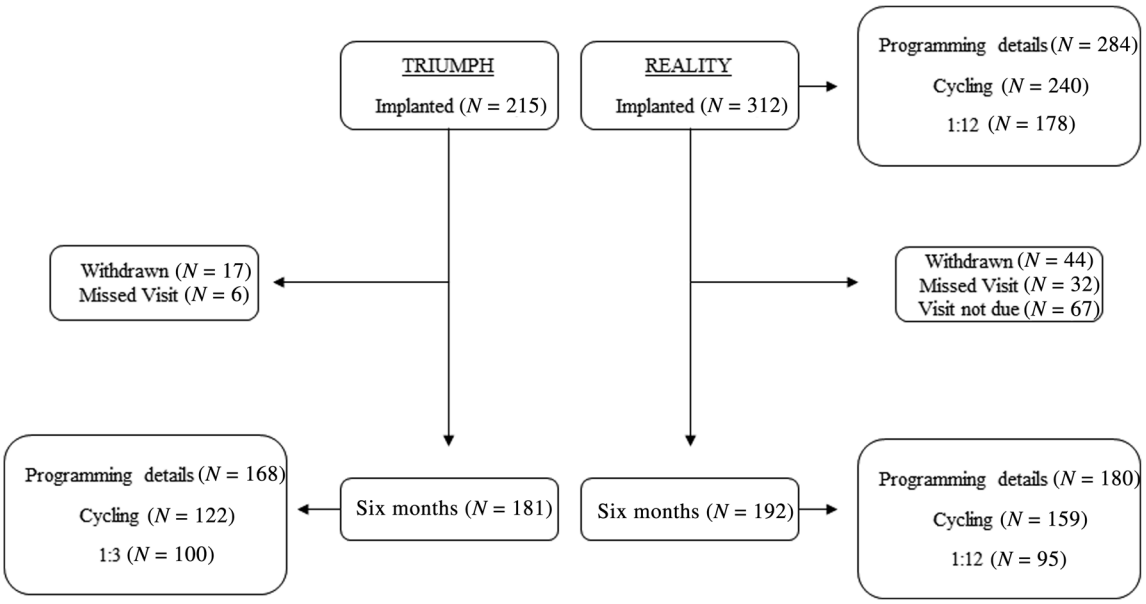

Figure 1. Subject disposition.

Table 1. Demographics.

	1:3 intermittent cycle ($N = 100$)	1:12 intermittent cycle ($N = 95$)	*p* value
Age (years)			
Mean ± SD	60.8 ± 13.8	58.9 ± 13.9	0.33
Range	18–86	31–89	
Gender, *N* (%)			
Female	66 (66%)	63 (66%)	0.96
Male	34 (34%)	32 (43%)	
BMI			
Mean ± SD	31.3 ± 6.9	33.8 ± 7.8	0.12
Range (Q1–Q3)	26.6–35.6	27.9–37.9	
Time with pain (years)			
Mean ± SD	9.1 ± 7.9	12.4 ± 10.6	0.06*
Median	7	9	
Range (Q1–Q3)	3.0–11.0	4.5–20.0	

*Nonparametric Wilcox rank test.

Unless otherwise stated, data are presented as proportions, means, and standard deviations (SDs). Normality of each group was assessed using Shapiro-Wilk. All observations that were outside the interval formed by the 2.5 and 97.5 percentiles were considered as potential outliers. Continuous data were compared using an unpaired *t*-test. Non-normally distributed data were compared using the Wilcox signed rank test. Responder analysis was analyzed using chi-square. Significance was set at $p < 0.05$. No adjustments for multiplicity have been made. All statistics were performed using R (Vienna, Austria).

Table 2. Pain Etiologies in Each Cohort.

Etiology	1:3 intermittent cycle ($N = 100$)	1:12 intermittent cycle ($N = 95$)
FBSS/back pain/radiculopathy	95	84
CRPS I	4	4
CRPS II	1	2
Peripheral neuropathy	0	3
Neck/upper limb pain	0	2

Abbreviation: CRPS, complex regional pain syndrome.

RESULTS

The TRIUMPH study completed enrollment in 2018 and reached its 24-month completion in 2020. A total of 269 subjects were enrolled; 181 had six-month follow-up data available and 168 had programming details captured at that time point.

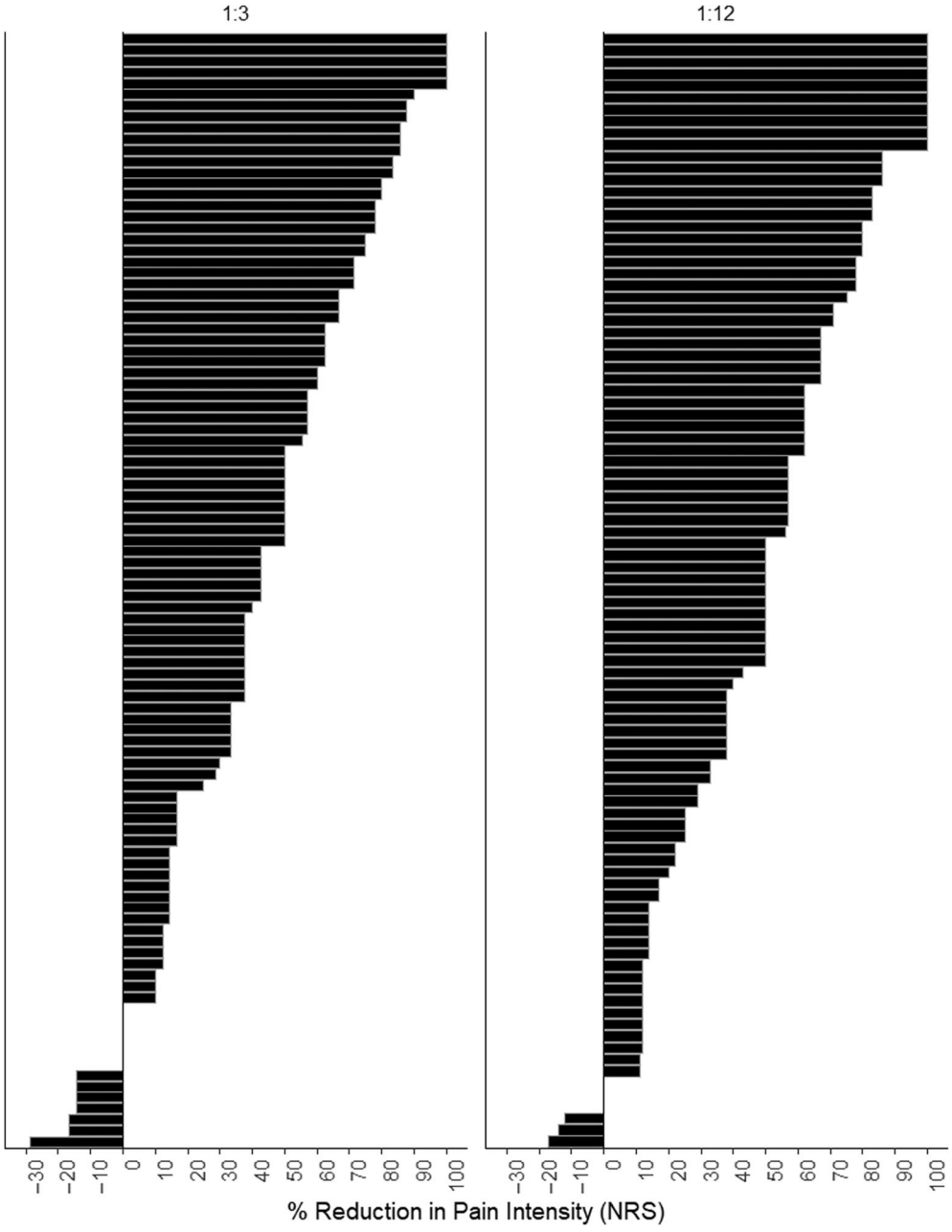

Figure 2. Tornado plots showing the percent change in NRS score at six months compared to baseline for both groups.

Table 3. Pain Intensity (NRS), Pain Catastrophizing (PCS), and PROMIS Physical Function for Each Cohort.

Outcome		1:3 intermittent cycle	1:12 intermittent cycle	*p* value
NRS	Baseline	7.5 (1.2)	7.7 (1.2)	0.51
	Six months	4.3 (2.4)	3.9 (2.4)	0.28
	Average point change from baseline	3.2 (2.6)	3.8 (2.5)	0.18
PCS	Baseline	24.6 (12.4)	24.8 (12.8)	0.89
	Six months	12.3 (12.0)	13.5 (12.1)	0.49
	Average point change from baseline	12.3 (11.6)	11.3 (13.0)	0.56
PROMIS physical function	Baseline	33.5 (4.2)	34.5 (5.3)	0.06
	Six months	38.2 (6.6)	38.8 (7.5)	0.42
	Average point change from baseline	4.7 (5.5)	4.3 (6.8)	0.35

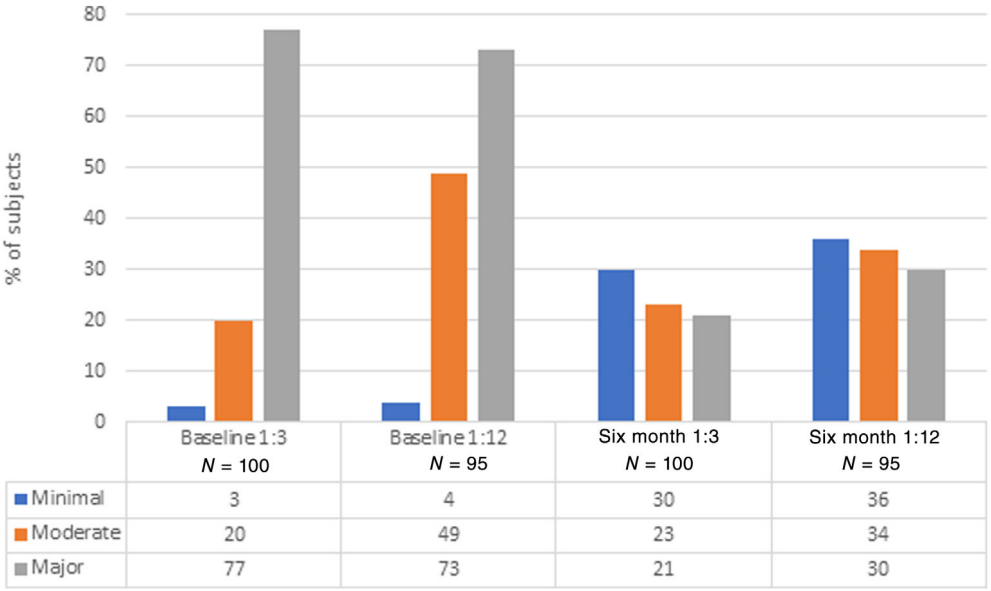

Figure 3. Impact of pain on daily life. [Color figure can be viewed at wileyonlinelibrary.com]

The REALITY study is currently enrolling. At the time of data analysis, 312 SCS subjects were enrolled and 192 reached the six-month time point. Programming details were available for 180 subjects. Intermittent stimulation was the most common programming choice in both studies (73% and 88%, respectively). Of these, 100 (82%) subjects from TRIUMPH (the 1:3 group) and 95 (60%) subjects from REALITY (the 1:12 group) met all of the inclusion criteria for the current report and were included in the analysis. Other intermittent cycling parameters or continuous stimulation were infrequently used in comparison and therefore limited a comparative analysis to the two largest groups identified. The disposition of subjects is shown in Figure 1. There were no differences between groups on age, sex or Body Mass Index (BMI) demographic variables, or duration of years with chronic pain (Table 1). The distribution of pain etiologies represented in both groups is shown in Table 2. Failed back surgery syndrome (FBSS)/back pain/radiculopathy represents the majority in both; 94% and 87% in 1:3 and 1:12, respectively.

Mean (SD) baseline pain intensity reported was 7.5 (1.2) in 1:3 and 7.7 (1.2) in 1:12 with no difference between groups. At six months, the mean scores were 4.3 (2.4) and 3.9 (2.4), respectively, a nearly 50% improvement for each group, with no difference between groups (3). Responder rates at 30% decrease in pain intensity were 66% and 67% (1:3 and 1:12 groups, respectively). Response rates were slightly higher, though not statistically different between groups at 50% pain relief (46%, 57%) (Fig. 2).

There was no difference in baseline or response rates on pain catastrophizing between groups. Baseline PCS scores were nearly identical, on average 24 points and on average 38% of subjects across groups were considered clinically catastrophizing. After six months of treatment, PCS scores were 12.3 (12.0) and 13.5 (12.1) for the 1:3 and 1:12 groups, respectively (Table 3); there was no statistically significant difference between groups. Of those clinically catastrophizing at baseline (PCS score > 30), 69% and 68% were no longer catastrophizing at follow-up.

Physical function was collected using PROMIS-8PF in TRIUMPH and PROMIS-29 in REALITY. No differences were observed between the two groups for mean scores reported at baseline or follow-up. The change in score at six months compared to baseline was also not significantly different between the two groups (Table 3).

A multidimensional responder rate was calculated for each group. This approach defines a responder to therapy by combining all patient reported outcomes collected. At six months, 80% and 77% response rates were shown with subjects on 1:3 and

Table 4. Patient Reported Activity Levels.

	1:3 intermittent cycle ($N = 100$)		1:12 intermittent cycle ($N = 95$)	
	Baseline	Six months	Baseline	Six months
Low activity	70% (70/100)	39% (39/100)	68% (65/95)	38% (36/95)
Moderate activity	26% (26/100)	51% (51/100)	22% (21/95)	41% (39/95)
High activity	4% (4/100)	10% (10/100)	9% (9/95)	21% (20/95)

1:12 cycling protocols, respectively, with no statistically significant difference observed between the groups. The three criteria used for this approach identified 68, 10, and 2 subjects in the 1:3 group. The majority (72 of 73 responders) in the 1:12 group met criteria 1. One additional subject improved on physical function and catastrophizing, and was identified by criteria 3.

At baseline, the majority of subjects in both groups report minimal activity (70% and 68% of patients in 1:3 and 1:12, respectively) and severe impact of pain on their lives (77% and 73% of patients) (Fig. 3; Table 4). At follow-up, the majority in both groups report moderate to high levels of activity and moderate to mild impact of pain on their lives (Fig. 2, Table 3).

Adverse events related to the device were calculated in each group. Four lead migrations were reported in each group. Three subjects on 1:3 cycling, and one subject on 1:12 cycling reported a lead fracture. No events related to stimulation or intermittent cycling were reported in either group.

DISCUSSION

In this real-world analysis of intermittent stimulation, participants received burst SCS systems that were programmed with long stimulation-off intervals. Because stimulation was applied at amplitudes that were below each patient's paresthesia threshold, the on–off cycling was imperceptible. Stimulation parameters, including the durations of on–off intervals, could be reprogrammed at any time if needed, consistent with standard practice. After six months of treatment, the devices were interrogated for program usage. Of the subjects in REALITY, 81% maintained their initial 1:12 cycle for six months. The majority of subjects that changed cycle parameters moved to 1:3 (68%), 24% changed to 1:1, and 8% changed to 1:5. In a previous pilot study of intermittent stimulation, only 45.8% of subjects used the 1:12 cycle after six months of treatment (34). However, the pilot study was designed so that participants were frequently offered shorter stimulation-off intervals, which may have influenced them to "try it and see." Conversely, in the current report, intermittent stimulation intervals were changed only if the treatment was not satisfactory. The higher rate of patients remaining at the 1:12 cycle suggests that the therapy delivered with this stimulation pattern was effective for the majority of patients.

Participants completed assessments of pain intensity, physical function, and emotional aspects of pain processing at baseline and after six months of treatment, outcomes unique to DeRidder's burst and with high clinical utility, as has been similarly demonstrated in the literature (9,40). There were no statistically significant differences between the on–off ratio groups for any of these patient-reported outcome measures. This was consistent with the findings of the previous studies, which showed that pain, disability, and/or health-related quality of life domains were improved by clinically equivalent levels for continuous versus intermittent stimulation, as well as across multiple on–off ratios (13,14,17,33,41). Thus, this suggests that the strategy to substantially reduce electrical dose (and potentially preserving battery capacity) via intermittent stimulation can be achieved with no decrement to clinical efficacy.

Likewise, no safety signal appeared to be related to intermittent stimulation. Adverse events occurred at low rates in this study, consistent in type and frequency with known complications for this intervention (42–44), and with no apparent relationship to the intermittent stimulation on–off cycle used. Similarly, six months of intermittent burst SCS had no unexpected adverse device effects in the previous report (34). A logical explanation for safety of intermittent stimulation extrapolates from the strategies employed in stimulation-related complications. Devices are simply shut off in these situations. This is different from a "stimulation holiday" intended to restore therapeutic effect that has faded over time, which is not often an effective strategy (45,46). As the device is already turned off most of the time with intermittent stimulation (18 and 22 hours off with 1:3 and 1:12 cycling, respectively), it may be that this represents considerably less opportunity for stimulation-related adverse events, or loss of efficacy due to habituation, to occur.

Biological tolerance or accommodation to SCS has been a persistent challenge to achieving long-term outcomes. If tolerance and accommodation is mitigated, the benefits are multiplied beyond simply device longevity. Rates of SCS tolerance historically run about 8% annually, with some studies showing much higher rates (47). Burst SCS may mitigate tolerance through its phasic patterns and low amplitude, and may further preserve efficacy via intermittent dosing. DeRidder's burst may be effectively employed to salvage SCS treatment in systems in which efficacy has been lost over time (46). Limitations of this study include a retrospective analysis of prospectively collected data, responder definitions were not prespecified in the study protocols, and the potential for unknown third variables to have introduced confounds in the data, due to the uncontrolled nature of the observational data capture. This is unavoidable for this study design. However, a goal was to identify real-world usage of burst cycling parameters; if intermittent stimulation were clinically unacceptable, this would have been reflected by frequent complaints of ineffective therapy or requests for reprogramming. Because these were not observed (at least, not at a rate higher than would be expected for usual clinical practice), it can be inferred that the day-to-day use of intermittent stimulation proceeds satisfactorily as expected. Statistical comparison of the average changes from baseline in pain, function, and affect scores between the 1:3 and the 1:12 groups are limited due to their relatively large SDs. This reduces statistical power and increases the possibility of a type II error. Additionally, a direct comparison between 1:3 and 1:12 within a

single study or inclusion of a continuous stimulation group was not feasible due to low number of subjects available for the 1:3 cycle time ($N = 25$) in the REALITY study and continuous stimulation ($N = 22$). The pilot study investigating the feasibility of the longer cycling ratio of 1:12 was initiated after nearly all participants completed the TRIUMPH study, making a within-study comparison not feasible (34). It also points to the rapid adoption of longer intermittent cycling adoption in the clinical community. The comparisons between the two groups have a great deal of face validity, in that broadly equivalent outcomes were observed across multiple assessments and both groups exhibited strikingly similar patterns of responses.

Intermittent stimulation is a programming option that can be used with multiple waveforms and is a standard component of SCS systems (48). However, published reports that include programming parameters rarely mention whether intermittent stimulation was applied. Prior to the series of burst stimulation studies, no prospective trial investigated the clinical utility of intermittent stimulation. Anecdotally, however, reports have indicated that patients use their devices in intermittent manner, albeit in a manual fashion that is independent of the automatic settings built into the SCS device. For example, it appears commonplace with tonic stimulation that patients may turn their device off after a few hours, and that patients with access to multiple waveforms may opt to use more than one depending on activities or time of day (49–51). This approach may harness the carry-over effects of active SCS into the stimulation-off times and would clearly help to preserve battery charge. Patients would then manually resume stimulation when the pain returns. This manual approach, then, would have ''peaks and troughs'' of pain symptoms. The alternate approach of optimizing stimulation dosage through automatic intermittent cycle programming may be able to maintain stimulation at the appropriate level throughout the day without requiring the patient's interaction or resulting in any perceptible changes in stimulation or therapy. Because many patients appreciate the paresthesia-free nature of burst stimulation (13), this ''hands-off'' approach to dosage optimization through intermittent stimulation may also be an attractive option.

The conservation of battery charge is another putative benefit of intermittent stimulation. An SCS system used with default burst parameters and use conditions and an amplitude of 0.6 mA at 500 Ω impedance requires an average of 104 μA of battery current to support stimulation delivery when used continuously. Used 24 hours per day in this way, a recharge-free battery may be depleted within 41 months. If, instead, 1:3 cycling was used, the battery life could be extended to 74 months, or to 117 months with 1:12 cycling (48). With the current frequency of battery replacement surgeries standing at 3.8 years for recharge-free batteries and 6.5 years for rechargeable batteries at a cost of many thousands of dollars (52), intermittent stimulation may be a straightforward approach toward improving health services and financial economy.

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Authorship Statement

Derron Wilson, David Schultz, Steven Falowski, Ed Tavel, Gregory Moore, Robert Heros, and Denis Patterson contributed to the acquisition of the data and assisted with document preparation. Timothy Deer and Magdalena Anitescu assisted with interpretation of data and document preparation. Marie Fahey contributed to the analysis and interpretation of the data and document preparation. Robyn Capobianco contributed to the study conduct, analysis and interpretation of the data, and document preparation. All authors reviewed and approved the final manuscript for submission.

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COMMENTS

This is an interesting study, demonstrating that "less is more" when using De Ridder burst spinal cord stimulation (SCS). The "less is more" concept of De Ridder burst SCS may be achieved by 1. lowering the amplitude, as previously shown by Leong et al or 2. by stimulation the spinal cord intermittently, as previously shown by Vesper et al.

The current manuscript adds to the early experience by prolonging the off-period to 6 minutes, instead of 10 seconds, and it is likely this stimulation-free period could be extended even further in a small group of patients. Searching for the lowest dose of stimulation that delivers a maximum of clinical benefit is not only of importance for extending battery life, but may reduce side effects, and hypothetically prevent tolerance. Timothy Deer and colleagues are BOLDly pushing the limits of reducing the electrical charge delivered to the spinal cord, thereby robustly optimizing pain reduction, reducing suffering and increasing the functional quality of life for chronic pain patients.

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The authors have expanded on previous work and shown that De Ridder burst applied with intermittent stimulation programming provides pain relief and improved quality of life for patients out to six months. Impressively, 81% of patients in this study continued to use the lowest ratio of stimulation (1:12). This has incredible value for the patient and should dramatically improve IPG battery life without the requirement of IPG recharging.

Additionally, I appreciate the inclusion of patient reported outcomes beyond simply pain scores. As we are all aware, the multidimensional experience of pain goes beyond the subjective measurement of NRS or VAS.

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This article shows a real world 6-month follow up of 2 cycling regimens with burst stimulation, both showing good long lasting effect with the advantage of lesser use of energy. It opens up the possibilities we have of offering patients burst stimulation while realizing that the ideal strategy for an individual patient does not exist. Having more possibilities will offer opportunities to look for the ideal regimen in every single patient that is a candidate for neuromodulation.

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