Prospective Study

Composite Treatment Response from a Prospective, Multi-Center Study (US-nPower) Evaluating a Miniature Spinal Cord Stimulator for the Management of Chronic, Intractable Pain

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Background: Measures of therapeutic efficacy in pain studies have historically focused on pain scores, such as the Visual Analog Scale (VAS) or the Numeric Rating Scale. However, pain scores capture a univariate measure of a multivariate condition present in patients with chronic pain, where the pain condition can affect activities of daily living, sleep, quality of life, and mood. Hence, examining composite endpoints, which incorporate outcomes from multiple facets of pain, may allow investigators to better assess improvements in chronic pain patients with various new treatments.

Objectives: This trial was designed to evaluate the performance of the Nalu™ Neurostimulation System (Nalu Medical, Inc.), a miniature implanted pulse generator (micro-IPG), in the treatment of low-back pain and leg pain with spinal cord stimulation therapy.

Study Design: This was a prospective, single arm, multicenter, open-label, postmarket study that followed patients for 90 days postimplantation of the Nalu Neurostimulation System.

Setting: Patients were recruited from, and treated at, 15 US-based comprehensive pain centers.

Methods: Patients with chronic, intractable, neuropathic pain of the back and/or leg(s), with a VAS pain score of at least 6 at the time of screening, were included. The micro-IPG was implanted per standard clinical practice. Patient-reported outcomes (PROs), including VAS pain scores, Oswestry Disability Index (ODI), Beck Depression Inventory, quality-of-life metric (EQ-5D-5L), Patient Global Impression of Change (PGIC), and sleep disturbance Patient-reported Outcomes Measurement Information System (PROMIS) were recorded. Literature-based minimal clinically important differences (MCIDs) were used to define the MCID responder rates as well as a composite endpoint analysis.

Results: Ninety-four percent (94%) of the study patients reached the MCID in at least 2 of the PROs. Five out of 6 PROs demonstrated a responder rate of > 75%. Forty-nine percent (49%) of the patients were holistic responders, meaning they responded in each of the 6 outcome measures under consideration. Overall VAS pain scores reached the MCID in 86% of the patients. PGIC demonstrated the largest MCID responder rate: 100%. The ODI score reached the MCID in 94% of the patients; the BDI score reached the MCID rate in 84% of the patients; the EQ-5D-5L score reached the MCID in 77% of the patients; and the PROMIS score reached the MCID in 67% of the patients.

Limitations: While this was a multicenter, prospective study, it was also a single arm,

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nonrandomized trial. The 35 study patients were only followed for 90 days post micro-IPG implant.

Conclusion: In the face of improving spinal cord stimulation pain outcomes, composite PROs are likely to become more common in evaluating therapeutic response. Responder rates, defined by the MCID, may help to establish composite endpoints. Since MCID was achieved across a variety of endpoints indicates that treatment with the Nalu Neurostimulation System provided a robust treatment response.

Key words: Spinal cord stimulation (SCS), chronic pain, radiculopathy, micro-IPG, battery-free, persistent spinal pain syndrome (PSPS), Failed Back Surgery Syndrome (FBSS), composite endpoints, holistic responders

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Spinal cord stimulation (SCS) for the treatment of chronic low back and leg pain, is a well-established therapy. Recent advances in novel stimulation waveforms have demonstrated an overall improvement in pain outcomes (1). As such, given an across-the-board improvement in pain scores, it is difficult to determine if one particular waveform is superior to another. For example, 10 kHz (2), closed loop (3), differential target multiplexed (4), and pulsed stimulation pattern (PSP) (5,6) all have similar outcomes in the range of 75% to 85% pain reduction, despite the significant difference in the waveforms utilized and their differential, putative mechanisms of action. Consequently, several investigators (7-12) have suggested utilizing composite outcome measures, where efficacy is evaluated based upon multiple patient-reported outcomes (PROs).

Composite outcomes come in many forms, such as responder rate-based, z score-based or rank-based methods (8). The method employed here was the responder-rate approach relying on the minimal clinically important difference (MCID) as the responder criterion (7). By combining multiple MCIDs in a composite outcome measure, one can better assess the overall improvements in outcomes in a clinically meaningful way, rather than simply relying on an improvement in a lone pain score (13).

The safety and efficacy results of a prospective, open-label, postmarket, multicenter, 90-day study evaluating the Nalu™ Neurostimulation System (Nalu Medical, Inc.) to treat severe, chronic low back pain and leg pain has been published (14). The results reported here are from a post-hoc analysis of predefined secondary outcome measures in the same patients evaluated in Desai, et al (14).

Methods

Patients, recruited from 15 US-based comprehensive pain centers, who met the inclusion/exclusion criteria, and signed written informed consent, were enrolled in the study. The study was approved by an independent institutional review board and conducted in compliance with institutional review board regulations and with ISO-14155:2020. The study was registered on Clinicaltrials.gov (NCT04503109). Desai, et al (14) has a detailed description of the methods we used and Malinowski, et al (15) has a device description.

Baseline assessments were completed prior to the study intervention with the following outcome measures collected in the office: 24-hr Visual Analog Scale (VAS) for overall pain, Beck Depression Inventory (BDI) for mood, Oswestry Disability Index (ODI) for functional disability, European Quality of Life-5 Dimensions-5 Level Version (EQ-5D-5L) for quality-of-life assessment, and the Patient-reported Outcomes Measurement Information System (PROMIS) sleep disturbance short form. Ninety days following the device implantation and activation, the assessments documented at baseline were repeated. Additionally, the Patient Global Impression of Change (PGIC) was documented. The 6 PROs employed here were based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (16); they were collected according to the study protocol as described in Desai, et al. (14). The MCIDs were chosen and defined based upon the literature cited in Table 1 (16-21) as follows: VAS pain scores (16; ≥ 30%), ODI (17; ≥ 10 points), BDI (18; ≥ 17.5%), EQ-5D-5L (19; ≥ 0.074), PGIC (16; minimally improved, much improved or very much improved), PROMIS (20; ≥ one-half SD of baseline). For this analysis, patients were evaluated for PRO responders based upon MCID. The MCID responder rate was the

percentage of patients who achieved the MCID for that particular PRO.

Devices were trialed, implanted and programmed following the usual standard of care and in accordance with the device labeling as described in Malinowski, et al (15). Multiple SCS therapies were offered including, Traditional (Tonic; T-SCS), PSP (as described by Desai, et al [6]) T-SCS/PSP combination, and scheduled PSP. The T-SCS/PSP combination entails interleaving the 2 therapies in a single program. The PSP family of waveforms are composite, multidimensional signals theorized to address up to 6 mechanisms of action (6). Scheduled PSP, on the other hand, refers to delivering one specific set of PSP parameters (e.g., electrode configuration, amplitude, pulse pattern, train, and dosage) for a brief period (i.e., several seconds to minutes) before automatically moving on to the next PSP parameter set. Patients returned to the clinic following 90 days of treatment with the permanent miniature implanted pulse generator (micro-IPG) device and were assessed by repeating the aforementioned questionnaires.

Using the SAS™ version 9.4 (SAS Institute Inc, Cary, NC), basic statistical analyses were completed on all endpoints, including computation of average, variance, SDs (± SD reported unless otherwise specified), SEM, and trend analysis. Parametric and nonparametric statistics were employed, as appropriate.

Results

A total of 35 evaluable patients were treated and followed out to the 90-day endpoint of the study. They ranged in age from 21.5 to 76.2 years(average: 55.9 ± 11.8); 54% were women. The average duration of chronic pain prior to enrollment was 10.46 years (range: 0.75 to 36.75). Thirty-three patients (94%) reported both leg and low-back pain – one reported leg pain only and one reported low-back pain only. Desai, et al (14) has a detailed description of patient demographics, disposition, and adverse events.

The MCID responder rates were computed based upon the MCIDs defined in Table 1. The pain responder rate at 90 days was 86% for overall pain ($P < 0.001$) assuming a ≥ 30% reduction in pain as the responder-rate criterion (Fig. 1A). Figure 1B shows the change in ODI score from baseline to 90 days, with the green line denoting the MCID ODI (17). Ninety-four percent of the ODI outcomes in this study were above the MCID (ODI score ≥ 10), demonstrating a strong functional improvement as a result of this therapy. The responder rates for the remaining 4 PROs were as follows: Fig. 2, PGIC = 100%; BDI = 84%; EQ-5D-5L = 77%; PROMIS = 67%. In the case of the PROMIS sleep evaluation, 15 of 35 patients (43%) had normal sleep patterns at baseline. This may explain why the lowest MCID responder rate (67%) was achieved for the sleep outcome measure (see Discussion).

Table 1. *MCID for outcome measures.*

Outcome Measure	MCID	Source
NRS-11, VAS - Pain	≥ 30%	Dworkin, et al (16)
BDI - Mood	≥ 17.5%	Button, et al (18)
ODI - Disability	≥ 10 points	Ostelo, et al (17)
PROMIS - Sleep	≥ one-half SD of baseline	Norman, et al (20)
PGIC – Overall Change	Minimally, Much or Very Much improved	Dworkin, et al (21)
EQ-5D-5L - QoL	≥ 0.074	Walters, et al (19)

VAS, Visual Analog Scale. NRS-11, Numeric Rating Scale. BDI, Beck Depression Inventory. ODI, Oswestry Disability Index. PROMIS, Patient-reported Outcomes Measurement Information System. PGIC, Patient Global Impression of Change. QoL, Quality of Life. EQ-5D-5L, EuroQol 5-Dimension 5-Level.

Each of the average PROs showed statistically significant improvement compared to baseline ($P < 0.001$; Fig. 3A). The average improvement in VAS pain scores was 74%, with the baseline average pain score of 78.5 ± 12.6 improving to 20.5 ± 21.4 at 90 days. ODI scores improved from an average of 57.0 ± 13.2 at baseline to 24.0 ± 14.4 at 90 days, which corresponds to a 58% improvement. BDI scores also improved by an average of 58% by dropping from 17.7 ± 11.6 at baseline to 7.2 ± 9.3 at 90 days. The EQ-5D-5L scores improved from 0.53 ± 0.17 at baseline to 0.76 ± 0.15 at the end of the study, demonstrating a 59% improvement. PROMIS scores improved by 14%, with 56.3 ± 8.4 at baseline compared to 47.6 ± 7.5 at 90 days.

The average improvement in each PRO exceeded the MCID by more than a factor of 2 (Fig. 3B). For example, the difference between ODI at baseline and ODI at 90 days was 33 points (57.0-24.0 = 33). Given that the MCID for ODI is 10 points (Table 1), a factor of 3.3 (33/10) was found in the case of ODI. The range in the mean number of MCIDs met was 2.1 for PROMIS (sleep) and 3.3 for both ODI and BDI. In the case of pain and quality of life, the mean number of MCIDs met was 2.5 and 3.1, respectively.

Composite outcomes were explored by plotting the VAS pain scores from each patient against another

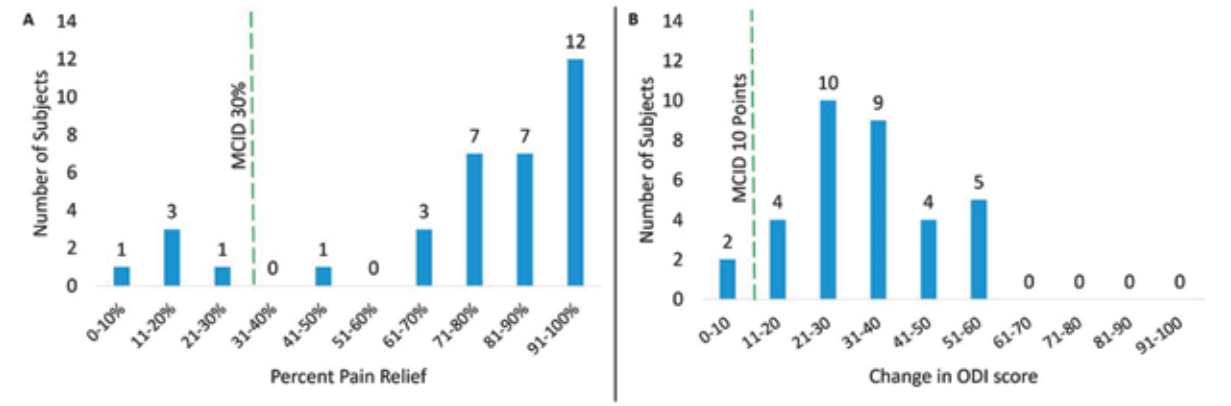

Fig. 1. *Improvements in pain and disability, from baseline to 3 months. Patients falling to the right of the green line are above the MCID. A) Histogram showing percent pain relief as measured by VAS. B) Histogram showing the improvement in disability as measured by ODI. MCID, Minimal clinically important difference.*
VAS, Visual Analog Scale. ODI, Oswestry Disability Index.

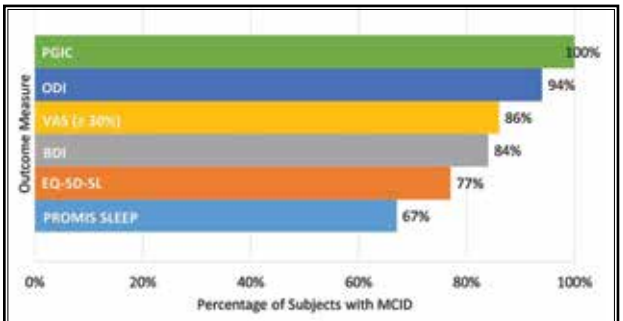

Fig. 2. *Responder rate for each outcome measure based on MCID. MCID, Minimal clinically important difference.*
VAS, Visual Analog Scale. NRS, Numeric Rating Scale. BDI, Beck Depression Inventory. ODI, Oswestry Disability Index. PROMIS, Patient-reported Outcomes Measurement Information System. PGIC, Patient Global Impression of Change. QoL, Quality of Life. EQ-5D-5L, EuroQol 5-Dimension 5-Level.

PRO in the same patient (Fig. 4). All correlations were statistically significant ($P < 0.001$), indicating a robust, multifaceted, therapeutic response. For example, Fig. 4A shows the relationship between the VAS and ODI. The high Pearson correlation coefficient of 0.86 and corresponding P value of < 0.001 demonstrates a strong relationship between improvement in VAS pain scores and improvement in functional disability following treatment with the micro-IPG. The VAS was then plotted against the EQ-5D-5L, BDI, and PROMIS (Figs. 4B, 4C, and 4D) with correlations of 0.74 (EQ-5D-5L), 0.43 (BDI) and 0.59 (PROMIS). The PGIC was not included in this composite analysis since this outcome inherently lacks baseline data.

Another way to evaluate composite outcomes is to define a responder as a patient that achieved the MCID in a pain outcome and/or a functional outcome. For example, one of the analyses looked at the VAS and ODI and showed a responder rate of 97% (33/34) i.e., 33 of 34 patients were responders in either the VAS or ODI or both. Similarly, the composite outcome linking the VAS and the PGIC demonstrated a 100% responder rate; VAS and BDI, VAS and EQ-5D-5L, and VAS and PROMIS, all demonstrated a 91% responder rate by this metric.

An aggregate analysis (Fig. 5) shows that 94% of patients were MCID responders in 2 or more of the PROs, 86% in 4 or more, and 75% in 5 or more. The remaining 14% were responders to 3, 2 or one of the PROs. Forty-nine percent were considered holistic responders, meaning they were responders in all 6 PROs. Another 46% were considered multimodal responders, meaning they were responders in 2 to 5 PROs (7). There were 2 patients who only responded in one PRO and therefore were neither a holistic nor a multimodal responder.

Discussion

This was a single-arm, prospective, postmarket study that followed patients with chronic pain for 90-days postimplantation of an SCS micro-IPG. PROs were evaluated for outcomes greater than the MCID and were combined to form a composite outcome measure to assess each patient's response to SCS with the micro-IPG.

When evaluating pain treatments, there are advantages to capturing and analyzing outcomes

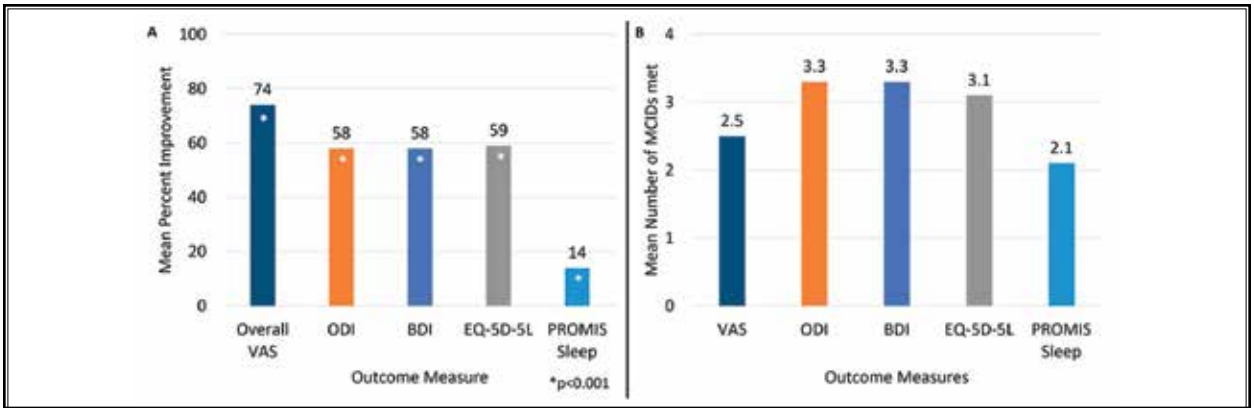

Fig. 3. *A) Percent improvement in all outcomes measures from baseline to 3-months. B) Mean number of MCIDs met by patients at 3-months.*
MCID, Minimal clinically important difference. VAS, Visual Analog Scale. NRS, Numeric Rating Scale. BDI, Beck Depression Inventory. ODI, Oswestry Disability Index. PROMIS, Patient-reported Outcomes Measurement Information System. QoL, Quality of Life. EQ-5D-5L, EuroQol 5-Dimension 5-Level.

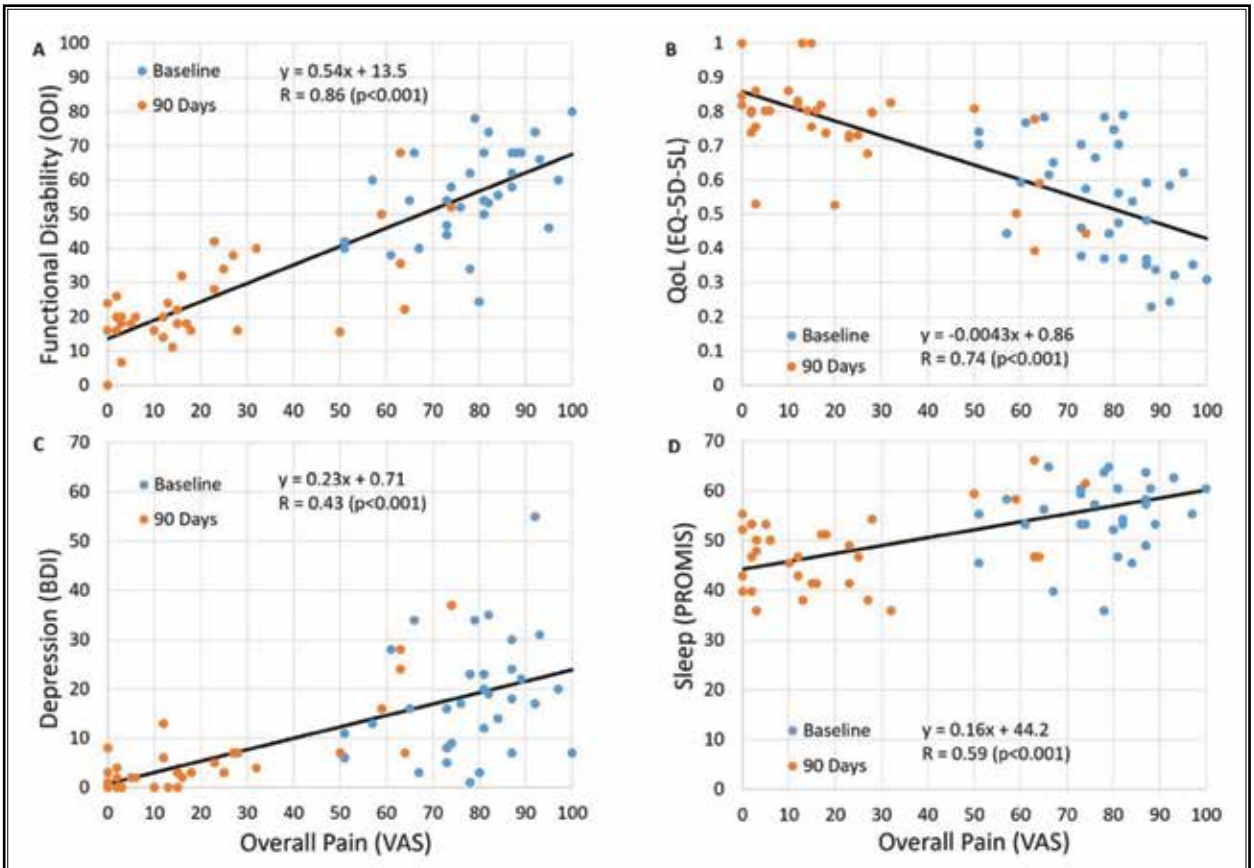

Fig. 4. *Scatter plots showing correlation between pain outcomes and functional outcomes. A) VAS and ODI; B) VAS and EQ-5D-5L; C. VAS and BDI; D. VAS and PROMIS.*
VAS, Visual Analog Scale. BDI, Beck Depression Inventory. ODI, Oswestry Disability Index. PROMIS, Patient-reported Outcomes Measurement Information System. QoL, Quality of Life. EQ-5D-5L, EuroQol 5-Dimension 5-Level.

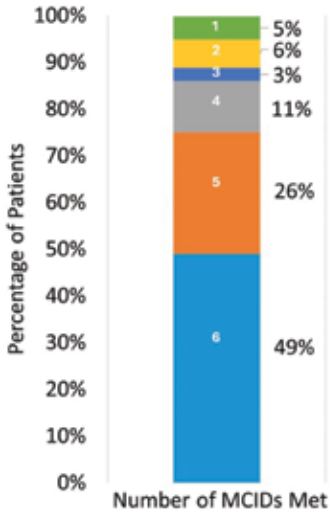

Fig. 5. *Holistic responder analysis. Each stacked bar represents a different number of MCIDs (one to 6). The percentage adjacent to each MICD corresponds to the proportion of patients who achieved that MCID. Holistic responders must have met the MCID in all 6 of the Patient Reported Outcomes. Thus, 49% of the patients were holistic responders, based upon this analysis.*
MCID, Minimal clinically important difference.

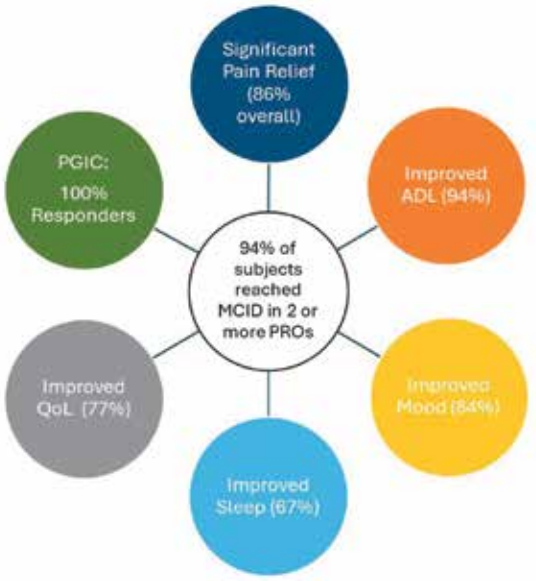

Fig. 6. *Illustration of multiple PRO domains driving a composite outcome.*
PRO, Patient-reported outcome. ADL, Activities of daily living. PGIC, Patient Global Impression of Change. QoL, Quality of Life. MCID, Minimal clinically important difference.

in multiple domains (7,21,22), since pain cannot be separated from its consequences. For example, quality of life, emotional and physical functioning, as well as sleep, are affected by pain (10-12,23). In our study, 6 PROs were captured and analyzed separately as well as in a composite manner. A robust, holistic therapeutic response was demonstrated by evaluating the MCID for multiple PROs, beyond just VAS pain scores alone.

At 90 days postimplantation, the overall VAS responder rate (30% criterion) was 86%, which is similar to the published results from the same cohort. In that report, Desai, et al (14) found the 24-hour VAS score in the back and in the legs had an 86% responder rate (50% criterion). In a different study using the same micro-IPG using the Numeric Rating Scale, Salmon, et al (5) showed an 86% responder rate in the leg and 81% in the back at 90 days postimplantation. In terms of long-term outcomes, Salmon, et al (24) followed these same patients out to one year, where possible. This responder rate analysis showed 91% in the leg and 82% in the back with a last observation carried forward of 80% and 83%, respectively. These particularly robust responder rates, all well over 80%, could in part be due to the use of the PSP waveform, which is postulated to operate under multiple mechanisms of action (6).

The PROs, when averaged across patients, demonstrates a statistically and clinically significant improvement relative to baseline, collected prior to the intervention ($P < 0.001$, Fig. 3A). A strong positive response to the therapy was indicated by the percent improvement in VAS, functional disability (ODI), quality of life (EQ-5D-5L), mood (BDI), and sleep (PROMIS; Fig. 3A) ranging from 14% to 74% improvement. The improvement in each PRO far exceeds the MCID by a factor of 2.1 to 3.3 (Fig. 3B). Kapural, et al (9) performed a similar analysis looking at 5 SCS outcome domains in a closed-loop therapy, rather than 6 outcome domains, as we did. They found that the MCID was exceeded by

a factor of 1.6 to 3.1, depending on the PRO – pain, the ODI, the EQ-5D-5L, the Profile of Mood States, and the Pittsburgh Sleep Quality Index.

Composite endpoint analysis can be displayed graphically by plotting individual VAS scores against the other PROs (ODI, EQ-5D-5L, BDI, PROMIS). This type of analysis is important because it can show a correlation between improvements in chronic pain and improvements in a second domain, which may be the chief concern of a patient. All 4 scatter plots (Fig. 4) showed high correlation ($P < 0.001$) via Pearson correlation coefficient, demonstrating 4, vigorous, bivariate, therapeutic responses. The highest correlation was obtained between VAS and ODI (r = 0.86). This is consistent with the results of Russo, et al (10), where they evaluated subperception SCS, while comparing 13 PROs. Their highest correlation was between "evening pain intensity" and "daily walking tolerance time" with an r value of 0.90 ($P = 0.004$).

Our analysis shows that 94% of the patients in our study were either a multimodal or holistic responder by reaching the MCID in 2 or more PROs, whereas 49% were holistic responders, meaning they improved by at least one MCID in all 6 PROs. Kapural, et al (9) found a similar holistic responder rate in 5 PROs of 53.7% in a closed-loop study. The strong multifaceted response to the therapy as evidenced by the combined holistic and multimodal responder rate of 94% argues for the clinical utility of this micro-IPG and the paresthesia-free PSP waveform. Up to 6 postulated mechanisms of action of the PSP waveform could account for the robust outcomes (see Desai, at al [6]).

As pain outcomes are approaching a ceiling and with the advent of multiple novel stimulation patterns, investigators are looking for more sensitive methods to differentiate among these various therapies. The composite analyses we made may be one such way to separate therapies. For example, examining composite endpoints may allow investigators to better assess how various new treatments affect improvements in patients with chronic pain. Figure 6 illustrates how multiple PRO domains feed into a composite outcome.

When examining responder rates, Levy, et al (7) discussed removing from the analysis those patients with baseline values that are within the normal range. The justification for doing so is that it is unreasonable to expect a patient with normal values to become "more normal" with the therapy. In our study, there were only 2 PROs in which multiple patients exhibited normal values at baseline – the PROMIS sleep index and the BDI. In the case of PROMIS, 15 of 35 patients (43%) had normal baseline PROMIS values. In the case of the BDI, 13 of 34 patients (38%) had normal baseline values. Nevertheless, these patients with normal baseline values were included in the analysis, given the small total sample of study patients. When patients with normal baseline PROMIS scores were excluded from the analysis, the sleep responder rate jumped to 80% (16/20) as opposed to 67% when patients with normal baseline values were included. However, in the case of BDI, excluding the patients with normal baseline values left the responder rate nearly the same 27/32 (84%) vs 17/20 (85%).

Limitations

Our study has several limitations. While this was a prospective study, it was a single arm, nonrandomized trial, and it only followed 35 patients up to 90 days post micro-IPG implant

Conclusion

The multimodal analysis contained here demonstrates that SCS treatment with the micro-IPG resulted in a robust improvement in the patients' conditions across multiple end points. The fact that nearly all of them (94%) showed an improvement in at least 2 of the PRO domains indicates that treatment with the micro-IPG can address multiple areas of concern beyond just pain. This was corroborated by the correlation between VAS pain scores and other PRO domains. These results should give treating physicians the confidence to take on complex clinical presentations of chronic pain with the micro-IPG. Given these results, along with the strong usability and comfort scores collected previously (5,14,24), this system carries potential advantages when compared to conventional, large, battery-containing IPGs. These positive outcomes may warrant further investigation and analysis.

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Conflict of Interest

Mehul J. Desai received grants for research from Nalu Medical, SPR Therapeutics, Abbott, Averitas, Mainstay, Saol, Vivex; consults for SPR Therapeutics, Nalu Medical and VYRSA and has stock options at SPR Therapeutics, VYRSA, SynerFuse and Virdio Health.

Leo Kapural consults for Avanos, FUS Mobile, Neuralace, Nevro, Xalud and Nalu Medical; participated in advisory board capacity at Avanos, Gimer, Neuralace, Nevro, Presidio and PainTeq; has stock options in GammaCore. James Makous consults for and has stock option in Nalu Medical. Shilpa Kottalgi is an employee of Nalu Medical. Peter Staats consults for Nalu Medical, SPR Therapeutics, Biotronik, Medtronic, Saluda, National Spine and Pain Centers, electroCore; has stock options at Nalu Medical, Saluda, SPR Therapeutics and electroCore; has leadership or fiduciary roles at the WIP, ASIPP and Florida Academy of Pain Medicine. Gary Heit consulted for Nalu Medical, Agitated Solutions, Nesos. Kasra Amirdelfan has a grant from Boomerang Healthcare and minor stock options at Nalu Medical. Chheany Ung had research grant from Nalu Medical for conduct of this study and consults and speaks for Nalu Medical and Nevro Dawood Sayed research grant from Nalu Medical. Joel Ackerman received research funding from Nalu Medical, Nevro, Boston Scientific. Michael Fishman received research funding from Nalu Medical and consulting fees from Biotronik, Saluda, Medtronic, Wise Neuro; speaker fees for Collegium, Mainstay and Medtronic and has stock options in Brixton Biosciences, Celeri Health and Aurora Spine. Robert Ball has received research funding from Nalu Medical, Vivex, Boston Scientific and speaker fees from Relievant. Ramana Naidu received consulting fees from Biotronik, SPR Therapeutics, Medtronic; speaker fees from Abbott, Boston Scientific, Nalu Medical, Bioventus, SPR Therapeutics and has stock options from Nalu Medical. Sailesh Arulkumar received research funding, consulting fees and speaker fees, from Nalu Medical. Sean Li received research funding from Nalu Medical; grants and consulting fees from Avanos, Averitas Pharma, Biotronik, Nalu Medical, Neuralace, Nevro, Saluda, SPR Therapeutics, PainTeq, Abbott,NeuroOne,Vertos and Presidio. He has leadership or fiduciary role in NJSIPP and ASPN, and has stock options from Nalu Medical and NeuroOne. David Rosenfeld: Abbott, Acel Rx. Tejal Raju received research funding and speaker fees from Nalu Medical. Aaron Calodney received consulting fees from PainTeq, TissueTech and speaker fees from Medtronic, Stryker, Nevro, Boston Scientific. Mayank Gupta received grants from Averitas, Nevro, Grunenthal, Scilex, Stratus, Boston Scientific, Nalu Medical, SGX-Nova and Sollis; consulting fees from Nalu Medical, speaker fees from Averitas and has a leadership or fiduciary role at KSIPP. Ajay Antony received research funding and consulting fees from Nalu Medical, Abbott, Saluda, Boston Scientific, PainTeq, SPR Therapeutics, Biotronik, Vertos.

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