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Randomized Controlled Trial

A Prospective, Multicenter, Double-Blinded, Randomized Controlled Trial Investigating the Effects of High-Frequency Stimulation at the Proximal Peripheral Nerves for Treating Chronic Back Pain with 36 Months of Follow-Up

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Background: Chronic back pain is a debilitating condition that significantly diminishes a patient's quality of life and imposes a substantial economic burden, driven by ongoing health care costs and lost workdays.

Objectives: This trial aimed to assess the efficacy and safety of an externally powered neuromodulation system targeting the proximal peripheral nerves at the T9 dermatome for chronic back pain refractory to surgery or standard treatment by comparing sub-threshold active stimulation therapy to sham.

Study Design: This is a prospective, multicenter, double-blinded, randomized controlled trial. Adhering to the highest standards of methodological quality control, the 38 patients who completed the study had been randomized in a 1:1 ratio to receive either subthreshold active stimulation or sham stimulation using the same Freedom® (Curonix LLC) Peripheral Nerve Stimulator System.

Setting: This is a randomized controlled trial conducted at 2 independent clinical sites representing distinct secondary and tertiary clinical settings.

Methods: Both the patients and the assessors were fully blinded. All patients were implanted with 2 4-electrode neurostimulators over the proximal peripheral nerves at the T9 level, in a single-stage direct to permanent procedure. The primary endpoint assessed the difference (at least 50% overall relief or a return to 30 mm or less on the Visual Analog Scale) between subthreshold stimulation and sham stimulation. Patients who received the sham treatment were unblinded and were then given the active treatment throughout the different visits if they reported a lack of response. A per-protocol analysis was conducted at the one-month visit. Patients were followed for 36 months.

Results: Thirty-eight (active: n = 19; sham: n = 19) patients completed the one-month primary endpoint. Superiority for the primary endpoint was confirmed for the active stimulation arm with a responder rate of 63% compared to the sham arm with only a 16% responder rate ($P = 0.007$). In addition, the active stimulation patients programmed with subthreshold frequencies experienced statistically and clinically significant improvements in Visual Analog Scale scores, the Oswestry Disability Index. the European Quality of Life Survey, the EuroQOL-5 Dimension Questionnaire, and the Patient Global Impression of Change compared to the sham group. Pain relief, improved functionality, and patient satisfaction were consistently reported throughout the study and were sustained through the 36-month follow-up.

Limitations: While the study was rigorously designed and executed, residual confounding cannot be entirely excluded.

Conclusion: This trial showed statistically or clinically significant reductions in low back pain in

patients with both Persistent Spinal Pain Syndrome Type 1 (chronic back pain without prior spine surgery) and Persistent Spinal Pain Syndrome Type 2 (chronic pain post spinal surgery), using neurostimulators applied to the proximal peripheral nerves at T9 using subthreshold high-frequency stimulation.

Key words: Proximal peripheral nerve stimulation, chronic back pain, sub-threshold stimulation, neuromodulation, permanent peripheral nerve stimulation, randomized controlled trial, double-blinded, PSPS T1, PSPS T2

Clinicaltrials.gov registry number: NCT03312010

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Chronic back pain can be a debilitating condition that negatively affects a patient's quality of life and generates a high health economic burden due to ongoing treatment costs and loss of workdays. Chronic back pain's prevalence is estimated to be the same order of magnitude as rheumatoid arthritis, with a prevalence of 5,800 per 100,000 and an incidence of 10 per 100,000 annually (1-3).

Treatment options include physiotherapy, nonsteroidal anti-inflammatory drugs, opioids, spine surgery, repeated spine surgery, and more invasive techniques such as radiofrequency ablation, neural injections, and spinal cord stimulation. Spinal cord stimulation has been commercially available for more than 40 years and is currently indicated for treating chronic intractable pain of the trunk and/or limbs in patients with Persistent Spinal Pain Syndrome Type 2 (PSPS T2; chronic pain post spinal surgery) (4-6). Expanded approaches utilizing subthreshold stimulation (7) have shown improved outcomes due to advancements in technology, waveforms, and advanced programming, which enable targeted placement and sustained energy delivery. Peripheral nerve stimulation (PNS) is a well-established treatment that can be used to treat pain in the trunk and back; it also provides a targeted solution for pain in the craniofacial region and pain in the lower and upper extremities (8-15).

The literature about externally powered PNS have consistently reported both efficacy and safety in multidisciplinary treatment settings for chronic pain. Multiple studies have reported significant and lasting pain relief for various types of neuralgia and anatomical targets (8-15). For example, Abd-Elsayed (9) reported an average long-term pain reduction of more than 70% in 57 patients with different neuralgias at all follow-ups. Patients have also reported a significant decrease in opioid use.

Further investigations have yielded comparable results: Früh et al (10) reported up to 75% pain relief and a reduction in analgesic consumption among 33 patients experiencing post-surgical knee pain (10). Pollina et al (11) reported an average long-term pain reduction of 65% in 15 patients suffering from chronic foot pain. Wiederholz et al (12) reported pain reductions of up to 83% in 7 patients with chronic shoulder pain treated via the brachial plexus. These findings are further corroborated by evidence from orthopedic studies: Mates (13) reported a 73% average pain reduction at 3 months post-implantation in 14 patients with upper and lower extremity pain. Kilbride (14) reported an 87% mean pain reduction in 7 patients with chronic knee pain.

In 2025, Hayek et al (15) published a pivotal randomized controlled trial of a US Food and Drug Administration investigational device exemption. The trial's results focused on the use of PNS in the craniofacial region. This study provided robust clinical evidence supporting the safety and efficacy of PNS in this complex anatomical area. This study effectively expanded the clinical reach of PNS, enabling full-body application and solidifying its role as a comprehensive treatment option for chronic pain across numerous anatomical regions (15).

Across all studies, patients consistently reported significant long-term pain relief, improved sleep quality, decreased reliance on pain medication, and high levels of satisfaction. Importantly, only one serious complication was reported in any of these studies, which collectively reviewed 214 patients, reinforcing the overall safety profile of the therapy (8-15).

Nociceptive signals that originate from the femoral and sciatic nerves, facet joints, paravertebral muscles, skin, and sympathetic chain all converge upon the spinal cord via the proximal peripheral nerve. In 1993 Tulgar et al (16) showed that T9/10 spinal cord stimulation resulted in paresthesias in the abdomen, low back, and buttocks, which has since become a standard level for spinal cord stimulation. Our study sought to show

that stimulating the proximal peripheral nerve at the T9 level could provide similar relief to stimulating the spinal cord itself.

With spinal cord stimulation, there is the potential for electrodes to move due to patient movement, which could change the level of stimulation and/or result in migration (17). Extraforaminal approaches to target the spinal nerves have recently been studied as another option (18). In our study, we applied targeted permanent PNS to the exiting proximal peripheral nerves, taking advantage of anatomical features such as bone structure encasement and stable positioning, in order to provide additional stability for the PNS implant. This enables a precise alternative approach to treating chronic back pain, similar to extraforaminal spinal nerve stimulation (18). Targeted proximal PNS broadens the available neuromodulation options by bridging the gap between spinal cord stimulation and PNS at the extremities. This approach provides an alternative treatment that is precise, effective, and durable for focal neuropathic pain that is often challenging to manage.

One of the primary challenges in clinical trials involving medical devices is achieving effective blinding of both patients and assessors. In neurostimulation studies, it is challenging to achieve the appropriate level of control design due to the surgical nature of the treatment. A recent study design proposed by Hayek et al (15) provided a strong control, utilizing the therapy as its own control in all patients who were implanted. Additionally, double-blinded trials remain the gold standard for generating the highest level of evidence. Effective blinding is only possible when the active treatment is indistinguishable from the sham (placebo) treatment in all aspects (19,20). Although this is often feasible in pharmacological studies, blinding in nonpharmacological interventions is considerably more difficult—and in some cases, unethical when the treatment is critical to a patient's health, such as managing chronic pain. Neurostimulation is a good example, since stimulation can create various tissue sensations and paresthesias. Because the sham group does not have the possibility to feel any sensation regardless of power levels, a satisfactory comparison with an active group can be challenging without setting the active arm patients at subthreshold power levels (40%–80% of motor threshold), thereby reducing the possibility of feeling sensations.

These methodological considerations suggest that the system used in our study (Freedom® PNS System [Curonix LLC]), when operated at subthreshold stimulation settings, is particularly amenable to placebo-controlled investigations, since subthreshold stimulation allows a direct comparison with inactive stimulation (sham), thereby enabling the identification of potential confounding placebo effects (20).

In our trial, all patients received an immediate permanent implant in order to prevent treatment and trial-responder bias. Since standard neurostimulation practice limits permanent implantation only to successful trial responders, including a trial phase would have introduced selection bias. Implanting every randomized patient avoided this issue.

This is the first prospective, multicenter, double-blinded, randomized controlled trial for proximal PNS with a primary endpoint at one month post-implant and a total follow-up of 36 months.

Methods

Device Description

The Freedom PNS system we used includes an implanted electrode array (with 4 contacts), a separate implanted receiver that the physician connects during the procedure, and an external transmitter assembly and wearable accessory (Fig. 1). The external transmitter uses high-frequency electromagnetic coupling technology to wirelessly transfer data and power to the 2-component implant. The physician is also required to create a separate, distinct pocket to permanently anchor the device.

Study Design

This prospective, multicenter, double-blinded, randomized controlled trial (clinicaltrials.gov registry number: NCT03312010) aimed to evaluate the safety and efficacy of externally powered subthreshold neurostim-

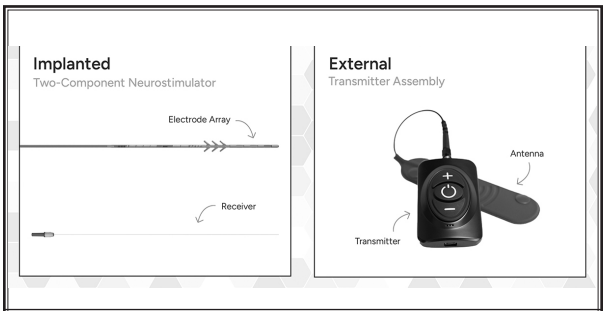


Fig. 1. *Freedom PNS System*.

ulation of the proximal peripheral nerves at the T9 vertebral level. The intervention was specifically applied for the treatment of chronic back pain, (encompassing both unilateral and bilateral presentations), that had proven refractory to conventional medical therapies or low back surgery, in comparison to sham stimulation. Patients went straight to implant with a permanent stimulator to avoid "trial responders only" bias.

Our study was conducted at 2 sites after being approved by the corresponding Investigational Review Boards. Thirty-nine patients with chronic back pain refractory to best medical treatment as well as patients with PSPS T2 were recruited into the study. After receiving informed consent, patients were block-randomized with a 1:1 ratio into 2 parallel arms to receive either active subthreshold stimulation or sham stimulation. Variable block sizes (4 and 6) with complete randomization assignments were sent to each site in a numbered, opaque, sealed envelope. Sealed envelopes were opened during the baseline visit in order to enable the proper programming parameters by the representatives of the sponsor (Curonix LLC). Both the patients and assessors were blinded to the assignment.

Patients who did not respond to the therapy at the one-month follow-up or a later follow-up were unblinded to their respective randomization. The patients randomized to the active arm who were nonresponsive were unblinded and then reprogrammed with new parameters to optimize their pain relief; these patients continued unblinded until the end of the study. Patients randomized to sham had their system activated with therapy, optimized, and continued until the end of the study, exactly like the active group.

Patient Selection

The study population consisted of patients diagnosed with refractory back pain, either unilateral or bilateral, without previous spine surgery (PSPS Type1[T1]) or post previous spine surgery (PSPS T2), refractory to standard medical treatment, who met all the selection criteria and did not meet any of the exclusion criteria (Appendix 1). The site investigators recruited potential patients from their clinics' patient pool; they were included in the study when they signed an informed consent.

Surgical Description

While under light sedation and local anesthesia, all patients were implanted with a permanent system (without a prior trial).

For planning and measurement purposes, the electrode array was placed on the skin with the distal electrode overlying the target nerve area. The first incision, needle entry point, and needle pathway from the contralateral side were planned using fluoroscopy. The skin and deeper tissues were anesthetized using local anesthetics along the initial introducer path. The first incision was made with a scalpel, and then a 13-G Tuohy needle was passed through the incision and advanced through the ligamentum flavum to the contralateral interlaminar space at T9-T10, using small amounts of local anesthetic as needed for patient comfort. A 4-contact electrode array with tines was inserted through the Tuohy needle and then advanced under image guidance to pass out the contralateral neuroforamen over the proximal peripheral nerves at the T9 vertebra level. This was repeated on the opposite side (Fig. 2).

A receiver pocket was created using blunt dissection through a second distinct incision. The steering stylets were removed from the previously implanted electrode arrays. Separate receivers were connected to the electrode arrays. After being connected, the electrode arrays and receivers were tunneled to the receiver pocket. The receivers were permanently connected by tying a knot and coiled, utilizing 2 nonabsorbable sutures to permanently form the receiver coils. The ends of the receiver coils were tucked underneath the coils to avoid protruding edges. Using nonabsorbable sutures, the receiver coils were sutured to the fascia in at least 2 locations, ensuring that the coils were flat in the pocket. The receiver pocket was then closed with deep and superficial absorbable sutures.

To ensure effective blinding of the patients in both groups, it was essential that their interaction with the device appeared identical. Both groups received a transmitter and antenna with identical indicators—such as lights and sounds—and experienced the same battery depletion and recharging process. The advanced programming sessions and parameters were also indistinguishable. The sole difference between the 2 groups was in the software. The sham group's software was configured so that the transmitter could not communicate with the implanted neurostimulator. This approach successfully maintained blinding for both patients and assessors.

Stimulation Parameters

At the time of implantation, patients had their devices programmed according to their randomization assignment with either high frequency subthreshold

stimulation or sham. Since stimulation is programmed below perception (subthreshold), patients in both arms as well as the assessors could remain blinded to the assignment.

The external antenna was placed over one layer of clothing covering the area of the implanted receiver; it provided the energy required for stimulation as needed throughout the study. Patients were instructed to use stimulation throughout the entire day.

Data Collection and Analysis

Data were secured on paper case report forms and questionnaire instruments at baseline and throughout the study. The integrity of the data was regulated via periodic monitoring by an independent research organization.

The sample size was calculated to be 19 patients per treatment group. The sample size was estimated to provide at least 80% power in a comparison of active to sham stimulation at $\alpha = 0.05$. The sample size was estimated by assuming 20% of patients receiving sham treatment and 70% of patients treated with active subthreshold stimulation would experience 50% or greater pain relief.

The primary endpoint (the proportion of patients experiencing at least 50% pain relief or reporting a return to 30 mm or less on a the Visual Analog Scale [VAS]) was compared at one month using a 2-sided Fisher's exact test at $\alpha = 0.05$. Primary endpoint analysis was performed on the per-protocol sample (patients completing a primary endpoint assessment).

The secondary endpoints of mean reduction of pain score and Oswestry Disability Index (ODI) scores were compared using 2-sided t-tests at $\alpha = 0.025$ and $\alpha = 0.05$, respectively. Additional datapoints of the Patient Global Impression of Change (PGIC) category scores, European Quality of Life (QoL) and 5 Dimension questionnaire (EQ-5D) scores were compared using 2-sided t-tests at $\alpha = 0.05$. VAS score improvement was compared in a hierarchical sequence using a 2-sided Fisher's exact test at $\alpha = 0.05$. Statistical significance was set at $P \leq 0.05$ in each test; subsequent tests were not executed unless all previous tests were significant (Table 1).

Bias was reduced by randomizing the patients, by blinding the patients and their evaluators to the true treatment, and by using self-reported data or data collected by the research team. Data analysis was done by a third-party statistician.

Adverse events were assessed descriptively



Fig. 2. *Anteroposterior image showing distribution of 2 quadripolar neurostimulators over exiting proximal peripheral nerves at the T9 vertebral level consistent for all patients in the study.*

through a checklist in the intent-to-treat population (n = 39) and were classified as 1) a serious adverse event (defined as any undesirable outcome in a patient that led to death or a serious deterioration in health; a life threatening illness or injury; a permanent impairment of a body structure or function; an in-patient hospitalization; or a surgical intervention necessary to prevent permanent impairment to body function) or 2) a nonserious adverse event with a related or nonrelated undesirable outcome without injury or hospitalization.

Results

Thirty-nine patients were enrolled in this study. One patient withdrew consent before the primary endpoint. Thirty-eight (sham:19/active:19) patients completed the one-month primary endpoint, at which time 16 patients who were receiving sham treatment and 7 patients who were receiving the active treatment were unblinded due to their not being responsive to treatment. The nonresponding patients who were receiving sham treatment were subsequently switched to the active treatment. The nonresponding patients who were receiving the active treatment had their devices reprogrammed as needed. One additional patient who was receiving sham treatment was unblinded between the first month and third month follow-ups and switched to the active treatment.

Thirty-seven patients completed the 3-month endpoint at which time another 2 patients in the sham group and one patient in the active group were unblinded due to their not being responsive to treatment. Nonresponding patients in the sham group were subsequently switched to the active group and nonresponding active patients had their devices reprogrammed as needed. Thirty-four patients completed the 6-month endpoint and 30 completed the 9-month follow-up visit with one patient in the active group requiring unblinding due to not being responsive to treatment. Finally, 30 patients completed the 12-month end of study visit (Fig. 3). Patients in the active group who remained blinded at 12 months, since they had demonstrated sustained positive pain responses over the 12-month period, were subsequently unblinded. The study continued in an open label fashion for a total duration of 36 months, at which point the VAS, ODI and PGIC results of 22 patients were recorded.

The thirty-eight patients that completed the one-month primary endpoint had a mean age of 49 (+- 9.6) years; 47% were women. The mean time to pain onset before entering the study was 9.2 (+- 8.3) years. Half of the patients suffered from PSPS T1 and half were diagnosed with PSPS T2. Nineteen patients were randomized to the active group and 19 to the sham group. Table 1 shows the demographics of both groups and the tests comparing the groups. There were no significant differences between the treatment groups.

Primary Endpoint

The primary endpoint, i.e., the proportion of patients experiencing at least 50% overall pain relief or reporting a mean pain score of 30 mm or less on the VAS scale, were compared at one-month post-implant. The responder rate in the sham group was 3/19 (16%) and in the active group it was 12/19 (63%) ($P = 0.007$). The primary efficacy endpoint passed the inequality test, demonstrating that the proportion of responders was significantly larger with subthreshold stimulation than with sham. The estimated difference in responder

Table 1. *Baseline demographics and characteristics*.

Characteristic	Active (n = 19) N (%) or Mean (SD)	Sham (n = 19) N (%) or Mean (SD)	Test, *P*-value
Age (years)	49.1 (8.5)	49.7 (10.7)	t-test, $P = 0.85$
Gender:			
Male, Female	7 (37%), 12 (63%)	11 (58%), 8 (42%)	X^2, $P = 0.19$
Etiology:			
FBSS, Virgin Back	9 (47%), 10 (53%)	10 (53%), 9 (47%)	X^2, $P = 0.75$
Onset of Pain (years)	9.4 (9.4)	9.1 (7.3)	t-test, $P = 0.92$
Back Pain VAS (mm)	75.7 (11.8)	73.2 (9.2)	t-test, $P = 0.48$
Leg Pain VAS (mm)	30.7 (25.8)	41.3 (26.2)	t-test, $P = 0.22$
ODI (%)	48.0 (14.1)	51.5 (11.6)	t-test, $P = 0.42$
EQ-5D-5L	0.392 (0.180)	0.489 (0.200)	t-test, $P = 0.12$

rates was 47.4%; consequently almost 50% more patients had clinically important relief with subthreshold stimulation (Table 2, Fig. 4).

Secondary Endpoints

All testing was done in a hierarchical fashion (Table 2) in order to conduct every test at 0.05 or 0.025 and not increase the global error rate above 5%.

In order to control the study-wise error rate at 5%, the secondary endpoints were tested since the primary endpoint passed with the stipulation that the secondary endpoints would be tested only if the primary endpoint passed. The further stipulation was that secondary-endpoint testing would stop when an inequality test was not passed.

The testing procedure continued until the end of the testing schedule because all tests were statistically significant at $P = 0.05$.

Pain Reduction

The secondary endpoints of mean pain relief in the back (1a) and legs (1b) were compared using two 2-sided t-tests at $\alpha = 0.025$ (the adjusted α level of the test was to control the study-wise error rate). The active group experienced an average back pain reduction of 35 mm compared to an average of 18 mm in the sham group ($P = 0.014$) (Table 4). The active group had leg pain reduction of 12 mm compared to 6 mm in the sham group ($P = 0.33$) (Table 5). The back pain reductions were clinically or statistically significantly higher in the active group than in the sham group.

At the one-month follow-up, the active group (n = 19) had a decrease in their mean VAS for back pain (46%), while the sham group's (n = 19) mean VAS decreased 25%. As our study's follow-ups continued with nonresponding patients in the sham group being shifted to the active group, mean pain reductions in the active group were 58% (n = 35 at 3 months), 66% (n = 34 at 6 months), 69% (n = 30 at 9 months) and 71% (n = 30 at 12 months). In comparison, a reduction of 40% was seen in 2 patients in the sham group at the 3-month endpoint. All patients in the sham group were unblinded and shifted to the active group by the 3-month follow-up. Pain relief remained consistent through 36 months (n = 22), with a mean reported reduction of 64% compared to baseline, demonstrating significant, sustained long-term pain relief (Fig. 5).

At the one-month follow-up, the active group (n = 19) had a decrease in their mean VAS for leg pain 40%, while the sham group's (n = 19) mean VAS decreased 15%. As our study's follow-ups continued with nonresponding patients in the sham group being shifted to the active group, mean pain reductions in the active group were 62% (n = 35 at 3 months), 64% (n = 34 at 6 months), 61% (n = 30 at 9 months) and 69% (n = 30 at 12 months). In comparison a reduction of 40% was seen in 2 patients in the sham group at the 3-month end-

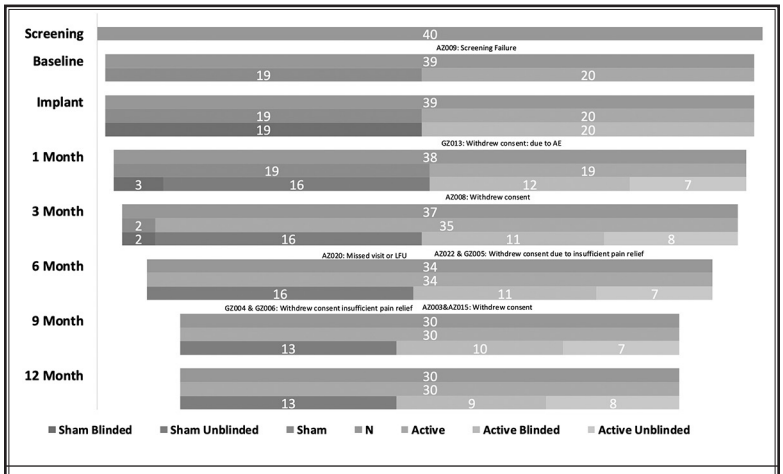


Fig. 3. *Study visit flow chart.*

Table 2. *Primary endpoint statistics (responder rate).*

Group	Obs	Responder Rate (N, %)	Std. Error	Std. Dev.	95% Confidence Interval	
Active	19	12 (63.2%)	11.4%	4.96%	39.3%	87%
Sham	19	3 (15.8%)	8.6%	37.5%	-2.3%*	33.8%
Combined	38	15 (39.5%)	8.0%	49.5%	23.2%	55.8%
Difference	-	9 (47.4%)	14.3%	-	18.5%	76.3%

*Negative value due to normal approximation of confidence interval.

point. All patients in the sham group were unblinded and shifted to the active group by the 3-month visit.

Functionality

The secondary endpoint of change in ODI score was compared using a 2-sided t-test at $\alpha = 0.05$.

Functionality, assessed with the ODI, improved 15.4% (ODI decreased from 48.1% at baseline to 32.7% at the one-month follow-up) in the active group and 7.7% (ODI decreased from 51.5% to 43.8%) in the sham group ($P = 0.046$). The patients' disability decreased clinically or statistically significantly more in the active group than in the sham group (Table 6).

The modal (most common) ODI classification in the active group decreased by one category, from "Severe Disability" to "Moderate Disability," whereas the modal ODI classification of the sham group remained in the "Severe Disability" category.

At the one-month follow-up, the mean ODI score in the active group decreased by one-third, from 48% to 33% (severe to moderate); the sham groups score went from 51% to 44% (no category change). The active group's mean ODI scores further decreased by a total of 44% at the 3-month follow-up, 48% at the 6-month follow-up, 52% at the 9-month follow-up, and 55% at the 12-month follow-up. In comparison, a reduction of 25% was seen in 2 patients in the sham group at the 3-month endpoint. All patients in the sham group were unblinded and shifted to the active group at the 3-month follow-up. At 36 months, a 46% reduction in disability from baseline confirmed improved long-term functionality, resulting in a shift in classification from severe to moderate disability (Fig. 6).

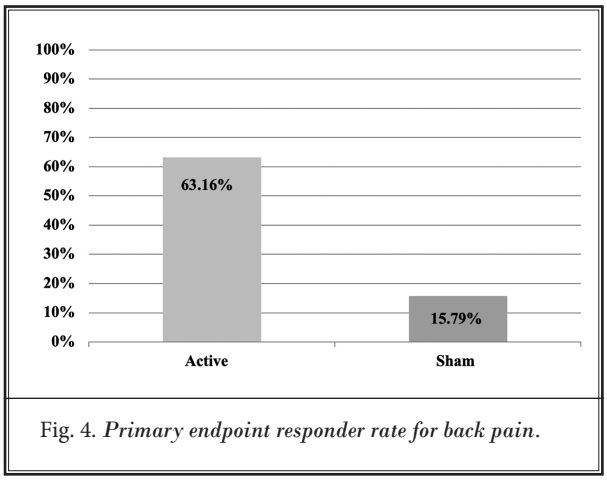


Fig. 4. *Primary endpoint responder rate for back pain.*

Satisfaction

The endpoint PGIC score was compared using a nonparametric t-test (the Wilcoxon rank-sum test) at $\alpha = 0.05$. Patient self-assessment of the results, as measured by the PGIC at the one-month follow-up, had a median category score (using categories numbered 1 through 7) of 5 in the active group and 3 in the sham group. The *P* value of the test for equality of category scores was 0.031. Patients' assessment of their improvement was significantly better in the active group than in the sham group. Ultimately, the

Table 3. *Secondary endpoint testing scheme and results.*

Secondary Endpoint		Test		Continue Testing?
Test	Description	Type	*P*-value	
1a	Reduction in back pain	t-test	0.014	Y
1b	Reduction in leg pain	t-test	0.33	
2	Functionality	t-test	0.046	Y
3	Patient Assessment	t-test	0.031	Y
4	Quality of life	t-test	0.011	Y
5	Degree of back pain relief	Fisher's Exact Test	0.010	NA

Table 4. *Secondary endpoint 1a (back pain reduction).*

Group	Obs	Mean	Std. Error	Std. Dev.	95% Confidence Interval	
Active	19	34.9	4.44	19.3	25.6	44.3
Sham	19	18.2	4.67	20.4	8.40	28.0
Combined	38	26.6	3.46	21.3	19.6	33.6
Difference	-	16.7	6.44		3.67	29.8

36-month follow-up showed a median satisfaction rate of 7 out of 7 among the 22 patients (Table 7, Fig. 7).

Quality of Life

The endpoint of change in the EQ-5D index was compared using a 2-sided t-test at $\alpha = 0.05$.

Quality of life, assessed with the EQ-5D-5L, improved by 0.248 (from 0.392 at baseline to 0.639 at the one-month follow-up) in the active group and by 0.083 (from 0.489 at baseline to 0.572) in the sham group ($P = 0.011$). Quality of life improved clinically or statistically significantly more in the active group than in the sham group (Table 8). Following the one-month follow-up, crossover patients from the sham group (n = 17) reported decreased pain and enhanced quality of life. The other 2 patients in the sham group were unblinded after the 3-month follow-up and subsequently transitioned into the active group (Fig. 8).

Degree of Back Pain

The endpoint of VAS improvement was compared using a 2-sided Fisher's exact test at $\alpha = 0.05$.

In the active group, 12 of the 19 patients (63%) reported good to excellent pain relief (≥ 50% reduction in VAS), 3 (16%) patients reported fair pain relief (25%–50% reduction) and 4 (21%) patients reported poor or no pain relief (0%–25% reduction). In the sham group, 3 of the 19 patients (16%) reported good to excellent pain relief (≥ 50% reduction in VAS), 4 (21%) patients reported fair pain relief (25%–50% reduction) and 12 (63%) patients reported poor or no pain relief (0%–25%) ($P = 0.010$). The distribution of patients' back pain relief was skewed significantly more toward "good to excellent" in the active group than in the sham group (Table 9).

Study Safety Results

There were no serious adverse events in any of the 39 study patients throughout the study's 12 months. Treatment-related complications occurred in 3 patients with a total of 3 adverse events (3/39; 8%) soon after the permanent implant. These 3 patients received a revision due to stimulator migration. Our study shows

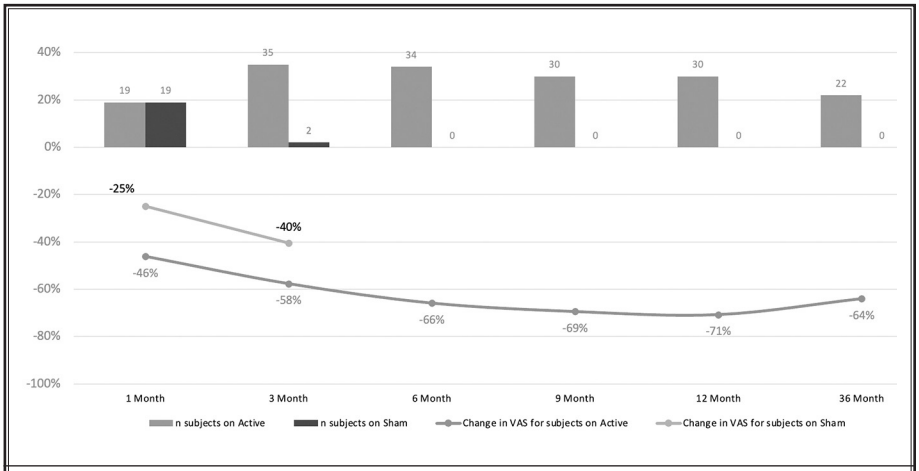


Fig. 5. *Visual Analog Scale back pain scores reductions at follow-up times.*

Table 5. *Secondary endpoint 1b (leg pain reduction).*

Group	Obs	Mean	Std. Error	Std. Dev.	95% Confidence Interval	
Active	19	12.4	4.00	17.4	3.96	20.8
Sham	19	6.00	5.09	22.2	-4.69	16.7
Combined	38	9.18	3.23	19.9	2.63	15.7
Difference	-	6.37	6.47		-6.76	19.5

Table 6. *Secondary endpoint 2 (reduction in ODI score).*

Group	Obs	Mean	Std. Error	Std. Dev.	95% Confidence Interval	
Active	19	15.4	2.89	12.6	9.30	21.4
Sham	19	7.68	2.35	10.3	2.74	12.6
Combined	38	11.5	1.94	12.0	7.59	15.5
Difference	-	7.68	3.72	-	0.131	15.2

that adverse events for patients receiving an external device is clinically or statistically significantly less compared to other neurostimulator studies (7,21).

Discussion

Efficacy

The primary endpoint of this on-going study was analyzed at one-month post-implant in order to report on the safety and efficacy of an externally powered permanent PNS system, specifically the Freedom PNS System, with subthreshold stimulation at the proximal peripheral nerves for treating back pain. Earlier studies showed the efficacy of this externally powered technology (7-9,11-15).

All of our testing was done in a hierarchical fashion; every test was conducted at either $\alpha = 0.05$ or $\alpha = 0.025$ so as to not increase the global error rate above 5%. To control the study-wise error rate at 5%, the secondary endpoints were tested, because the primary endpoint passed with the stipulation that the secondary endpoints would be tested only if the primary endpoint passed. The further stipulation was that secondary endpoint testing would stop when an inequality test was not passed. The testing procedure continued until the end as all tests were statistically significant at $P = 0.05$.

We conclude from the secondary endpoint tests that subthreshold stimulation results in clinically or statistically significantly less back pain, not just in percentage but in qualitative categories (good, fair, and poor) that are easily perceivable by patients. Functionality, as measured by the ODI, was also clinically or statistically significantly improved. Shifts in the ODI scores are additional measurements, demonstrating that the therapy is positively affecting patients on a day-to-day basis, allowing them to resume activities of daily living.

Using the EQ-5D-5L provides a simple, generic measure of a patient's health. The improvement in QoL is especially noteworthy because it is uncommon for generic QoL instruments to show clinically or statistically significant changes due to treatments for a specific condition. We considered using a disease-specific instrument for this study, but there does not appear to be a widely accepted disease-specific QoL instrument for low back pain (22).

Confidence in the PNS system's effectiveness is confirmed through the scores reported by the patients with the PGIC. This metric is a self-reported measure of the patient's satisfaction and perceived efficacy of treatment using a 7-point scale (7 being very much improved and 0 being very much worse). Patients reported a median "5, moderately improved" in the active group compared to "3, a little better" in the sham group.

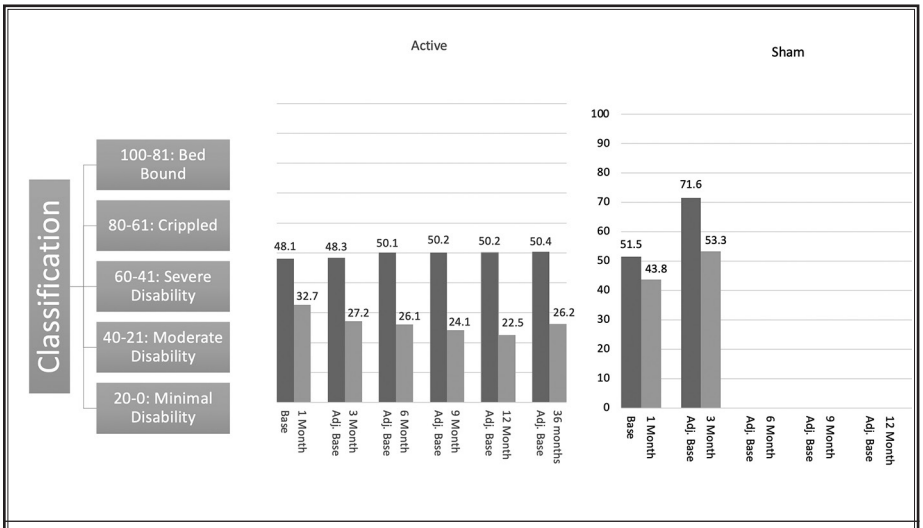


Fig. 6. *Oswestry Disability Index scores at follow-up times (100–81: Bed Bound; 80–61: Crippled; 60–41: Severe Disability; 40–21: Moderate Disability; 20–0: Minimal Disability).*

Table 7. *PGIC category.*

Group	Category							Total
	1	2	3	4	5	6	7	
Active	0 (0%)	3 (16%)	1 (5%)	4 (21%)	5 (26%)	5 (26%)	1 (5%)	19 (100%)
Sham	4 (21%)	2 (11%)	4 (21%)	3 (16%)	4 (21%)	2 (11%)	0 (0%)	19 (100%)
Total	4 (11%)	5 (13%)	5 (13%)	7 (18%)	9 (24%)	7 (18%)	1 (3%)	38 (100%)

By targeting the T9 proximal peripheral nerves to treat the chief concern of axial back pain, we also noted a meaningful improvement in patients' secondary leg pain. This broader pain relief aligns with how PNS can influence multiple spinal segments. Modulating sensory input at the thoracic dorsal rami can calm overactive pathways that connect to nearby levels, reducing pain signals that travel downward. Peripheral stimulation may also activate descending inhibitory pathways, allowing relief to extend beyond the immediate area of stimulation. These combined effects likely explain the unexpected but clinically helpful reduction in leg symptoms (23-25).

Externally Powered Peripheral Nerve Stimulation

There are several key advantages to using a high-frequency electromagnetic coupling powered permanent PNS system. A major benefit is eliminating the need to implant a battery-powered pulse generator in the trunk region. Instead, using a flexible, receiver-based design enables greater adaptability, allowing the implant to be optimally positioned in challenging and anatomically complex areas. This design also reduces risks associated with conventional pulse generator placement, such as surgical complications, surgical battery replacements, and the potential need for revision procedures in these delicate regions (26).

Limitations

Although our study was rigorously designed and conducted, the possibility of residual confounding cannot be fully ruled out.

Conclusion

Our prospective, multicenter, double-blinded, randomized controlled trial demonstrates that subthreshold proximal PNS produced clinically or statistically significantly greater pain reduction and functional improvement than sham stimulation in patients with chronic back pain. Benefits were reflected across multiple validated outcomes, including the VAS, ODI, PGIC, and EQ-5D-5L, and were sustained during long-term follow-up of 36 months.

Adverse events were infrequent and limited to lead migration (8%), which is consistent with all other neurostimulation treatments.

Our findings provide the highest level of RCT evidence supporting the safety and efficacy of subthreshold proximal PNS as a treatment option for refractory chronic back pain due to PSPS T1 or PSPS T2.

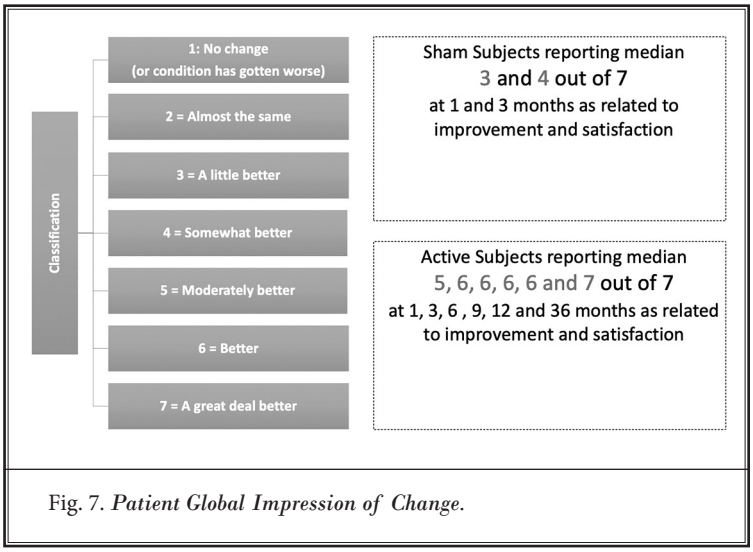


Fig. 7. *Patient Global Impression of Change.*

Table 8. *Improvement in EQ-5D-5L score.*

Group	Obs	Mean	Std. Error	Std. Dev.	95% Confidence Interval	
Active	19	0.248	0.0376	0.164	0.169	0.327
Sham	19	0.0834	0.0479	0.209	-0.0173	0.184
Combined	38	0.166	0.0329	0.203	0.0987	0.232
Difference	-	0.164	0.0609	-	0.0406	0.288

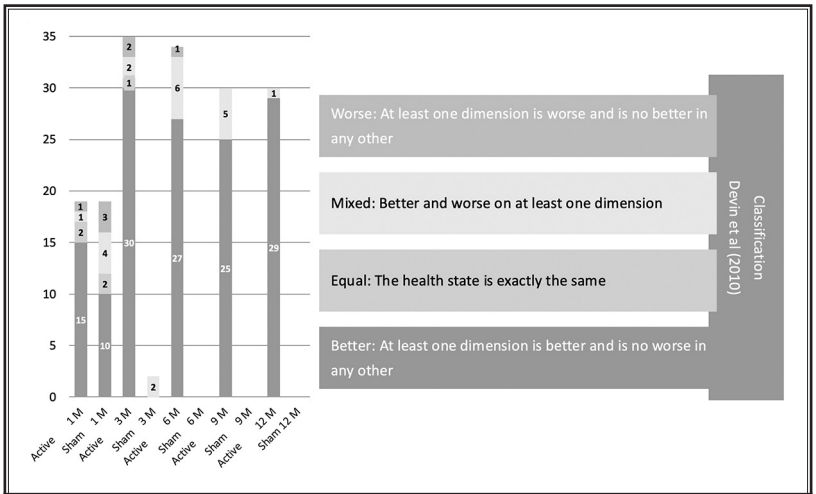


Fig. 8. *EuroQOL-5 Dimension Questionnaire Health Profile at follow-ups.*

Table 9. *Secondary endpoint 2 (degree of back pain relief).*

Group	Obs	Poor (N, %)	Fair (N, %)	Good to Excellent (N, %)
Active	19	4 (21%)	3 (16%)	12 (63%)
Sham	19	12 (63%)	4 (21%)	3 (16%)
Combined	38	16 (42%)	7 (18%)	15 (39%)
Difference	-	-42%	- 5%	47%

Supplemental material is available at www.painphysicianjournal.com

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Appendix 1. Study Inclusion and Exclusion Criteria

Inclusion criteria:

A. 18 years of age or older at time of written informed consent
B. A diagnosis of predominant, chronic, intractable back pain with a Visual Analog Scale pain score > 50 mm on a 100-mm scale
C. A diagnosis of predominant, chronic, intractable back pain for at least 6 months before study participation
D. Based on the medical opinion of the Principal Investigator, the patient has a stable pain medication regimen
E. Based on the medical opinion of the Principal Investigator, there is no evidence of anatomic abnormalities that could jeopardize the placement of the device or pose a hazard to the patient
F. The patient is willing to undergo the surgical implant procedure, attend visits as scheduled, and comply with the study requirements
G. The patient is willing and able to operate the patient programmer and recharging equipment and has the ability to undergo study assessments and provide accurate responses
H. Based on the opinion of the implanter, the patient is a good surgical candidate for the implant procedure
I. Subject is a man or nonpregnant woman
J. The patient is deemed to be neuropsychosocially appropriate for implantation therapies based of the assessments of a clinical psychologist and principal investigator, using face-to-face encounters and the psychological testing described in the measures
K. The patient is capable of giving written informed consent.

Exclusion criteria:

A. Obvious mechanical instability related to pain (diagnosed by imaging taken within the previous 6 months)
B. Unresolved malignancies in the previous 6 months
C. The patient has postherpetic neuralgia (shingles)
D. The patient has an active systemic infection or is immune-compromised
E. Based on the medical opinion of the Principal Investigator, the patient has other psychological conditions (e.g., psychosis, suicidal ideation, borderline personality disorder, somatization, narcissism), other health conditions (e.g., substance abuse, another chronic condition requiring the regular use of opioid medication), or other legal concerns that would preclude enrollment in the study or potentially confound the results of the study
F. The patient is currently enrolled in or plans to enroll in any concurrent drug and/or device study while participating in this study
G. The patient has insulin-dependent diabetes that is not controlled through diet and/or medication (determined by the physician) or has noninsulin dependent diabetes that is not well controlled through diet and/or medication
H. Bleeding complications or coagulopathy issues
I. Pregnant/lactating or not using adequate birth control
J. A life expectancy of less than one year
K. Any active implanted device whether turned off or on
L. A previous spinal cord stimulation implant
M. Conditions requiring magnetic resonance imaging evaluation or diathermy procedures.