Prospective Study

Options: A Prospective, Open-Label Study of High-Dose Spinal Cord Stimulation in Patients with Chronic Back and Leg Pain

Ramsin Benyamin, MD[1], Vincent Galan, MD[2], John Hatheway, MD[3], Philip Kim, MD[4], Daniel Choi, MD[5], Steven Falowski, MD[6], Aaron Calodney, MD[7], Jennifer Sweet, MD[8], Cong Yu, MD[9], Leonardo Kapural, MD, PhD[10], and David Provenzano, MD[11]

From: [1]Millennium Pain Center, Bloomington, IL; [2]Pain Care, LLC, Stockbridge, GA; [3]Northwest Pain Care Inc., Spokane, WA; [4]The Center for Interventional Pain and Spine, Wilmington, DE; [5]Valley Pain Consultants, North Scottsdale, AZ; [6]St. Luke's University Health Network, Bethlehem, PA; [7]Precision Spine Care, Tyler, TX; [8]University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH; [9]Swedish Pain Services, Seattle, WA; [10]The Center for Clinical Research, Winston-Salem, NC; [11]Pain Diagnostics and Interventional Care, Sewickley, PA

Address Correspondence:
Ramsin Benyamin, MD
Millennium Pain Center
1015 S. Mercer Ave.
Bloomington, IL 61701
E-mail:
ramsinbenyamin@yahoo.com :

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Background: Therapeutic approaches to spinal cord stimulation (SCS) continue to evolve and improve patient outcomes in patients receiving SCS therapy secondary to failed back surgery syndrome.

Objectives: The aim of this study was to evaluate pain relief and other patient outcomes of SCS using selected high-dose programming parameters.

Study Design: This was a prospective cohort study.

Setting: This study took place at 11 centers in North America.

Methods: Forty-four SCS-naive patients underwent trialing, starting with 1,000 Hz frequency, 90 µs pulse width followed by 300 Hz frequency, 800 µs pulse width, if pain relief was inadequate. Patients with 50% or greater pain relief were eligible for permanent implantation. Patient's pain rating, global impression of change, health-related quality of life, functional disability, satisfaction/recommendation, stimulation perception, device programming, and adverse events were assessed at 3 months postimplant.

Results: There were significant improvements from baseline in mean Numeric Rating Scale (NRS-11) pain scores for overall pain (7.5 to 3.8; $P < 0.01$), back pain (7.2 to 3.4; $P < 0.01$), leg pain (7.2 to 3.1; $P < 0.01$), Oswestry Disability Index (ODI) score (51.5 to 32.1; $P < 0.01$), and European Quality of Life–Five Dimensions, version 5L score (EQ-5D-5L) (0.58 to 0.74; $P < 0.01$). Twenty-eight of 32 patients (88%) had significant, favorable improvement in Patient Global Impression of Change (PGIC). Eighty-four percent of patients were "satisfied," and 78.1% would "definitely" recommend SCS. Eighteen patients (56%) used 1,000 Hz frequency and 90 µs pulse width exclusively; these patients experienced mean NRS-11 overall pain score improvement of 4.7 points. Device-, therapy-, or procedure-related adverse events were experienced in 19 patients (40%, 19 of 48), and all events resolved without reoperation and were similar to those observed with traditional SCS systems.

Limitations: There was no active or sham comparator group, and therefore the reported effects may not be solely attributable to therapy effects and may be related to other, nonspecific effects of SCS.

Conclusions: Improvements in pain relief, PGIC, EQ-5D-5L, ODI, and patient satisfaction were all clinically relevant and statistically significant. Future studies are needed to understand how these high-dose parameters perform versus a standard comparator.

Key words: Spinal cord stimulation, high-frequency electrical stimulation, failed back surgery syndrome, neurostimulation, prospective, nonrandomized study

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Spinal cord stimulation (SCS) uses electrical pulses to activate or modulate the nervous system resulting in pain relief. Stimulation parameters (amplitude, pulse width, frequency, and electrode configuration) can be modified to provide patient-specific pain relief and comfort. Traditionally, pain relief with comfortable paresthesia has been achieved with parameters ranging from 40 to 80 Hz frequency and 300 to 450 μs pulse width (1). Recently, high frequency (10,000 Hz) SCS and high pulse width (1,000 μs) burst SCS have demonstrated the ability to provide further pain control in select patients (2-4).

Miller et al (5) hypothesized that high frequencies and wide pulse widths are programming approaches to increase charge delivery in SCS, and that multiple frequency and pulse width combinations deliver a high-dose therapy. Three single-center retrospective studies have explored different high-dose parameters and reported pain relief benefits with 409 Hz/409 μs, 1,200 Hz/200 μs, high frequency (300-1,200 Hz) and wide pulse width (200-800 μs) (6-8).

Stimulation at 1,000 Hz has also been suggested as a frequency that could be used in high-dose stimulation (5,9,10). Although this setting has been a therapy option since the development of rechargeable SCS systems, there has been little guidance on when and how to use this type of high-dose setting. Two recent studies tested 1,000 Hz in patients with prior conventional low-dose therapy (11) and in patients after a traditional low-dose stimulation trial (12) with reported outcomes of no more than 4 weeks.

Options is the first study to test high-dose therapy starting at 1,000 Hz in patients naive to SCS therapy. The study objective was to evaluate whether high-dose SCS could provide pain relief and other patient benefits in patients with failed back surgery syndrome (FBSS). The results from temporary trialing through 3 months postsystem implantation are reported.

Methods

Study Design and Patient Selection

This open-label, prospective, multicenter study evaluated high-dose SCS programming parameters with adaptive stimulation in the management of chronic, intractable pain of the trunk and limbs secondary to FBSS, the most common indication for SCS. Eleven North American sites enrolled patients in accordance with the Declaration of Helsinki ethical principles, Good Clinical Practices, principles of informed consent, and public clinical trial registration at www.Clinicaltrials.gov, NCT02503787. All patients were naive to high-dose parameters and followed an algorithm to trial high-dose SCS. Each investigator obtained approval from an institutional review board and followed a process to secure written informed consent from each patient.

Major inclusion criteria were:

- Candidates for SCS system (trial and implant) per labeled indication
- Baseline diary completed for a minimum of 5 days
- Baseline diary-reported average Numeric Rating Scale (NRS-11) ≥ 5 for overall pain

Major exclusion criteria were:

- Enrolled in any concurrent drug or device study with potential to confound results
- Psychological or health concerns that may preclude participation or confound results
- Prior exposure to stimulation therapy or intrathecal drug delivery
- Implanted cardiac device

Study visits were screening, baseline, trial, implant, device activation, AdaptiveStim technology activation, 1-month, 1.5-month telephone call, 2-month, 2.5-month telephone call, and 3-month (Medtronic, Minneapolis, Minnesota). The trialing system consisted of 2 percutaneous leads (Model 977D260 Vectris 1 x 8 Compact Trialing Lead, Medtronic, Minneapolis, Minnesota) and an external neurostimulator (Model 37022 external neurostimulator, Medtronic, Minneapolis, Minnesota). The implantable SCS systems consisted of 2 percutaneous leads (Models 977A260, 977A275, or 977A290 Vectris SureScan MRI 1 x 8 Compact, Medtronic, Minneapolis, Minnesota) and an implantable rechargeable neurostimulator (Model 97714 RestoreSensor, SureScan MRI, Medtronic, Minneapolis, Minnesota). Leads were placed into the thoracic epidural space to optimize paresthesia coverage.

Trialing

At baseline, enrolled patients completed a 7-day NRS-11 pain diary. Patients with a mean NRS-11 ≥ 5 were eligible for the trial, during which temporary leads and an external neurostimulator provided stimulation for up to 10 days. The trial began using 1,000 Hz frequency and 90 μs pulse width, with amplitude adjusted to patient comfort, the lowest level of stimulation described as comfortable by the patient. If not successful by day

4, the settings were changed to 300 Hz frequency and 800 μs pulse width. A successful trial was defined as a 50% or greater improvement in overall pain (back and leg), and those who did not respond were exited from the study.

Permanent Implant

The successful trial settings were programmed at the device activation visit, 9 to 12 days postimplant, and patients were followed for 3 months. AdaptiveStim technology was activated in all 6 positions approximately 4 weeks postimplant, when the implanted components were sufficiently stabilized for orientation. This technology holds the stimulation sensation constant as the patient changes position. Previous research has shown that use of this technology results in increased patient convenience and/or pain relief when used with low-dose parameters (13).

Follow-Up

During the follow-up period, programming parameters were changed if a 2-point reduction in overall pain scores was not maintained (14). Acceptable programming parameters were 1,000 Hz, 90 μs; 300 Hz, 800 μs; 1200 Hz, 200 μs; or 500 Hz, 500 μs. The number of active electrode contacts was not restricted. Prescription and over-the-counter pain medication changes were documented via protocol deviations (increased, decreased, discontinued, started). Patients were closely followed including telephone contact at 1.5 months and 2.5 months to assure adequate pain relief was maintained. Record completion and accuracy were actively monitored at each site at regular intervals.

Primary Objective

The primary objective evaluated average overall (back and leg) pain scores from baseline to the 3-month visit using the NRS-11, an 11-point scale from 0 to 10 with 0 meaning "no pain" and 10 meaning "worst pain imaginable" (15). Patients recorded their pain scores in a paper diary once daily for 7 days prior to each visit (16,17).

Statistical Analysis

The intention-to-treat population was the main analysis population for the primary and secondary objectives and was defined as all patients who received a full system implant and whose implanted devices were successfully programmed to high dose at the device activation visit. If no diary days were available for the 3-month diary, a last observation carried forward (LOCF) imputation was applied. All assessments were tested for statistical significance comparing baseline to 3-month visit data using 2-sided t tests at an alpha level of 0.05 with no adjustments for multiplicity. The planned sample size was 30 patients, to provide 94% power to detect a change in the diary-reported average NRS-11 for overall pain from baseline to the 3-month visit of a clinically significant effect of 2.0 points (14), assuming the within-patient standard deviation (SD) for change in pain of 3.0 and a 2-sided significance level (alpha) of 0.05. The estimate of clinically significant difference in change in NRS-11 was based on the summary of 10 placebo-controlled trials in 2,724 patients (14).

Secondary Objective

The secondary objective assessed the patient's global impression of change since beginning treatment using the Patient Global Impression of Change (PGIC) (18), which reflects change in 4 domains: activity limitations, symptoms, emotions, and overall quality of life. Patients rate change on a 7-point scale in which 1 means "no change (or worsening)" and 7 means "a great deal better." A significant, favorable change is a response within the top 3 levels (a great deal better, better, or moderately better).

Additional Outcome Measures

Additional endpoints were measured from baseline to the 3-month visit:

- Back and leg pain intensity using the diary-reported NRS-11
- Health-related quality of life using the European Quality of Life–Five Dimensions, version 5L (EQ-5D-5L) (19)
- Functional disability using the Oswestry Disability Index (ODI) version 2 (20)

Back and leg pain intensity were reported once daily for 7 days prior to each visit, in the same manner as the primary endpoint.

EQ-5D-5L is a standardized, validated measure of health-related quality of life whose index considers 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of problem severity: no problems, slight, moderate, severe, or extreme problems. The patient selects the most appropriate statement in each di-

mension; responses are combined into a single index value ranging from 0 (worst) to 1 (best) describing the respondent's health state. The utility score is based on the United States value set.

The ODI is a validated questionnaire consisting of 10 patient-reported sections on the functional ability to perform activities of daily living. The minimum score category is 0% to 20% and indicates "minimal disability" or minimal limitations due to pain, whereas the maximum score category is 81% to 100% and indicates "bed-bound patients."

Patient satisfaction questions ranked the patient's willingness to recommend the therapy and satisfaction with the therapy. Stimulation sensation questions, asked at each visit, solicited information on (1) whether paresthesias are felt; (2) if felt, how often; and (3) if felt, the degree to which the sensation was liked or disliked. In addition, device descriptive characteristics (e.g., lead placement configuration and perception threshold, stimulation programming, system configuration, and implant to trial ratio) were also evaluated.

Safety

Device- or therapy-related adverse events and device deficiencies were monitored from trial lead implant through the 3-month visit.

Results

Demographics

From July 22, 2015 to February 5, 2016, 64 patients were enrolled; their mean age was 57.5 years, mean overall pain was 7.6, mean back pain was 7.4, and mean leg pain was 7.1. Baseline demographics and characteristics of enrolled patients and device-activated patients are summarized in Table 1.

Table 1. *Baseline demographics and characteristics.*

Variable	Enrolled Patients Mean (SD) (n = 64)	Device Activated Patients Mean (SD) (n = 32)
Age in years	57.5 (12.9)	56.0 (11.9)
Gender	34 (53%) female 30 (47%) male	19 (59.4%) female 13 (40.6%) male
Mean NRS-11 overall	7.6 (1.0)*	7.5 (0.9)
Mean NRS-11 back	7.4 (1.4)*	7.2 (1.2)
Mean NRS-11 leg	7.1 (1.7)*	7.2 (1.3)
Mean EQ-5D-5L index	NA	0.58 (0.15)
Mean ODI	NA	51.5 (11.3)

NA, not available.
*n = 53.

Forty-four patients began the at-home trial with stimulation parameters programmed to 1,000 Hz and 90 μsec with amplitude adjusted to patient comfort, and 11 of those also tried 300 Hz and 800 μsec. Patient disposition by visit and reasons for discontinuation are provided in Fig. 1. At the end of the trial, 37 of 44 (87%) patients experienced 50% or greater pain relief, although 5 of these chose not to proceed to permanent implantation. The implant to trialing ratio was 32 of 44 (72%).

Thirty-two patients proceeded to permanent system implant, 28 with successful trial stimulation parameters of 1,000 Hz and 90 μsec, and 4 with 300 Hz and 800 μsec. Patients received Model 977A260 leads (n = 29) or Model 977A275 leads (n = 3). Patients' lead tips were level (both lead tips were positioned over the same disc level) in 17 patients, and staggered (lead tips were staggered over more than one vertebral disc level) in 5. Lead tip location ranged from T7 to T10. Lead tips were at T8 or T9 in 19 patients (62.5%).

Primary Objective: Overall Pain

Twenty-nine patients provided complete data through 3 months. In an intent-to-treat analysis and using the LOCF method for missing data, 3 additional patients, who exited before the 3-month visit, also contributed data for this analysis, with all 3 classified as nonresponders. All patients completed at least 5 of 7 diary days. In the 32 patients analyzed, there was a statistically significant decrease in mean overall pain score from 7.5 at the baseline visit to 3.8 at the 3-month visit ($P < 0.01$), a mean improvement of 3.7 points (95% confidence interval, 2.8-4.5) as shown in Fig. 2. The primary objective was met. Pain scores decreased at least 2 points in 23 of 32 (72%) patients, and at least 3 points in 22 of 32 patients (69%).

Secondary Objective: PGIC

Patients rated their change in status since the beginning of treatment using the PGIC. Patient ratings were a great deal better (n = 10), better (n = 12), moderately better (n = 6), somewhat better (n = 1), a little better (n = 1), almost the same (n = 2), and no change or worse (n = 0). Twenty-eight of 32 patients (88%) reported a significant, favorable change.

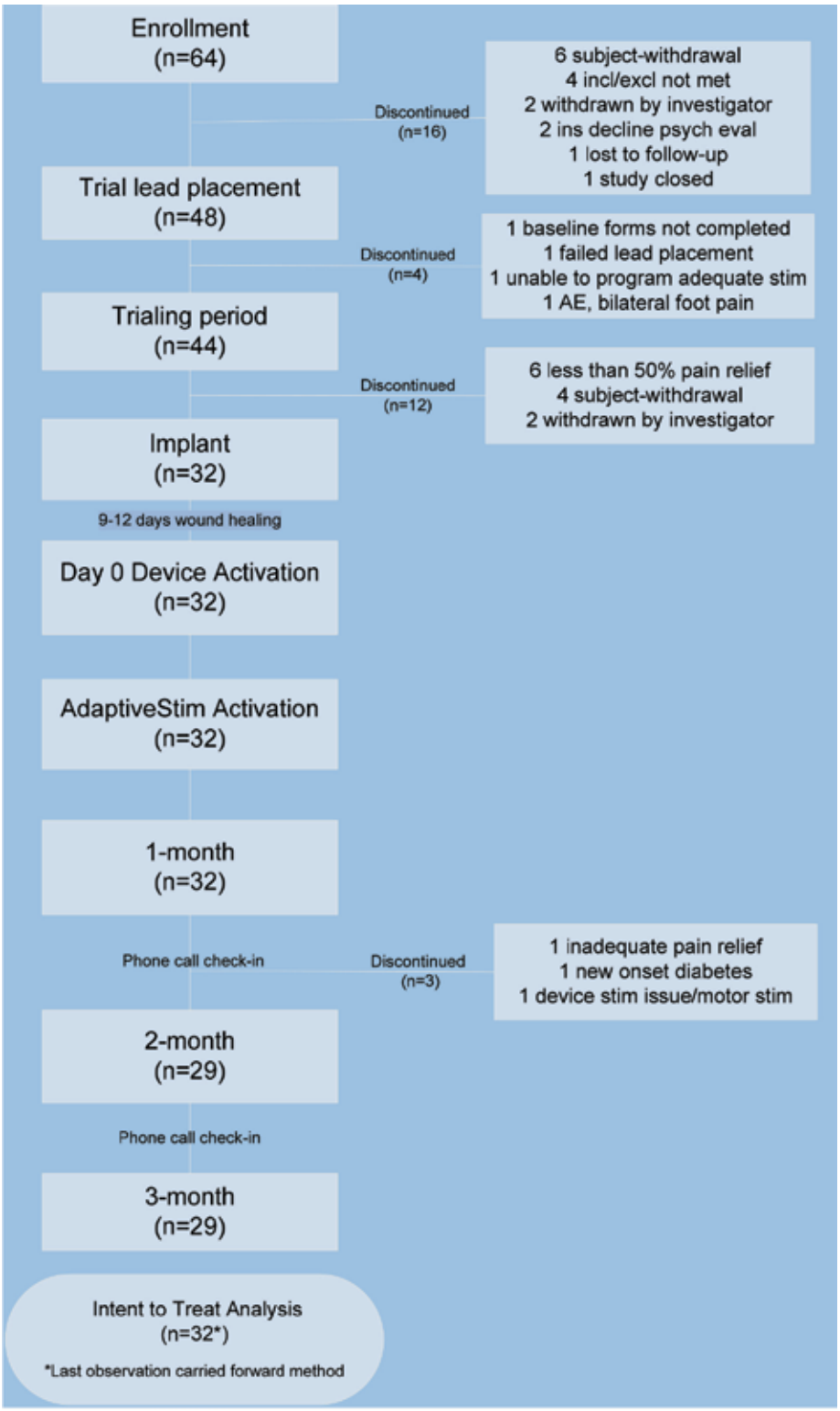

Fig. 1. *Patient disposition.*

Additional Outcome Measures

Back and Leg Pain

Back and leg pain scores showed improvement from baseline, 52% and 54%, respectively. There was a statistically significant decrease in mean (SD) back pain score from 7.2 (1.2) to 3.4 (1.9) ($P < 0.01$), a mean improvement of 3.8 (2.0) points. Similarly, there was a statistically significant decrease in leg pain score from a mean (SD) of 7.2 (1.3) to 3.1 (2.3) ($P < 0.01$), a mean improvement of 4.1 (2.7) points.

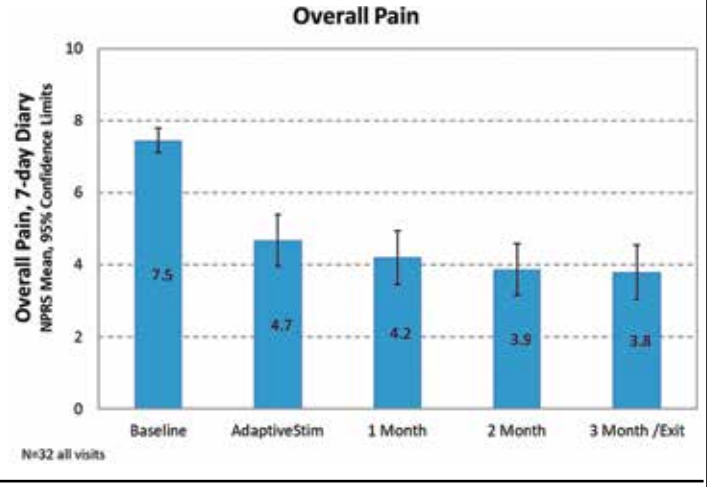

Fig. 2. *Mean overall pain score across visits. NPRS, Numeric Rating Scale.*

EQ-5D-5L

At baseline, the mean (SD) EQ-5D-5L index was 0.58 (0.15) and improved to 0.74 (0.13) at 3 months ($P < 0.01$), an improvement of 0.16 from baseline. There was a statistically significant improvement in mean health quality index from baseline to 3 months.

ODI

Mean (SD) ODI improved 19.4 (17.2) points from baseline to 3 months, from 51.5 to 32.1 ($P < 0.01$). At baseline, 20 patients' disability was in the category of "severe," 5 in "crippled," and 7 in "moderate" or "minimal." At 3 months (or discontinuation), 6 patients' disability category was "severe," 1 was "crippled," and 25 were in "moderate" or "minimal." The ODI results by visit and category are summarized in Fig. 3. There was a statistically significant improvement in mean disability index from baseline to 3 months.

Additional Evaluations

At 3 months, 28 of 32 patients (88%) would recommend this therapy to a patient suffering from pain like theirs, and 27 patients (84%) were satisfied with the therapy.

At any visit, from 66% to 75% of patients reported feeling a sensation of electrical stimulation. Combining the 4 follow-up visits, among patients who reported feeling a sensation of electrical stimulation, 60% felt it at

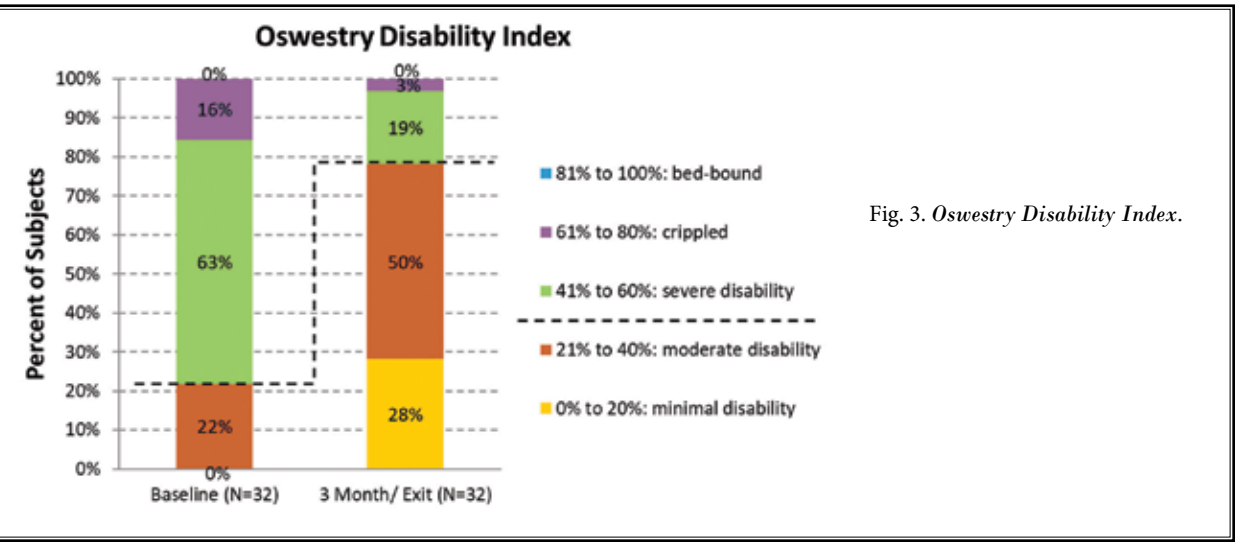

Fig. 3. *Oswestry Disability Index.*

least daily or several times a day. Among those patients, 36% liked it very much, 28% liked it a little, 14% were not sure, 18% disliked it a little, and 4% disliked it very much. Results are provided in Fig. 4.

Safety

Overall, there were no deaths or unanticipated adverse events reported. One serious, adverse device effect was reported in a patient who experienced bilateral foot pain immediately following temporary trial lead placement. The leads were immediately removed, and a magnetic resonance imaging scan with contrast medium was performed the same day without any significant findings. The event resolved without sequelae within 2 days. This adverse event was categorized as serious due to hospitalization for 2 days.

Of 48 patients who underwent trial lead procedures, 24 (50%) experienced one or more nonserious adverse events, with uncomfortable stimulation in 7 (15%) patients and implant site warmth in 5 (10%) patients being the most frequently reported. The remaining events were experienced in 3 or fewer patients. Events resolved with reprogramming or no further action. No permanent leads or neurostimulators were explanted or replaced. All adverse events are provided in Table 2.

Device deficiencies, product issues with or without associated patient symptoms, were also reported. Of 32 permanently implanted patients, 6 (19%) experienced beeping/unresponsive rechargers or external device breakage, 5 (16%) reported difficulty with the recharge process requiring retraining, 2 (6%) reported device use error of inadvertently turning stimulation OFF, one (3%) experienced a stuck programmer key that the patient resolved without assistance, and one (3%) experienced repeated motor stimulation that could not be resolved through reprogramming, and exited the study to try conventional stimulation; this final event was also reported as an adverse event of "device stimulation issue" and "pain (back and leg)."

Programming

Trialing parameters were either 1,000

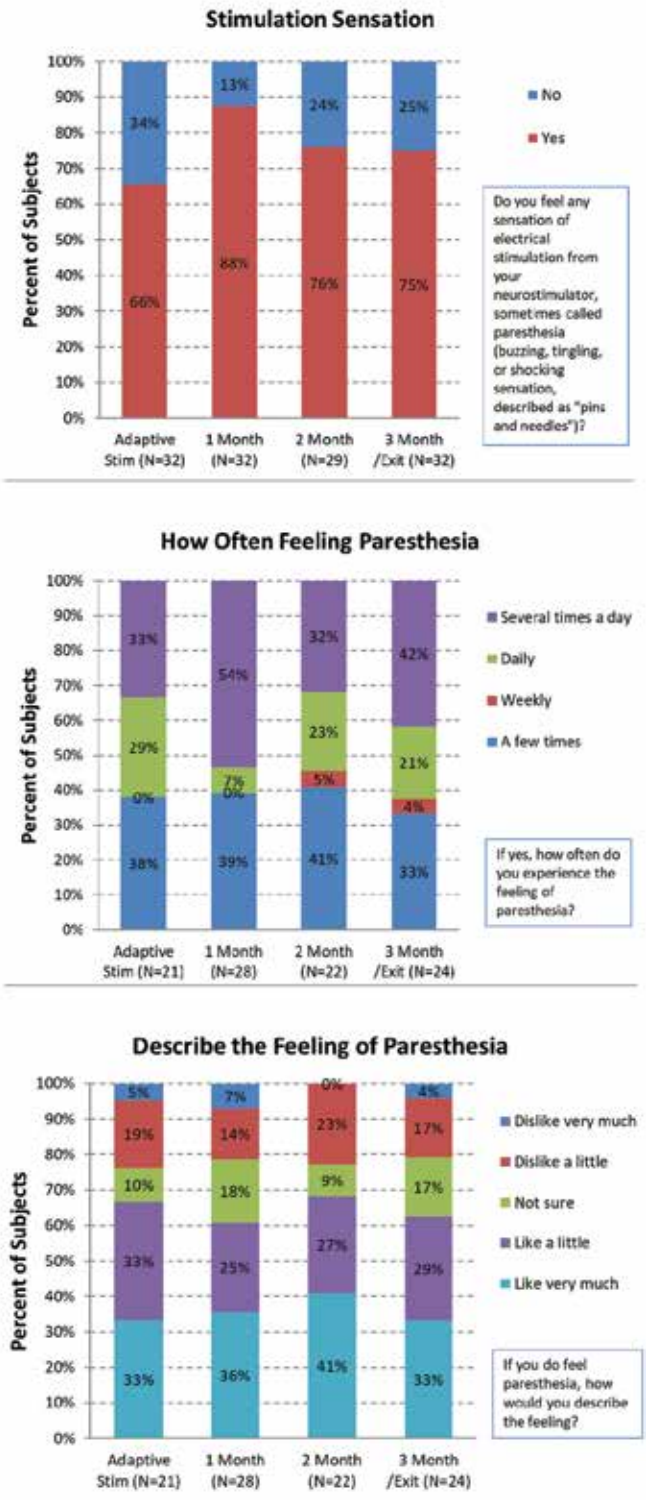

Fig. 4. *Stimulation sensation questionnaire.*

Table 2. *All adverse events (device-, therapy-, or procedure-related).*

MedDRA Preferred Term	Serious Adverse Events	Adverse Events	Patients with Adverse Event	Percent of Patients with Adverse Event (n = 48)
Paresthesia	.	9	7	15%
Implant site warmth	.	5	5	10%
Pain (back and leg)	.	3	3	6%
Pain in extremity	1*	3	3	6%
Device stimulation issue	.	3	2	4%
Back pain	.	2	2	4%
Cerebrospinal fluid leakage	.	2	2	4%
Implant site pain	.	2	2	4%
Implant site pruritus	.	2	2	4%
Hypoesthesia	.	1	1	2%
Implant site bruising	.	1	1	2%
Implant site cellulitis	.	1	1	2%
Implant site dermatitis	.	1	1	2%
Implant site irritation	.	1	1	2%
Incision site infection	.	1	1	2%
Incision site pain	.	1	1	2%
Muscle spasms	.	1	1	2%
Total	**1**	**39**	**19**	**40%**

*Bilateral foot pain occurred on trial lead implant. Leads were removed, and event resolved within 2 days.
MedDRA, Medical Dictionary for Regulatory Activities.

Table 3. *Programming sequences: Device activation to study exit.*

Rate [Hz] / Pulse Width [μs]	Number of Patients	Percent of Patients
1,000/ 90	19*	59%
90/ 1,000† --> 300/ 800	1	3%
1,000/ 90 --> 300/ 800 --> 500/ 500	1	3%
1,000/ 90 --> 300/ 800 --> 1,200/ 200	1	3%
1,000/ 90 --> 1,200/ 200	1	3%
1,000/ 90 --> 1,200/ 200 --> 500/ 500	3	9%
1,000/ 90 --> 1,200/ 200 --> 500/ 500 --> 800/ 300	1	3%
1,200/ 90‡ --> 1,000/ 90 --> 500/ 500	1	3%
300/ 800 --> 1,200/ 200	1	3%
300/ 800 --> 1,200/ 200 --> 500/ 500	1	3%
300/ 800 --> 1200/ 200 --> 1200/ 180 --> 500/ 500	1	3%
800/ 300§ --> 300/ 800 --> 1200/ 200 --> 500/ 500	1	3%
Total	**32**	

* 1 patient discontinued prior to the 3-Month Visit
** Deviation at Device Activation Visit. Device reprogrammed at AdaptiveStim Visit
† Deviation at Device Activation Visit, reprogrammed 2 days later to 1000 Hz and 90 μsec
†† Deviation at Device Activation Visit, reprogrammed 7 days later to 300 Hz and 800 μsec

Hz and 90 μsec or 300 Hz and 800 μsec. Table 3 displays the unique programming sequences that were used during the study and the number of patients who followed that sequence. From the device activation visit to study exit, 59% (19 of 32) of patients used only 1,000 Hz, 90 μsec. Of those, one patient discontinued prior to the 3-month visit and 18 patients experienced a mean NRS-11 improvement in overall pain of 4.7 points at 3 months. The remaining 13 patients experienced 2 (n = 3), 3(n = 7), or 4 (n = 3) sets of different parameters. Analysis of pain scores in these small subgroups of patients showed a trend toward diminishing pain relief as the number of changes increased.

Device programmer reports provide the percentage of time stimulation has been ON since the previous visit. The usage data are skewed, with most patients having high usage and a few with low usage. Thus median percent usage is more representative of therapy exposure. At 3 months, the median percent usage was 87%, and 24 of 29 patients (83%) reported over 50% usage. Table 4 summarizes ON-time.

Stimulation was adjusted to the patient's preferred, comfortable level. Perception thresholds, the level of stimulation at which a patient first perceives paresthesias, and comfort thresholds, the lowest level of stimulation described as comfortable by the patient, are summarized in Table 5. Regardless of the parameters used, comfort amplitude was usually lower than perception amplitude. The median difference from perception to comfort ranged from 0.1 to 0.3 V for all parameters programmed.

Recharging

The median number of recharge sessions per day was 1.3, and the median duration of each session was 1.5 hours, with 81% of patients recharging on average one or more times per day. The maximum average recharge frequency, reported in one patient, was 3.3 times a day. Lead

systems used on average 4 to 5 active electrodes within each system, with 7 patients using a single bipole of one positive and one negative electrode contact for some period of time during the study. Recharging frequency was influenced by the substantial number of patients with multiple active electrode contacts. Table 6 summarizes the recharge session frequency and duration.

Discussion

The options study showed that the high-dose parameters studied can provide clinically meaningful and statistically significant improvements in overall pain scores in patients with chronic, intractable pain secondary to FBSS. In addition to pain relief, the secondary objective was met with 88% of patients reporting a significant, favorable change in PGIC. All additional measurements were favorable with patients also experiencing improvements in back pain, leg pain, health-related quality of life, and functional disability. There was high patient satisfaction with the therapy, and patients would recommend it to others.

Most patients (76%) reported feeling the stimulation at least once daily and liked the stimulation sensation, when recalling their stimulation experience over time. When comparing comfortable stimulation to stimulation perception thresholds within the office setting, comfortable stimulation was often below perception thresholds. This may be consistent with Abejon et al (21), who reported on stimulation perception thresholds, therapy thresholds, and discomfort thresholds in patients exposed to SCS frequencies ranging from 40 Hz to 1,200 Hz. They found that the therapeutic range between perception and discomfort threshold narrows considerably at higher frequencies, suggesting less room for amplitude titration after reaching perception threshold. Their patients also reported dissatisfaction with frequencies

Table 4. *Time on stimulation: Percent usage.*

Study Visit	N Patients	Mean	SD	Minimum	Median	Maximum
AdaptiveStim	32	78%	25%	21%	87%	100%
Month 1	32	78%	22%	25%	83%	100%
Month 2	28	80%	23%	18%	86%	100%
Month 3	29	78%	26%	15%	87%	100%

Table 5. *Threshold testing at final programming parameters.*

Rate = 1,000 Hz, PW = 90 µs		Supine Amplitudes, V		
Study Visit	Patients N	Perception Median	Comfort Median	Median of Differences*
Trial day 1	45	2.6	2.7	0.2
Device activation	26	3.3	2.9	0.2
AdaptiveStim	26	3.6	3.3	0.3

Rate = 300 Hz, PW = 800 µs		Supine Amplitudes, V		
Study Visit	Patients N	Perception Median	Comfort Median	Median of Differences*
Trial day 4	11	1.3	1.2	0.1
Device activation	3	1.7	1.6	0.3
AdaptiveStim	5	2.8	2.6	0.3

Rate = 1,200 Hz, PW = 200 µs		Supine Amplitudes, V		
Study Visit	Patients N	Perception Median	Comfort Median	Median of Differences*
Month 1	9	3.9	3.6	0.3

Rate = 500 Hz, PW = 500 µs		Supine Amplitudes, V		
Study Visit	Patients N	Perception Median	Comfort Median	Median of Differences*
Month 2	4	1.9	1.6	0.3

Visits and/or settings with at least 3 samples are included.
*Perception minus comfort was calculated for each patient, and then the median of those differences was found.

Table 6. *Recharging.*

Measure	N Programmer Reports	Mean	SD	Minimum	Median	Maximum
Recharge sessions, number per day	125	1.6	0.9	0.03	1.3	6.2
Typical duration, hours	125	1.6	1.2	0	1.5	11.1

above 900 Hz, describing the sensation as "poor." This may explain why patients in the current study tended to prefer amplitudes at or below perception threshold.

Learnings from this study will be applied to additional studies. First, multiple active electrodes contacts are a major contributor to energy drain (22) and the number of active electrode contacts was not restricted in this study. The average number of active electrode contacts was 4 to 5, and many patients recharged daily. Second, there was no protocol or instruction about amplitude, except that it should be comfortable to the patient. Comfortable stimulation was sometimes above the perception threshold and sometimes below, with most patients (76%) reporting feeling stimulation paresthesias at some point. Third, more information is needed about how frequently programming changes are needed. This study was designed to offer multiple programming options, but 18 of 32 (56%) patients needed only 1,000 Hz and 90 μs, the first settings offered during the trial screening period. For this group of 18 patients, the mean improvement in overall pain was 4.7 points, a 60.7% improvement from baseline. The remaining patients changed settings once or twice in the same period (3 months).

The next study, already underway, is investigating the relationship between amplitude and pain relief. Another study is testing a bipole, one active positive and one active negative, electrode contact. Other methods to affect recharge burden include employing the cycling feature, combining high- and low-dose programming, reducing guarded electrode arrays, and using newer neurostimulators with faster recharge ability should also be investigated.

The safety profile of SCS is well established, and this study did not identify any new events.

Limitations

As with all clinical studies, there are limitations to consider. There is no active or sham comparator group, and therefore the reported effects may not be solely attributable to therapy effects and may be related to other, nonspecific effects of SCS. Future studies are needed to understand how these high-dose parameters perform versus a standard comparator. High-dose settings were not changed if successful, and most of the patients who started on 1,000 Hz and 90 μs parameters also ended the study on the same parameters, limiting information on other parameter combinations. The follow-up time of 3 months was relatively short, and a longer observation period is desirable. The LOCF method for handling missing data is only appropriate as a first-line analysis method, and in this study 3 imputations were made with all 3 classified as nonresponders. Finally, the programming goal was to achieve adequate pain relief, defined as a 2-point reduction in NRS-11; therefore additional work is needed to identify optimal programming.

Conclusions

The primary efficacy endpoint showed improvement in the mean overall pain score at 3 months compared with baseline. The magnitude and stability of these improvements indicate a clinically significant effect of high-dose stimulation on overall back and leg pain. Back and leg pain each individually showed improvement from baseline as well.

Changes in additional efficacy measures support the observed effects on pain. The patients' overall impression of change (secondary objective variable), as measured using the PGIC, showed 88% of patients reported a significant, favorable change. Patient satisfaction (84% satisfied) and willingness to recommend the therapy to others (88%) were similarly high. Quality of life (via the EQ-5D-5L) improved 0.16 points, and patient disability (via the ODI) improved 19 percentage points, both clinically meaningful improvements.

Although questions remain regarding the role of paresthesia, the safety profile reported in the options study was consistent with the safety profile in current SCS labeling. Patients in this study experienced improvements in pain relief, global impression of change, functional disability, quality of life, and satisfaction with high-dose parameters.

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Conflict of interest

None of the physician authors received funding or reimbursement for their work on this publication. Dr. Benyamin is a consultant for Medtronic, Vertos Medical, and Vertiflex. Dr. Galan has received research grants from Medtronic, NEVRO, Vertiflex, Neuros, St. Jude (Abbott), Archimedes Pharmaceutical, and GW Pharma. Dr. Hatheway is a consultant for Medtronic and is involved with clinical research for Medtronic and Biotronik. Dr. Kim is a consultant for Biotronik, Medtronic, Jazz, and Collegium. Dr. Choi declares no conflicts of interest. Dr. Falowski is a consultant for Abbott, Medtronic, Nevro, and Saluda and receives research support from Medtronic, Nuvectra, and Abbott. Dr. Calodney is a consultant and conducts research for Medtronic, Stimwave, SI Bone, Stryker, a consultant and speaker for Nevro, a speaker for Apex Biologix, and conducts research for Boston Scientific. Dr. Sweet receives grant support from National Institutes of Health, and she served as an advisory board member for Helius Medical Technologies, for which she received stock options. Dr. Yu is a consultant for Medtronic. Dr. Kapural is a consultant for Biotronik, Halyard, Nevro, Sollis, Abbott, Gimer, Nalu, Vertiflex, and Best Doctors. He receives research support from Neuros, Nevro, Stimwave, Boston Scientific, Halyard, SPR Therapeutics, and Saluda. Dr. Verdolin is a consultant for Medtronic. Helen Berrier and Tim Brelje are employees of Medtronic. Dr. Provenzano is a consultant for Bioness, Biotronik, Boston Scientific, Halyard, Medtronic, Nevro, Sollis, and Abbott. He receives research support from Medtronic and Abbott.

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