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A Novel Pulsed Stimulation Pattern in Spinal Cord Stimulation: Clinical Results and Postulated Mechanisms of Action in the Treatment of Chronic Low Back and Leg Pain

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ABSTRACT

Objectives: The aim of this article is to discuss the possible mechanisms of action (MOAs) and results of a pilot study of a novel, anatomically placed, and paresthesia-independent, neurostimulation waveform for the management of chronic intractable pain.

Materials and Methods: A novel, multilayered pulsed stimulation pattern (PSP) that comprises three temporal layers, a Pulse Pattern layer, Train layer, and Dosage layer, was developed for the treatment of chronic intractable pain. During preliminary development, the utility was evaluated of anatomical PSP (aPSP) in human subjects with chronic intractable pain of the leg(s) and/or low back, compared with that of traditional spinal cord stimulation (T-SCS) and physiological PSP. The scientific theory and testing presented in this article provide the preliminary justification for the potential MOAs by which PSP may operate.

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Results: During the pilot study, aPSP ($n = 31$) yielded a greater decrease in both back and leg pain than did T-SCS (back: −60% vs −46%; legs: −63% vs −43%). In addition, aPSP yielded higher responder rates for both back and leg pain than did T-SCS (61% vs 48% and 78% vs 50%, respectively).

Discussion: The novel, multilayered approach of PSP may provide multimechanistic therapeutic relief through preferential fiber activation in the dorsal column, optimization of the neural onset response, and use of both the medial and lateral pathway through the thalamic nuclei. The results of the pilot study presented here suggest a robust responder rate, with several subjects (five subjects with back pain and three subjects with leg pain) achieving complete relief from PSP during the acute follow-up period. These clinical findings suggest PSP may provide a multimechanistic, anatomical, and clinically effective management for intractable chronic pain. Because of the limited sample size of clinical data, further testing and long-term clinical assessments are warranted to confirm these preliminary findings.

Keywords: Chronic pain, mechanism of action, persistent spinal pain syndrome, pulsed stimulation pattern, spinal cord stimulation

Conflict of Interest: Mehul J. Desai consults for Avanos, Nalu, SPR Therapeutics; receives research support from Abbott, Avanos, Averitas, Mainstay, Nalu, Nature Cell, Saol, SPR Therapeutics, and Vivex; and owns stock options in SPR Therapeutics, SynerFuse, and Virdio. Girish Vajramani, Adam Williams, Nikunj Patel, Bruce Mitchell, Neels Du Toit, Serge Nikolic, Alia Ahmad, Nick Christellis, and Sam Harkin reported no conflict of interest. Lakshmi Mishra, Melissa Hartley, and Shilpa Kottalgi are employees of Nalu Medical, and hold nonexercisable stock options in the company. Nicholas Sullivan was an employee of Nalu Medical but is no longer employed by Nalu as of date of publication. John Salmon consults for Abbott, Nevro, and Saluda. Paul Verrills consults for Abbott, Nalu Medical, Biotronik, and Saluda; and owns stock options in Nalu Medical. Sarah Love-Jones serves on the MAB for Boston Scientific, Nevro, Medtronic, and Mainstay Medical. She reports honoraria, travel assistance and research funding from Nevro, Boston Scientific, Saluda, Mainstay Medical, and Abbott. She reports research funding from Nalu Medical and honoraria/travel assistance from Pfizer and Medtronic. Dan Bates owns stock options with, and has received travel support from, Nalu Medical. Vivek Mehta consults for Boston Scientific and serves as Chief Investigator for Investigator Initiated Studies for Boston Scientific, Medtronic, and Mainstay Medical. He reports honorarium and travel support from Boston Scientific, Medtronic, and Mainstay Medical. James Yu reports payments for review of a clinical evaluation plan and report from Nalu Medical. Robert Levy owns stock options with Nalu Medical and Saluda. Peter Staats consults for Nalu Medical, SPR Therapeutics, AIS Healthcare, Medtronic, and Saluda; serves as the CMO for National Spine and Pain Centers and electroCore; and owns stock options in Nalu Medical. James Makous owns stock options in Nalu Medical and consults for Nalu Medical and ReStalsis Health. Ganesan Baranidharan has a consulting agreement and is on the advisory board for Nevro, Nalu, Abbott, and Boston Scientific. Mark N. Malinowski consults for Nalu Medical and SI Bone, Inc; reports equity in PrescribeFIT LLC; conducts research with Abbott Laboratories; serves on the Medical Advisory Board and consults for Biotronik.

INTRODUCTION

Spinal cord stimulation (SCS) is widely used for the treatment of chronic pain of various origins. On a fundamental level, SCS involves generating electrical fields between contacts on leads placed in the epidural space to affect and disrupt ascending signals from the periphery. Various mechanisms of action (MOAs) have been proposed to explain the analgesic effect of SCS since the first implementation of traditional SCS (T-SCS) for chronic pain in 1967.[1] Melzack and Wall's[2] gate-control theory of pain proposed that the perception of pain is modulated by the opening and closing of an interneuron "gate" through summation of neural activation in the dorsal column of the spinal cord, and served as the foundation and mechanistic rationale for both spinal and peripheral nerve stimulation.[1] Linderoth and Foreman[1,3] elaborated on this theory by proposing that stimulation of larger, myelinated axon collaterals branching from primary sensory neurons in the dorsal columns produces antidromic action potentials that modulate neurons in the dorsal horn. This impact on neurons in the upper dorsal horn laminae is thought to create the "gating" effect and inhibition of nociceptive pain signals through the wide dynamic range and other phenotypic neuronal subtypes.[3,4] Although the gate-control theory continues to influence even the most recent SCS applications, it does not explain the complexity of pain modulation on a neurophysiological or perceptual level.[1]

T-SCS delivers constant, uniform, pulses repeated at fixed intervals, with typical frequency ranges of 40 to 100 Hz and pulse widths commonly of 200 to 500 µs. Until approximately ten years ago, this paradigm was the predominant waveform.[1] T-SCS is delivered at a suprathreshold amplitude to elicit paresthesia that overlaps regions of pain. Recently, paresthesia-independent stimulation paradigms have become more prominent because paresthesia may not be well tolerated by some subjects and may interfere with certain activities (such as driving) owing to the risks associated with the sudden changes in posture.[1,5]

Despite expanding neurostimulation treatment options, pain remains a complex problem with multiple potential underlying mechanisms. Therefore, treatment options that address multiple MOAs with a unique multilayered waveform(s) may have improved benefits over therapies with single mechanisms of action.

Novel Waveform

The pulsed stimulation pattern (PSP) family of waveforms is composite signals created by layering specific temporal patterns (Pulse Patterns, Trains, and Dosages) in a hierarchical pyramidal structure (Fig. 1). Each independently configurable layer of the PSP waveform targets a different MOA to afford greater potential to achieve customized, optimal pain relief for each patient. The Pulse Pattern layer operates with the finest granularity of the three layers

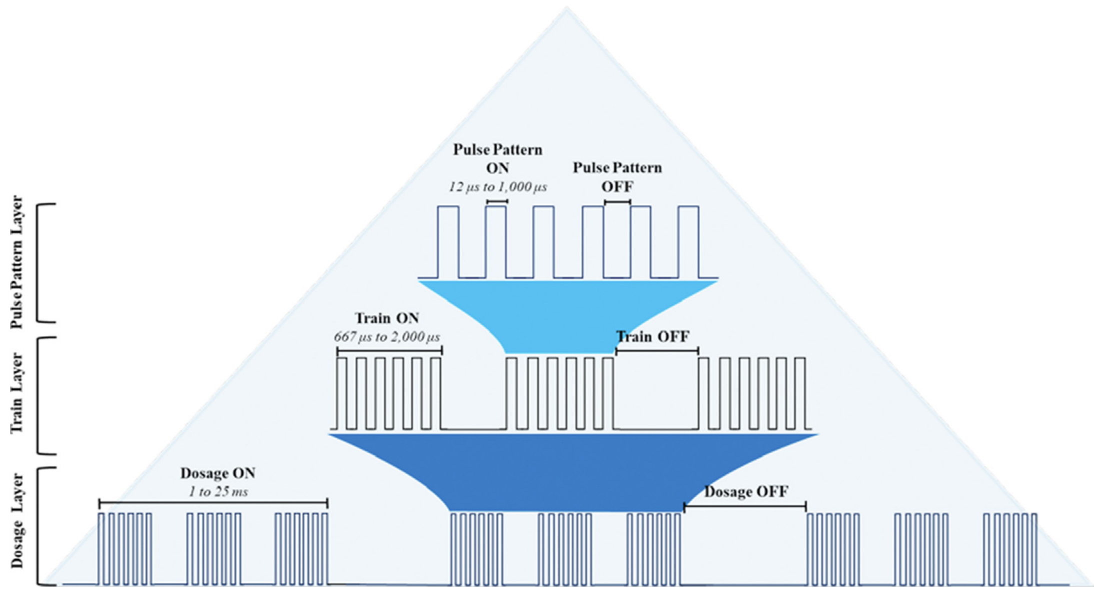

Figure 1. Pulsed Stimulation Pattern waveform structure comprised of three layers in descending hierarchical order. The train layer and subsequent Pulse Pattern layer are magnified for visualization with the timescale of each layer. [Color figure can be viewed at www.neuromodulationjournal.org]

and comprises uniform, repeating periods of stimulation and quiescence. The stimulation period is set by configuring the Pulse Pattern ON parameter, and the quiescent period is configured by setting the Pulse Pattern OFF parameter, both independently programmable between 12 μs and 1000 μs. The Train layer modulates the Pulse Pattern layer and is the next level of the PSP pyramid. It defines sequences of stimulation "trains" during which the underlying Pulse Pattern is repeated. Train ON controls the time in which the Pulse Pattern will be applied and is programmable between 667 μs and 2000 μs. Train OFF controls the quiescent period between Pulse Patterns. The Dosage layer, the final level of the PSP pyramid, imposes a periodic ON and OFF mechanism on the underlying Pulse Pattern and Train layers. In the Dosage ON state, the Pulse Pattern and Train layers are active, and in the Dosage OFF state, the system enters a nonstimulating charge recovery mode (either passive or active), which enforces systemic charge balance. The Dosage layer is programmable by Dosage ON (charge delivery) and Dosage OFF (charge recovery), each independently within a range of 1 to 25 milliseconds.

MATERIALS AND METHODS

Clinical Testing

A prospective, open-label proof-of-concept pilot study was conducted at eight study sites in Australia and the UK to evaluate and test the ideal electrode placement for PSP. The study was publicly registered (ACTRN12616001304426) and had the oversight of local Ethics Committees and the UK Medicines and Healthcare products Regulatory Agency. Subjects granted their written informed consent before any study activities.

Subjects were pragmatically recruited from investigators' clinical populations of candidates for SCS based on reporting chronic, intractable pain of the low back and/or legs after at least one surgical intervention of the lumbar spine (failed back surgery syndrome or persistent spinal pain syndrome). The key inclusion criteria were visual analog scale (VAS) ≥ 6 for one or both leg(s) and/or back pain, and medical suitability to undergo the proposed procedure. All subjects were medically and psychologically evaluated before participation, in line with the pragmatic standard of care in the participating sites. The key exclusion criteria included medical conditions or pain in other area(s) not intended to be treated with SCS that could interfere with study procedures, accurate pain reporting, and/or confounding evaluation of study end points. The full inclusion and exclusion criteria are described in Table 1. The subjects completed baseline pain severity ratings (diary) for back and leg pain (standard 0–10 numeric rating scale [NRS], 0 = no pain; 10 = worst pain imaginable). One of the primary measures for pain was the pain diaries (NRS), which the patients completed twice a day throughout the trial. Additional outcome measures collected included pain through in-clinic VAS, patient satisfaction through a Likert scale, Brief Pain Inventory, pain mapping, and paresthesia coverage map.

Eligible subjects were implanted with trial leads with one of two commonly accepted techniques for lead placement: physiologic placement, in which intraoperative testing achieved concordant paresthesia with anatomical regions of pain, or anatomic placement, in which leads were placed according to visible fluoroscopic landmarks without intraoperative testing. The primary objective of this study was to evaluate the clinical outcomes of anatomically placed and programmed PSP (aPSP) compared with T-SCS. Each anatomic subject underwent percutaneous implantation with one of two commercially available cylindrical epidural leads (eight-contact with 4 mm intercontact distance); (Nevro, Redwood City, CA or Abbott, Abbott Park, IL), with one lead at the top of the T8 vertebral body (near the midline) and the second lead at the top of the T9 vertebrae (on the side of predominant pain). An external pulse generator (EPG) capable of delivering the novel PSP waveform in addition to traditional tonic stimulation was attached to the externalized leads by a connector cable. Subjects used PSP at a variety of spinal levels in the range of 50% to 90% of paresthesia threshold, with each level tested for approximately three days before switching, for up to ten days. Before starting the T-SCS treatment, stimulation was turned off until

Table 1. Full Inclusion and Exclusion Criteria for the Clinical Testing.

Inclusion criteria

Patients enrolled in this study must meet the following inclusion criteria:

1. Subjects will have had a minimum of one surgical intervention (ie, laminectomy, discectomy, or fusion) on the lumbar spine for degenerative disc disease, mechanical mal-alignment and/or lumbar radiculopathy.
2. Subjects have been diagnosed with chronic, intractable pain of the low back and/or leg(s) (VAS ≥ 6 for one or both leg(s) and/or back), which has been refractory to conservative therapy, after surgical intervention for a minimum of 6 months (postlumbar laminectomy syndrome, failed back surgery syndrome). Conservative pre- and postoperative measures may have included, but not exclusive to, physical therapy, medication management, epidural injections, and/or denervation without material long-term response. Failure of any intervention is defined as return of symptoms to pre-intervention levels after 6 weeks.
3. Subjects will not have a clear surgical option to alleviate their current symptoms and chronic pain management has been recommended.
4. Have been approved by their doctor to undergo a commercial trial of SCS.
5. Have passed a neuropsychologic screen as per standard of care for SCS.
6. Be an appropriate candidate for the surgical procedures required in this study based on the clinical judgement of the implanting physician.
7. Be on a stable dose (no new, discontinued, or changes in dose) of all prescribed medication for a least 4 weeks prior to the trial.
8. Be 18 years of age or older at the time of enrollment.
9. Be willing and capable of giving informed consent.
10. Be willing and able to comply with study-related requirements, procedures, and visits.
11. Females of childbearing age must have a negative urine pregnancy test at baseline (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile or be at least 2 years postmenopausal.

Exclusion criteria

Patients enrolled in this study must not meet the following exclusion criteria:

1. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study end points, as determined by the investigator.
2. Have evidence of an active, disruptive psychologic or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcomes.
3. Are not a surgical candidate due to a diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease, progressive neurologic disorder (eg, polyneuropathy, multiple sclerosis) or uncontrolled diabetes mellitus.
4. Have a condition, treatable with SCS, that requires leads to be inserted into the cervical region.
5. Have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker.
6. Have a condition currently requiring or likely to require the use of magnetic resonance imaging or diathermy.
7. Have pain due to a malignant disease.
8. Have a life expectancy of less than 1 year.
9. Have an active systemic or local infection.
10. Be pregnant or nursing
11. Have withing 6 months of enrollment a significant untreated addition to dependency producing medications or have been a substance abuser (including alcohol and/or illicit drugs).
12. Be concomitantly participating in another clinical study
13. Are under active workers' compensation (or personal injury) litigation or adjudication.

pain returned to 80% of baseline levels. The EPG was then reprogrammed to provide T-SCS for three days. Subjects then exited the study, and it was anticipated that all would go on to complete their SCS trial with their commercially available SCS system, according to standard practice. Aside from the lead placement assignment, all subjects were evaluated under an identical study design, and aPSP vs T-SCS was the key comparison.

The locations of active contacts were recorded, and close monitoring for adverse events was completed throughout the study. During the trial, suspected lead migration was assessed by x-ray examination. Standard data management procedures were used.

RESULTS

Clinical Testing

A total of 52 subjects were screened in this study, of whom 48 were allocated to a study arm, and four were excluded before allocation (one failed screening, and three withdrew consent) (Fig. 2 provides a Consolidated Standards of Reporting Trials diagram). All enrolled subjects were assigned to receive one of the two lead placement techniques: anatomic (n = 33) or physiologic (n = 15). Seven subjects (five from the physiologic group and two from the anatomic group) were withdrawn from the study before completing the trial period, owing to lead migration (n = 5), infection (n = 1), and unrelated illness (n = 1). Because the primary objective of this study was to validate aPSP, physiologic lead placement was used only to confirm the postulated utility of aPSP over physiological PSP (pPSP). To do so, an interim analysis of pain relief in the first 20 subjects to complete the 14-day end point (ten anatomic and ten physiologic) was conducted. Of these 20 subjects, the PSP responder rate for leg pain was greater with aPSP (75%; n = 8; two subjects had no leg pain at baseline) than with pPSP (50%; n = 10). Similarly, PSP responder rate for back pain was 40% (n = 10) with aPSP and 30% (n = 10) with pPSP. These findings

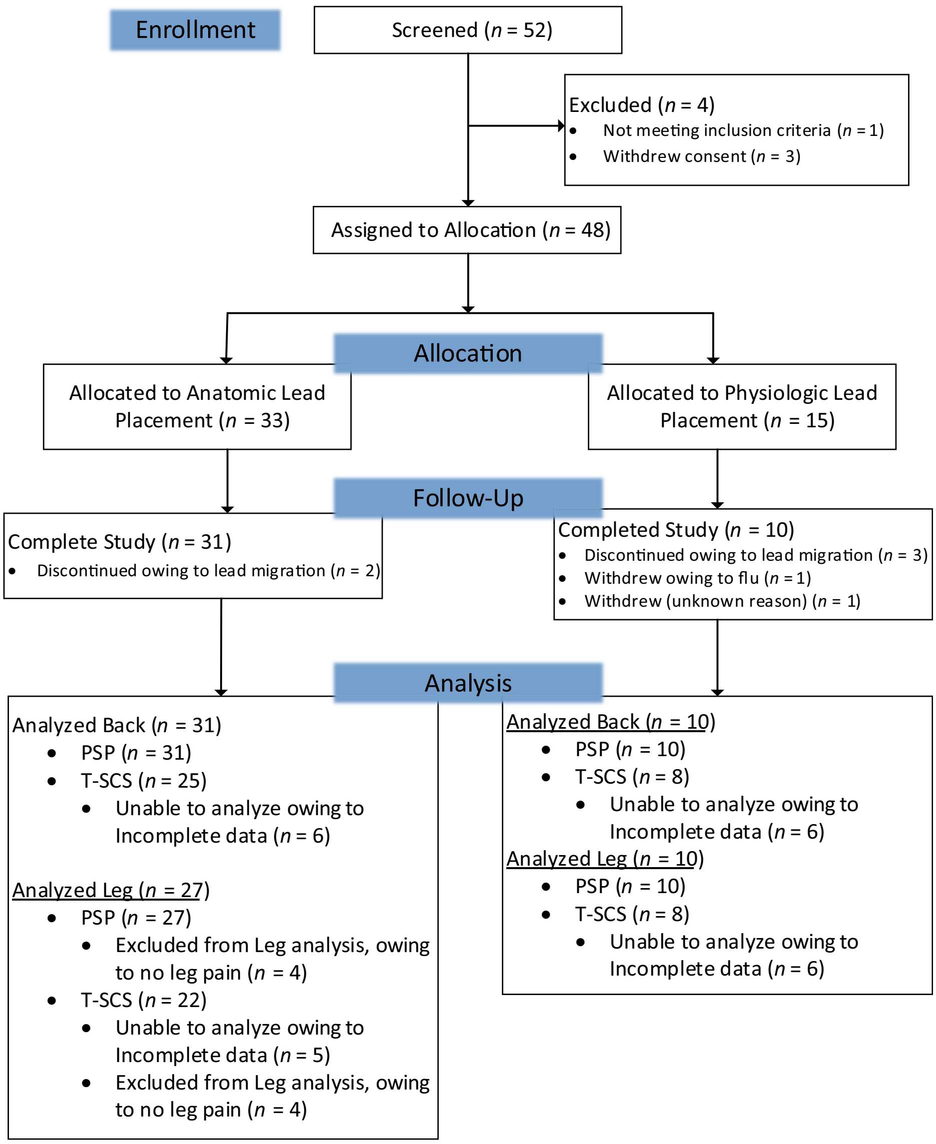

Figure 2. Acute clinical study Consolidated Standards of Reporting Trials diagram detailing study participation from enrollment, allocation, follow-up, and analysis periods. [Color figure can be viewed at www.neuromodulationjournal.org]

provided the justification for the decision to assign all subsequent enrollments to the anatomic lead placement group to allow within subject comparison of pain relief with aPSP vs T-SCS.

A total of 31 anatomic subjects and ten physiologic subjects in the clinical study completed the 14-day end point. The data from all evaluable anatomic subjects with back pain ($n = 31$) and leg pain ($n = 27$; four subjects had no leg pain at baseline) were pooled and analyzed. The subjects were programmed with both suprathreshold T-SCS and subthreshold PSP; however, some subjects were not evaluable for T-SCS (six subjects in the back and five subjects in the leg) owing to missing or incomplete outcomes reported in subject pain diaries. Demographics and baseline pain characteristics are summarized in Table 2. No differences between groups were apparent.

Both T-SCS and aPSP decreased low back pain and leg pain relative to baseline scores. Among all evaluable anatomic subjects ($n = 31$), the average back pain score decreased from 7.1 ± 1.6 at baseline to 3.7 ± 2.5 with T-SCS and to 2.9 ± 2.3 with aPSP, a 46% ($n = 25$) and 60% ($n = 31$) decrease in average pain, respectively. Similarly, the average leg pain score decreased from 7.1 ± 1.7 at baseline to 3.8 ± 2.5 with T-SCS and to 2.6 ± 1.6 with aPSP, a 43% ($n = 22$) and 63% ($n = 27$) decrease in leg pain, respectively. aPSP yielded greater responder rates (defined as ≥ 50% pain relief) than did T-SCS for both low back and leg pain (61% vs 48% and 78% vs 50%, respectively) (Fig. 3). Overall, aPSP produced greater levels of pain relief and responder rates relative to baseline in the low back and legs than did T-SCS.

The cathode locations were identified for both aPSP and pPSP responders. Eleven percent of responders had cathodes programmed at T8; 74% (and 100% of the anatomic placements) had cathodes programmed at T9; and 16% of responders had cathodes programmed at T10 (Fig. 4). Thus, the optimal target of stimulation, based on the preponderance of the data, was at T9.

DISCUSSION

The favorable clinical outcomes shown in the pilot human study may be attributed to the qualities observed in the PSP waveform. PSP showed favorable outcomes in subjects who were programmed on the basis of anatomically placed electrodes, and it resulted in pain relief relative to baseline in the low back and legs. In addition, responder rates and pain relief in both the low back and legs were greater with anatomically placed PSP stimulation than with T-SCS.

PSP Mechanisms of Action

The multiple mechanisms driving these findings remain unconfirmed, but the results of these studies suggest that pre- and postsynaptic consequences of the PSP multilayered structure and parameters may play a role in the therapeutic effects observed. We would like to propose a hypothesis that PSP may be inducing therapeutic effect through multiple mechanisms, and we nominate these distinct MOAs: preferential fiber activation, onset effect and neural adaptation optimization, medial and lateral pathway activation, and interleukin (IL)-10 upregulation.

The short duration of Pulse Pattern ON/OFF parameters used in PSP may promote activation of large-diameter fibers over small-diameter fibers, as supported by mathematical models of electrical fields and neural activation using stimulation pulse widths between 60 µs and 1000 µs.[6] The ability to independently program Pulse Pattern ON and Pulse Pattern OFF allows individualized optimization of pain relief. Furthermore, this programmability enables the delivery of stimulation patterns with short ON and OFF durations, which has been found to promote preferential fiber activation,[7] as illustrated in Figure 5.

Parameterization of the Train layer is designed to enable optimization of the onset response at the start of each train. The onset response is characterized by a large neural recruitment occurring in nearby neurons, immediately after the introduction of electrical stimulation, and lasting anytime from a few to hundreds of milliseconds.[8–11] Much work has been done to elucidate this onset response, including the illustration by Bhadra et al[12] of the large neural response at onset of below threshold stimulation. Kral et al[13] indicated a decrease in neural activation with increasing stimulus duration (longer pulse trains) across different neuronal structures. A similar finding in auditory nerve recordings supports this notion of neural adaptation because stimulus duration is prolonged.[10,11] Although stimulation in short and frequent on/off patterns can promote maximum neural recruitment at onset, if the stimulation duration is too short, it can elicit a phase-locking effect (neural responses locked to the phase of stimulation) that may produce paresthesia. Optimizing stimulation parameters in such a way that they produce a robust and sustained onset response without inducing phase locking or paresthesia is of clinical importance (as illustrated in Fig. 6). The ability to independently program the Train ON and Train OFF parameters creates an opportunity to optimize the onset response and prevent phase locking.

The Dosage layer draws on earlier work showing robust medial and lateral pathway activation when the spinal cord is stimulated in a series of subthreshold pulses rather than perceptible tonic pulses. Prevailing literature indicates that pain perception involves nociceptive and modulatory systems that also play critical roles in affective and cognitive function, suggesting that chronic pain is multidimensional.[14] The neural pain matrix consists of a lateral and medial pathway through the thalamic nuclei. The lateral pathway is

Table 2. Acute Clinical Study Demographics and Baseline Characteristics.

	Physiologic lead placement	Anatomic lead placement
N	10	31
N with back pain	10	31
N with leg pain	10	27
Age, y	52.5 ± 8.3	56.5 ± 12.4
Female, *N* (%)	6 (60%)	16 (52%)
Weight (kg)	88.9 ± 15.6	94.4 ± 19.4
Height (m)	1.7 ± 0.1	1.7 ± 0.1

* Four subjects did not report leg pain at baseline; these patients were followed only for back pain.

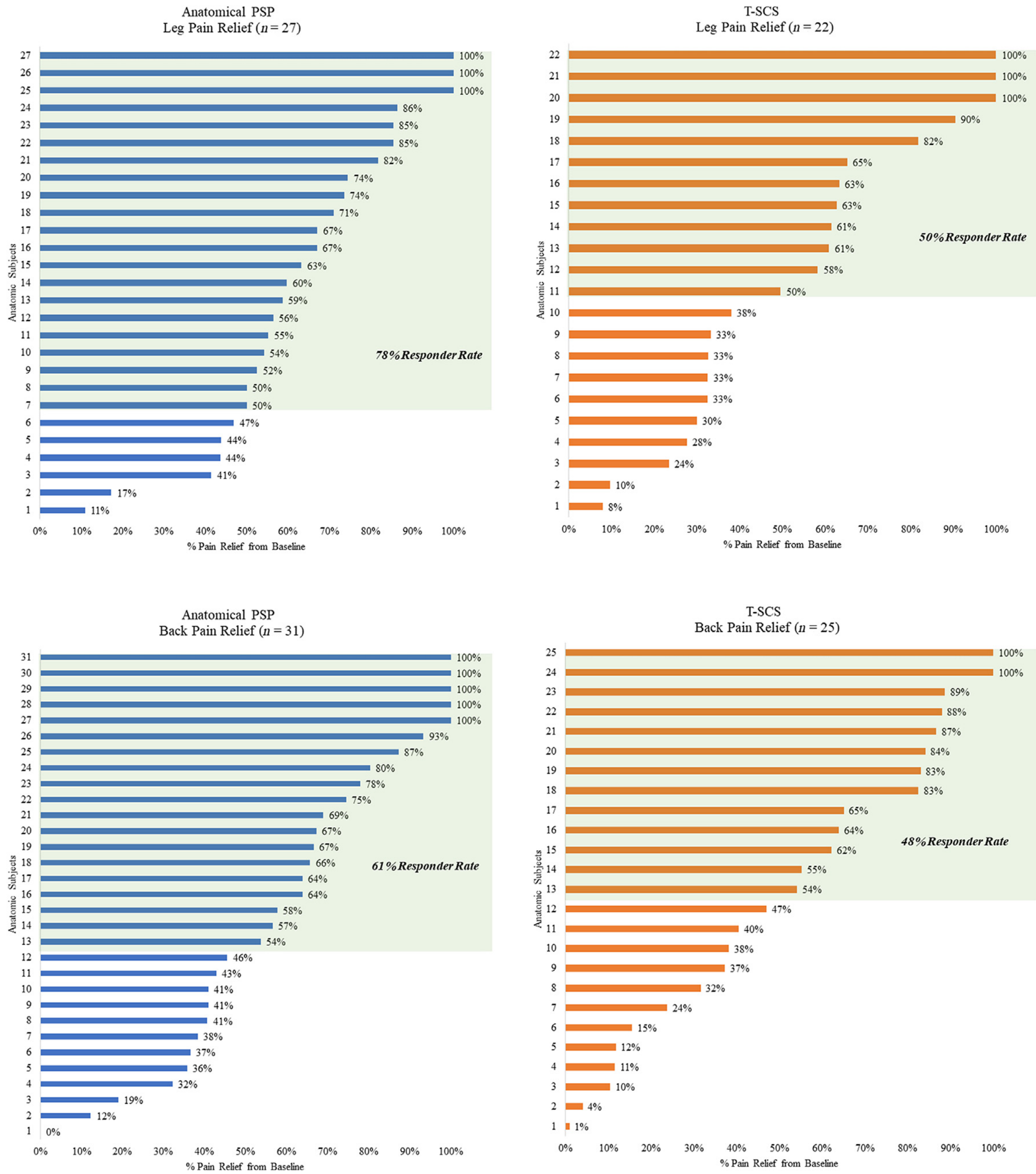

Figure 3. Responder rates for low back and leg pain for T-SCS vs PSP stimulation with anatomically placed leads. [Color figure can be viewed at www.neuromodulationjournal.org]

associated with the sensation and location of pain, whereas the medial pathway is associated with the affective aspects of the pain experience.[14,15] Sherman[16] found that thalamic cells exhibit lateral thalamocortical relay response modes when firing both tonically and intermittently. However, unlike T-SCS, delivery of a series of subperception pulses appears to activate both the lateral and medial pathways.[17] When the medial pathway is activated, medial thalamic cells fire in temporal clusters, resulting in activation of the anterior cingulate cortex (ACC). The ACC is a critical site for emotional regulation and affective perception of pain in humans. Results from Deer et al[18] revealed a more robust improvement in depression measures with long (360-second) stimulation off intervals compared with that of shorter (90-, 120-, 150-second) stimulation off intervals. This suggests that a longer off period between dosages may result in more robust activation of the medial pathway. Thus, under proper parameterization, the Dosage layer may elicit the activation and modulation of both the lateral and medial pathways, thereby expanding the MOAs of PSP.

IL-10, which is an antiinflammatory cytokine and is thus suspected to have analgesic properties, is known to be expressed by glial cells, which exist primarily in gray matter and are in greatest abundance in the T9 region of the spinal cord.[19,20] In this study, PSP

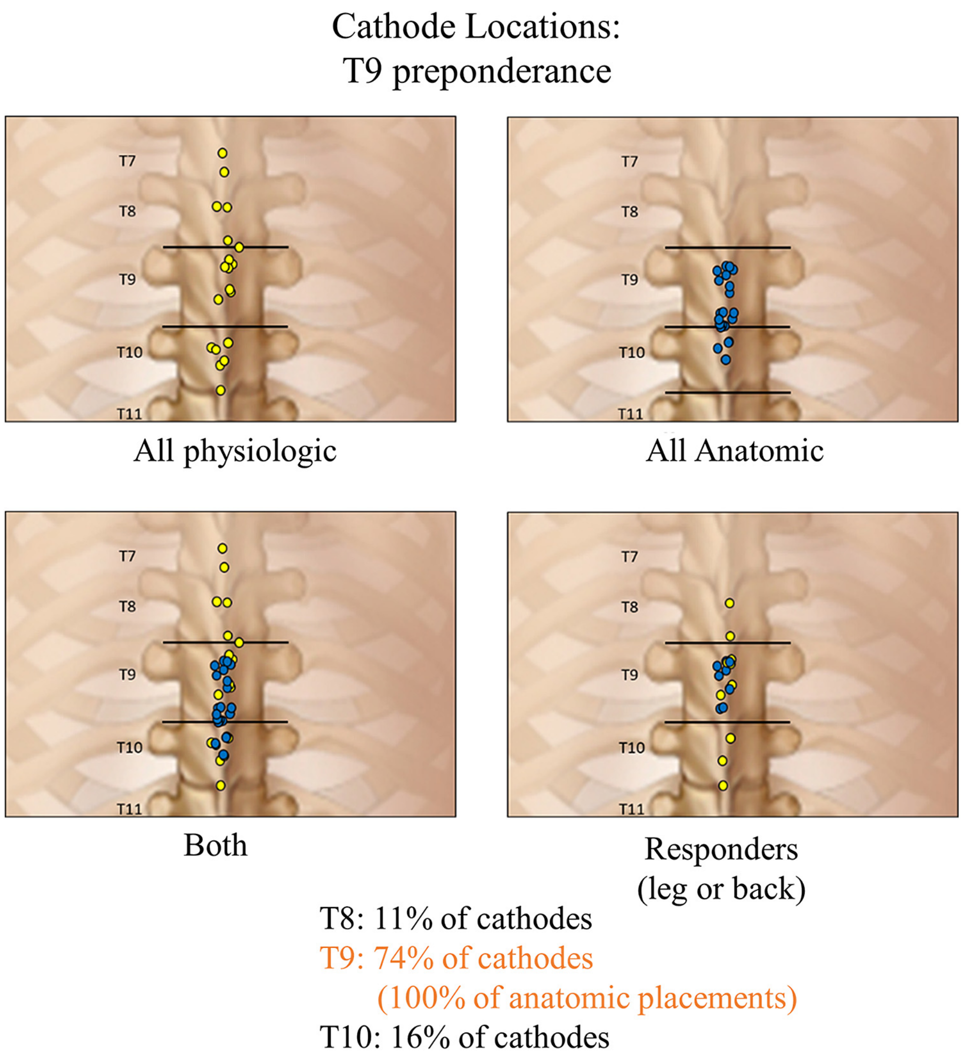

Figure 4. All cathode locations of all study subjects. Yellow dots represent cathode locations mapped physiologically. Blue dots represent cathode locations that were programmed anatomically. Responders only (those subjects with ≥ 50% pain relief) are shown in the lower right panel. Note that 74% of responders (and 100% of those with anatomic lead placements) had cathodes at T9. [Color figure can be viewed at www.neuromodulationjournal.org]

delivered to anatomically placed leads at T9 suggested clinical benefit over the alternative T-SCS therapy. As such, it may be hypothesized that the therapeutic effect of PSP is aided by optimal anatomical location of SCS electrodes in the T9 region, but more investigation is warranted to confirm this.

The novel PSP waveform described here requires further study, but it may be another helpful tool in the treatment of intractable chronic pain.

Limitations

This was an early safety and feasibility trial in which primary end points were achieved. Ongoing clinical efficacy trials are being conducted in multiple ongoing prospective, open-label, clinical studies in Australia and the USA. Interim analysis for the ongoing Australian study has revealed favorable findings thus far.[21] Given the scope of this article, the study design was determined to be sufficiently sensitive to differences between the treatment options. However, there remain notable limitations in this work. Although it is typical to initiate the testing of new neuromodulation technology in a trial-only fashion, the authors would like to acknowledge the limitation of the short duration of clinical follow-up.[22–24] Despite the efforts to account for washout period in the clinical study, there remains a possible order effect due to the sequence of stimulation conditions. Of course, when comparing two therapy modalities within a single patient, the order-effect bias exists. Subparesthesia therapy (PSP) was delivered before T-SCS to prevent the subject from assuming perceptible therapy is equivalent to a functioning system. The authors would like to acknowledge that the clinical testing presented here is limited to the comparison of T-SCS with PSP only, yet future investigation into the comparative effects of PSP and other available waveforms may be of value.

Given these limitations, the authors recommend that further clinical investigation be conducted to provide robust confirmatory evidence for the MOA theory introduced in this article.

CONCLUSIONS

This study examined preliminary clinical experience with a novel stimulation waveform. Moreover, this report provides preliminary

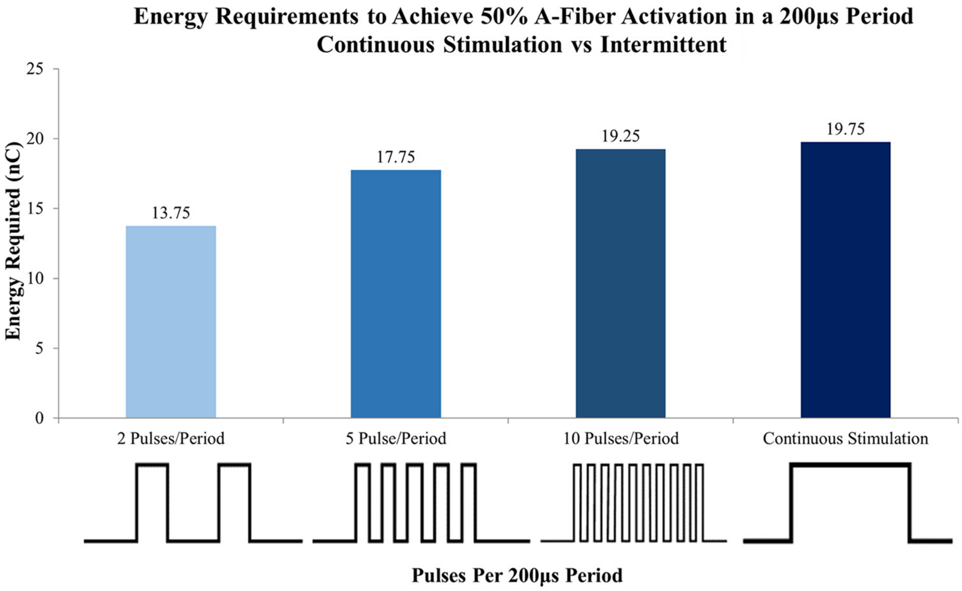

Figure 5. Energy required to recruit 50% of type-A fibers when a 200 µs pulse is broken up into two, five, and ten pulses (constructed using data published in Qing et al[7]). [Color figure can be viewed at www.neuromodulationjournal.org]

clinical evidence that a novel PSP waveform delivers significantly improved pain relief in the low back and leg(s) compared with T-SCS. This effect was optimized when epidural leads were placed and programmed by anatomical methods compared with the conventional physiological paresthesia-mapping approach. The PSP waveform may provide multimechanistic therapeutic relief through preferential activation of large-diameter fibers in the dorsal column,[6] optimization of the neural onset response,[8–13] and use of both the medial and lateral pathway through the thalamic nuclei.[15] Preliminary human data support the utility of the measured system, although additional clinical outcomes from the ongoing studies will be helpful to confirm and further explore achievable clinical efficacy by modulating PSP layer parameters (Pulse Pattern, Train, and Dosage) for their ability to activate proposed neurophysiological MOAs. This paper serves as a foundation in an ongoing longitudinal research and publication plan, providing context to the ongoing long-term clinical studies and routine medical use of the PSP family of waveforms.

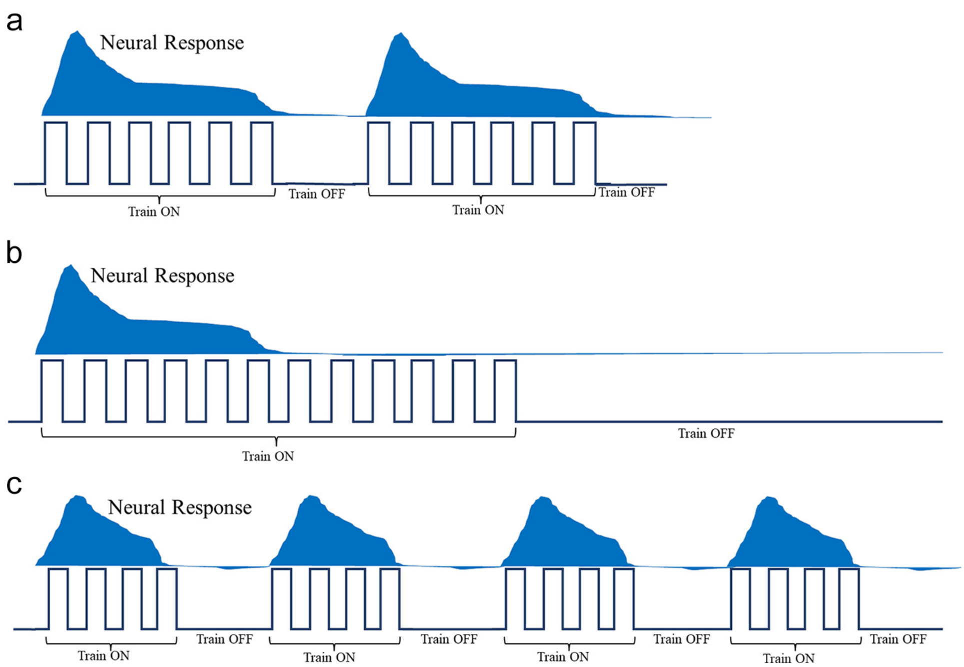

Figure 6. Neural recruitment onset responses modeled with various pulse train durations: (a) optimal response; (b) neural adaptation; (c) phase locking (based on the theory described in Bhadra and Kilgore,[8] Gerges et al,[9] Hughes et al,[10] He et al,[11] Bhadra et al,[12] and Kral et al[13]). [Color figure can be viewed at www.neuromodulationjournal.org]

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Authorship Statements

All authors made substantial contribution to the concept, design, and/or analysis of the material discussed in this manuscript. All authors approved the final version of the manuscript.

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REFERENCES

1. Linderoth B, Foreman RD. Conventional and novel spinal stimulation algorithms: hypothetical mechanisms of action and comments on outcomes. *Neuromodulation*. 2017;20:525–533.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971–979. https://doi.org/10.1126/science.150.3699.971.
3. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation*. 1999;2:150–164.
4. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. *Int Rev Neurobiol*. 2012;107:87–119.
5. Abbott Neuromodulation. Important safety information. Accessed July 16, 2021. https://www.neuromodulation.abbott/us/en/important-safety-info.html.
6. Lee D, Hershey B, Bradley K, Yearwood T. Predicted effects of pulse width programming in spinal cord stimulation: a mathematical modeling study. *Med Biol Eng Comput*. 2011;49:765–774. https://doi.org/10.1007/s11517-011-0780-9.
7. Qing KY, Ward MP, Irazoqui PP. Burst-modulated waveforms optimize electrical stimuli for charge efficiency and fiber selectivity. *IEEE Trans Neural Syst Rehabil Eng*. 2015;23:936–945. https://doi.org/10.1109/TNSRE.2015.2421732.
8. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. *Muscle Nerve*. 2005;32:782–790. https://doi.org/10.1002/mus.20428.
9. Gerges M, Foldes EL, Ackermann DM, Bhadra N, Bhadra N, Kilgore KL. Frequency- and amplitude-transitioned waveforms mitigate the onset response in high-frequency nerve block. *J Neural Eng*. 2010;7:066003. https://doi.org/10.1088/1741-2560/7/6/066003.
10. Hughes ML, Castioni EE, Goehring JL, Baudhuin JL. Temporal response properties of the auditory nerve: data from human cochlear-implant recipients. *Hear Res*. 2012;285:46–57. https://doi.org/10.1016/j.heares.2012.01.010.
11. He S, Mcfayden TC, Shahsavarani BS, et al. The electrically evoked auditory change complex evoked by temporal gaps using cochlear implants or auditory brainstem implants in children with cochlear nerve deficiency. *Ear Hear*. 2018;39:482–494. https://doi.org/10.1097/AUD.0000000000000498.
12. Bhadra N, Lahowetz EA, Foldes ST, Kilgore KL. Simulation of high-frequency sinusoidal electrical block of mammalian myelinated axons. *J Comput Neurosci*. 2007;22:313–326. https://doi.org/10.1007/s10827-006-0015-5.
13. Kral A, Aplin F, Maier H. *Prostheses for the Brain: Introduction to Neuroprosthetics*. Academic Press; 2021.
14. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci*. 2013;14:502–511. https://doi.org/10.1038/nrn3516.
15. Kulkarni B, Bentley DE, Elliott R, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur J Neurosci*. 2005;21:3133–3142. https://doi.org/10.1111/j.1460-9568.2005.04098.x.
16. Sherman SM. Thalamic relay functions. *Prog Brain Res*. 2001;134:51–69. https://doi.org/10.1016/s0079-6123(01)34005-0.
17. Chakravarthy K, Kent AR, Raza A, Xing F, Kinfe TM. Burst spinal cord stimulation: review of preclinical studies and comments on clinical outcomes. *Neuromodulation*. 2018;21:431–439.
18. Deer TR, Patterson DG, Baksh J, et al. Novel intermittent dosing burst paradigm in spinal cord stimulation. *Neuromodulation*. 2021;24:566–573. https://doi.org/10.1111/ner.13143.
19. Ruiz-Sauri A, Orduña-Valls JM, Blasco-Serra A, et al. Glia to neuron ratio in the posterior aspect of the human spinal cord at thoracic segments relevant to spinal cord stimulation. *J Anat*. 2019;235:997–1006. https://doi.org/10.1111/joa.13061.
20. Kinfe TM, Muhammad S, Link C, Roeske S, Chaudhry SR, Yearwood TL. Burst spinal cord stimulation increases peripheral antineuroinflammatory interleukin 10 levels in failed back surgery syndrome patients with predominant back pain. *Neuromodulation*. 2017;20:322–330. https://doi.org/10.1111/ner.12586.
21. Salmon J, Bates D, Du Toit N, et al. Early experience with a novel miniaturized spinal cord stimulation system for the management of chronic intractable pain of the back and legs. *Neuromodulation*. 2023;26:172-181. https://doi.org/10.1016/j.neurom.2022.11.002.
22. De Vos CC, Bom MJ, Vanneste S, Lenders MW, De Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. *Neuromodulation*. 2014;17:152–159. https://doi.org/10.1111/ner.12116.
23. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation*. 2014;17:443–450.
24. Tiede J, Brown L, Gekht G, Vallejo R, Yearwood T, Morgan D. Novel spinal cord stimulation parameters in patients with predominant back pain. *Neuromodulation*. 2013;16:370–375.

COMMENT

The development of novel waveforms continues apace. This company sponsored research documents a novel waveform in the short-term application of this in patients with mixed neuropathic/nociceptive pain during a SCS trial phase. These patients were stimulated at 50%–90% of sensory perception threshold and since the sensory perception in the rat is held (for now) as being 30% of the motor threshold (MT) they received the equivalent of 15% to 27% of MT in the rat. It will be interesting to compare future animal data with these human subject observations. The results are interesting and should certainly spur further research and refinement in this area. The raw delta for NRS reduction for low back pain in anatomical PSP vs tonic was 0.8 which is a moderate improvement. There is a clear difference in favor of PSP over tonic when looking at 50% responders, but the opposite is true if one is looking at high responders/remitters (>80% relief) where that was achieved in 32% of tonic and 26% of PSP waveform patients. Perhaps of more concern is the 35% nonresponder rate (<50% relief) in the PSP group which suggests that further work and refinement may be worthwhile. I have a general (not particularly well founded) hope that varying some aspect of what we do with SCS (whether that be frequency, amplitude, pulse width, bipole selection, or some combination thereof) may improve results and may prevent neurophysiological accommodation of nociceptive block. Thus, I am encouraged to see research in this area, and I believe there will be much we discover as we let go of the iron hand of constant tonicity.

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