Retrospective Review

A Retrospective Review of Real-world Outcomes Following 60-day Peripheral Nerve Stimulation for the Treatment of Chronic Pain

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Background: Real-world data can provide important insights into treatment effectiveness in routine clinical practice. Studies have demonstrated that in multiple different pain indications temporary (60-day) percutaneous peripheral nerve stimulation (PNS) treatment can produce significant relief, but few real-world studies have been published. The present study is the first real-world, retrospective review of a large database depicting outcomes at the end of a 60-day PNS treatment period.

Objectives: Evaluate outcomes during a 60-day PNS treatment in routine clinical practice.

Study Design: Secondary retrospective review.

Methods: Anonymized records of 6,160 patients who were implanted with a SPRINT PNS System from August 2019 through August 2022 were retrospectively reviewed from a national real-world database. The percentage of patients with ≥ 50% pain relief and/or improvement in quality of life was evaluated and stratified by nerve target. Additional outcomes included average and worst pain score, patient-reported percentage of pain relief, and patient global impression of change.

Results: Overall, 71% of patients (4,348/6,160) were responders with ≥ 50% pain relief and/or improvement in quality of life; pain relief among responders averaged 63%. The responder rate was largely consistent across nerve targets throughout the back and trunk, upper and lower extremities, and posterior head and neck.

Limitations: This study was limited by its retrospective nature and reliance on a device manufacturer's database. Additionally, detailed demographic information and measures for pain medication usage and physical function were not assessed.

Conclusions: This retrospective analysis supports recent prospective studies demonstrating that 60-day percutaneous PNS can provide significant relief across a wide range of nerve targets. These data serve an important role in complementing the findings of published prospective clinical trials.

Key words: Peripheral nerve stimulation, neuromodulation, 60-day PNS, nonopiod, real-world evidence

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Peripheral nerve stimulation (PNS) has been used successfully for more than 50 years to provide patients with effective, nonpharmacological pain relief. In the midst of the ongoing opioid crisis in the United States, PNS has demonstrated utility as a nonopioid pain management solution for a variety of pain conditions, including low back pain, joint pain, posttraumatic and neuropathic pain, postoperative pain, types 1 and 2 complex regional pain syndrome, oncologic pain, and others (1-3).

In recent years, a percutaneous PNS system was developed that includes fine-wire, open-coil leads designed to reduce infection risk; they can be safely implanted for up to 60 days (4-6). This novel 60-day PNS treatment has demonstrated the potential to produce significant pain relief, resulting in improvements in function, quality of life, and reductions in pain medication usage without requiring permanently implanted hardware (6-9). Prospective clinical trials, including multiple randomized controlled trials, have supported the safety and efficacy of this treatment to produce significant pain relief during the active treatment, and sustained relief following completed treatment, including targeting the lumbar medial branch, axillary, femoral, and sciatic nerves (6-8,10,11). However, few analyses have been published regarding the use of 60-day PNS in routine clinical practice.

Real-world data is defined by the US Food and Drug Administration to include data relating to patient health status and/or the delivery of health care from a variety of sources, such as electronic health records, product registries, and patient-generated data. Real-world data that are routinely collected, as opposed to traditional clinical trials, can provide key insights into treatment effectiveness and safety in clinical practice outside of the research environment. There are increasing calls to leverage these data sets to help improve clinical practice and guidelines in the field of neuromodulation (12-14).

While real-world data can vary widely in scope and data quality and may lack the high internal validity in specific target populations provided by prospective, randomized controlled trials, large observational real-world studies may better represent routine clinical practice (15). Accordingly, studies have begun to capitalize on the real-world data made available through the proliferation of novel neurostimulation technologies, highlighting the value of such data as a complement to formal clinical trials by adding to the breadth and depth of clinical evidence (15,16). Within the neuromodulation field, device manufacturers have begun to facilitate the aggregation and availability of such information through digital platforms. These data sets have natural limitations that must be considered due to provenance and potential sources of bias in data collection. Nonetheless, they provide examples of the potential value that can be derived by evaluating therapies in routine clinical practice. Large data sets, especially, help drive innovation and identify trends, such as patient outcomes, safety, and technology usage patterns within physicians' practices (15,17-19).

Evaluating real-world outcomes during a 60-day PNS treatment period is thus an important step to complement previous prospective clinical trials. This study presents the largest real-world analysis to date regarding effectiveness of 60-day PNS through a retrospective anonymized review of more than 6,000 patients from a device manufacturer's database to assess outcomes during the 60-day treatment period.

Methods

Study Design

This study was an IRB-approved (WCG IRB, WIRB), retrospective review of anonymized data from a device manufacturer's database, consisting of patients who received implantation of temporary PNS leads (SPRINT® PNS System, SPR Therapeutics, CLeveland, OH, USA) and gave written approval at the time of treatment to collect such data. Treatment-related and outcomes data were recorded by device representatives during standard interactions to help guide patient education and compliance, technical troubleshooting, stimulation programming, and treatment optimization as part of the routine use of the device. For example, patient reports of percentage pain relief or average pain score were used to inform adjustment of stimulation parameters or device usage recommendations to optimize outcomes during the treatment period.

The review retrospectively analyzed the anonymized data from patients who met the following inclusion and exclusion criteria: 1) patients must have been implanted for 60-day PNS treatment from August 2019 through August 2022; 2) the baseline and end of treatment (EOT) data provided were sufficient to assess the primary outcome, moderate to severe pain before beginning PNS (average Numeric Rating Scale [NRS-11] pain score ≥ 4); 3) received at least 7 days of PNS treatment. Patients who were treated for acute postoperative pain were excluded because of the differences in

acute and subacute pain management and trajectory compared to chronic pain. There were no other exclusionary criteria.

60-Day PNS Treatment

The SPRINT PNS System consists of open-coil leads implanted percutaneously, typically using ultrasound or fluoroscopic guidance, with stimulation delivered by an external pulse generator for up to 60 days (5,6). The stimulating leads are intended to be placed remote from the stimulation target (e.g., 0.5 – 3 cm distant from the nerve). Stimulation utilizes an asymmetric charge-balanced biphasic pulse train (amplitude: 1 – 30 mA; pulse width: 10 – 200 μs; frequency: 5 – 150 Hz).

Patients control the intensity of stimulation with a wireless remote in order to maintain comfortable stimulation coverage during the treatment period. At the conclusion of the treatment period, the percutaneous leads are removed in the clinic and patients proceed to follow-up as directed by their physician. Pre- and post-implantation patient management as part of routine care included the support of a local clinical specialist under the guidance of a physician. The principal role of the clinical specialist was to assist in carrying out treatment optimization as needed, and to present patients with a series of validated patient-reported outcome questions at the EOT.

Outcomes and Analysis

Anonymized patient data extracted from the database included treatment characteristics such as nerve target and the number of implanted leads. Data at baseline and EOT were based on validated outcome measures including average and worst pain in the previous week (NRS-11; Brief Pain Inventory – Short Form [BPI-SF] items #5 and #3, respectively) as well as patient-reported percentage of pain relief at the EOT (BPI-SF #8) (20,21). Patient Global Impression of Change (PGIC) as a global measure of quality of life was assessed from -3 to +3, or very much worse to very much improved (21). Thresholds for clinically significant pain relief (≥ 30%), substantial pain relief (≥ 50%), and minimum clinically significant improvement on the PGIC (≥ 1) were based on guidelines for the interpretation of treatment outcomes in chronic pain (22,23). Safety was analyzed by compiling product complaints from the manufacturer's database that were associated with the patients included in the review.

Although pain intensity has historically served as the primary outcome in the field of pain management, recent studies have highlighted the value of incorporating multiple domains into patient assessment in addition to pain intensity, including physical and emotional function, sleep, and quality of life (21,24-27). Studies have suggested that reductions in pain intensity may not capture the overall benefit of pain therapies, and that a more comprehensive set of outcome measures may improve the quality of real-world assessments of pain interventions (24,27-29). Accordingly, in the primary outcome of the present retrospective analysis, patients were defined as responders if they reported ≥ 50% pain relief (based on patient-reported percentage of pain relief) and/or improvement in quality of life as measured on the PGIC (i.e., at least Minimally Improved). Outcomes were also stratified by nerve target.

In addition to the primary outcome, a sensitivity analysis was performed to assess the impact of missing data. In a worst-case scenario, all patients who otherwise qualified but were excluded due to missing data at the EOT considered to be nonresponders. In a best-case scenario, those patients missing data at the EOT were considered to be responders. In a reasonable approximation scenario, those patients missing data at the EOT were considered to be responders according to the distribution of nerve targets in the missing data and the observed responder rates stratified by nerve target.

Continuous data are summarized descriptively as mean (standard deviation [SD]). Categorical data are summarized as percentages. Since patient-reported outcomes were not compulsory, and not all patients answered every question at baseline or EOT, the actual sample sizes are shown for each outcome.

Results

Study Population and Treatment Characteristics

A total of 6,160 patients qualified to be included in the retrospective review. Treatment targets included peripheral nerves throughout the upper and lower extremities, back and trunk, and posterior head and neck. Prior to treatment, patients had a mean baseline average pain score of 6.6 (SD 1.7) and mean baseline worst pain score of 9.0 (SD 1.2). A total of 46% (2,864/6,160) underwent stimulation with a single lead and 54% (3,296/6,160) with dual leads (e.g., bilateral stimulation or stimulation of 2 different nerves innervating the pain region) (Table 1). The most common nerve targets receiving treatment were the lumbar medial branches (n = 1,977), femoral

nerve and its branches (e.g., saphenous) (n = 1,173), sciatic nerve and its branches (e.g., tibial, common peroneal) (n = 1,050), suprascapular nerve (n = 772), and axillary nerve (n = 553) (Fig. 1).

Primary Outcome

At the end of the PNS treatment period, 71% (4,348/6,160) of patients were responders based on the definition of the primary endpoint, reporting ≥ 50% pain relief and/or improvement in quality of life. The mean percentage of pain relief was 63% (SD 25%) among responders. The percentage of responders was stratified by and consistent across a range of nerve targets, including targets in the upper and lower extremities, low back, trunk, and posterior head and neck (Fig. 1).

Table 1. *Baseline and treatment characteristics.*

Age, mean (SD), years	63.5 (16.2)
Number of leads	
1 (single-lead PNS)	46% (2,864/6,160)
2 (dual-lead PNS)	54% (3,296/6,160)
Average pain at baseline, mean (SD)	6.6 (1.7)
Worst pain at baseline, mean (SD)	9.0 (1.2)

A sensitivity analysis was performed to assess the effect of missing data on the primary outcome. Among otherwise eligible patients, 1,290 (17% of a possible 7,450) were excluded due to a lack of data at the EOT. In a worst-case scenario, all records missing EOT data were considered to be nonresponders, resulting in an overall responder rate of 58% (4,348/7,450). In a best-case scenario, all records missing EOT data were considered to be responders, resulting in an overall responder rate of 76% (5,638/7,450). In a third scenario representing a reasonable approximation that takes into account the distribution of nerve targets in the missing data, the percentage of responders was computed by nerve target based on the rates in the existing data stratified by nerve (Fig. 1), resulting in an overall responder rate of 71% (5,256/7,450).

Additional Outcomes

At the end of treatment, the mean average pain score and mean worst pain score were substantially lower compared to baseline (Table 2). In particular, among those who qualified as responders to the 60-day PNS treatment, the distribution of average pain scores shifted markedly from baseline to EOT, with more than 60% reporting mild or no pain (≤ 3) at the

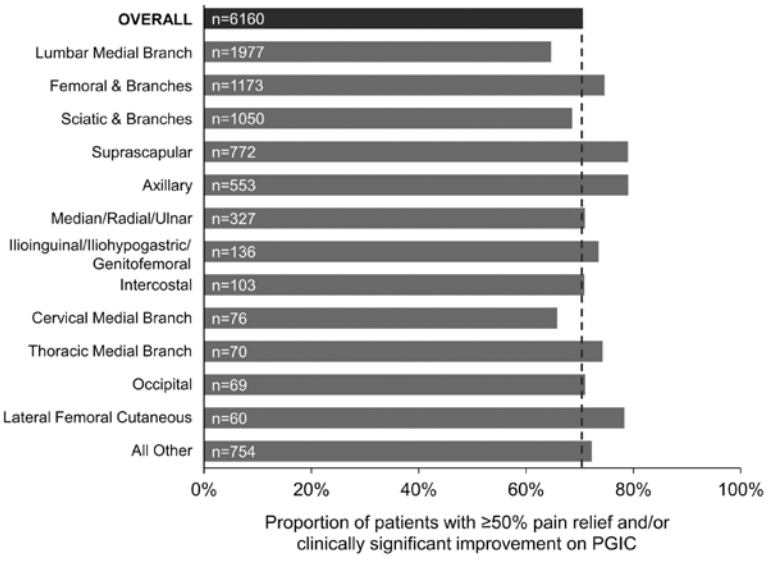

Fig. 1. *Composite responder rate by nerve target. The percentage of patients (total n = 6,160) reporting ≥ 50% pain relief and/or clinically significant improvement in Patient Global Impression of Change (PGIC) at the end of treatment is shown overall and stratified by nerve target. Patients are included in the subtotals for each individual nerve receiving stimulation; for example, a patient receiving stimulation with 2 leads targeting the suprascapular and axillary nerves appears in the subtotals for each of the 2 nerves.*

EOT (30) (Fig. 2). In addition to the primary composite outcome shown in Fig. 1, the percentages of patients with clinically significant (≥ 30%) pain relief and substantial (≥ 50%) pain relief alone are reported in Table 2. Stratification of patient-reported percentage pain relief by PGIC response revealed that patients reporting Minimally Improved, Much Improved, and Very Much Improved each had a mean percentage of pain relief in the clinically significant range (i.e., ≥ 30% [22]) (Fig. 3).

Safety

The total rate of reported medical events in the product complaint database for the present study population was 6.0%, with the most frequent event being skin irritation (e.g., due to bandages or adhesives) (Table 3). Among the study population, 2 serious adverse events were reported (2/6,160, 0.03%); overall, the device manufacturer's database indicates a serious adverse event rate of 0.06%. Infection was confirmed in 0.1% of patients, with unconfirmed reports (i.e., "suspected" infection based on clinical presentation) in another 1.1% of patients. Lead dislodgement was reported in 6.0% of patients, or 4.3% of leads when considering that 54% of patients had 2 leads placed (Table 1). Lead fracture during therapy or at the time of lead removal was reported in 8.1% of patients, or 6.4% of leads. Of note, 94% of the reported lead fractures occurred with an older version of the lead before the strengthened design intended to reduce fracture risk was introduced. Per the system instructions for use, lead remnants are magnetic resonance conditional (31).

Discussion

The present study represents one of the largest publicly reported evaluations of real-world outcomes for an implantable pain management system reviewed retrospectively across a wide range of nerve targets employing neurostimulation technology, with anonymized records from 6,160 patients who received a 60-day PNS treatment. Overall, 71% of patients had at

Table 2. *Additional outcomes at end of treatment (EOT).*

Average pain at EOT, mean (SD)	4.0 (2.6)
Worst pain at EOT, mean (SD)	5.9 (2.9)
Percentage with clinically significant pain relief (≥ 30%)	66% (3,925/5,968)
Mean patient-reported percentage of pain relief among those with ≥ 30%, mean (SD)	67% (21%)
Percentage with substantial pain relief (≥ 50%)	55% (3,275/5,968)
Mean patient-reported percentage of pain relief among those with ≥ 50%, mean (SD)	73% (18%)

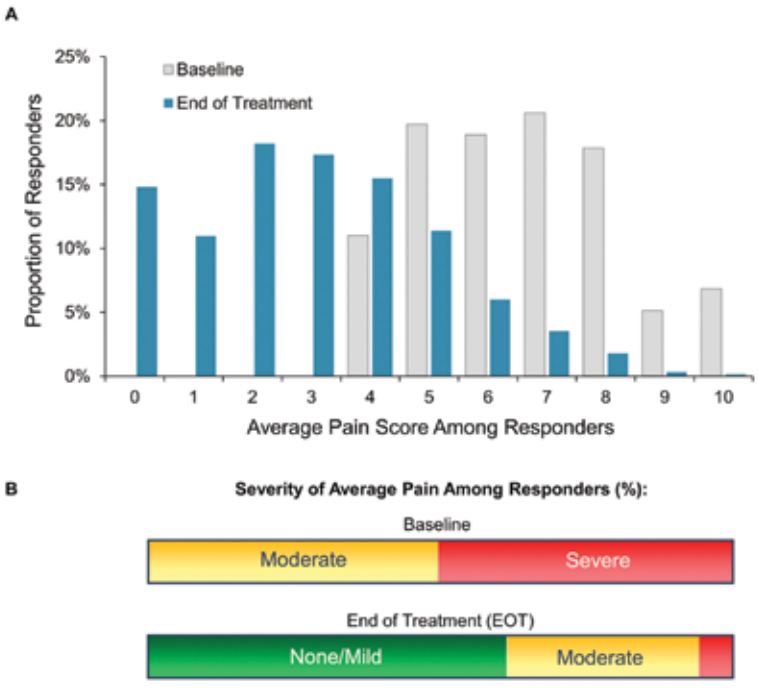

Fig. 2. *Distribution of average pain scores among responders. A) The percentage of treatment responders (n = 4,348/6,160) with each numerical rating scale average pain score (0-10) shown at baseline and at the end of treatment. B) The categorical severity of average pain scores is shown at baseline and at end of treatment among responders, where none/mild corresponds to average pain ≤ 3 on an 11-point scale from 0-10, moderate corresponds to average pain from 4-6, and severe corresponds to average pain ≥ 7 (30).*

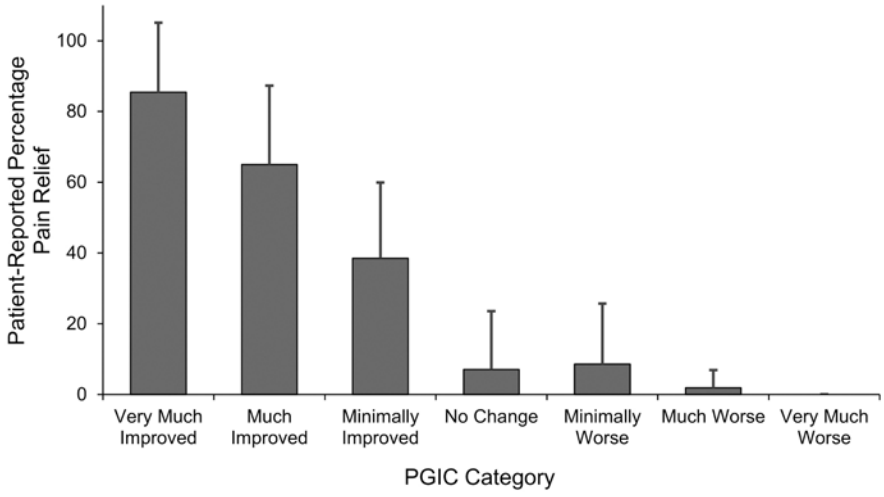

Fig. 3. *Patient-reported percentage pain relief by Patient Global Impression of Change (PGIC) response at end of treatment. The mean patient-reported percentage pain relief is stratified by PGIC response at the end of treatment. Error bars = SD.*

Table 3. *Medical events.*

	Number of Patients	Number of Events	Percentage of Patients
Overall	369	435	6.0%
Skin irritation	160	163	2.6%
Infection			
Confirmed	7	7	0.11%
Suspected	70	73	1.1%
Painful or uncomfortable stimulation	70	73	1.1%
Change in sensation/ location of stimulation	35	38	0.6%
Pain at lead exit site	18	20	0.3%
Swelling	11	11	0.2%
All other	48	50	0.8%

least 50% pain relief and/or improvement in quality of life (as measured by the PGIC) at the end of the 60-day PNS treatment. These outcomes were found to be similar across nerve targets throughout the extremities, back and trunk, and posterior head and neck (Fig. 1). Improvements in individual outcomes, such as average and worst pain score and quality of life, were also observed (Table 2).

PNS has previously been used to treat a wide range of pain conditions by targeting nerves throughout the periphery that innervate the region of pain, including low back pain, joint pain, posttraumatic pain, neuropathic pain, postoperative pain, Types 1 and 2 complex regional pain syndrome, oncologic pain, and others (1-3).

One of the strengths of the present large real-world observational data set is the diversity of nerve targets, which includes most of the major peripheral nerves throughout the upper extremities, lower extremities, trunk (including low back), and posterior head and neck (Fig. 1). Patients were included in the retrospective review if they opted in to provide data, all required data fields were present, and had moderate to severe chronic pain without any exclusion criteria. The analysis therefore represents a comprehensive review of patient responsiveness to a 60-day PNS treatment and is reflective of trends both in clinical implementation and patient outcomes observed in routine clinical practice across the United States.

While specific pain conditions or diagnoses are not reported in the present study, the nature of the database used implies the inclusion of a wide range of different etiologies. The relative consistency in responder rate across nerve targets (Fig. 1) may therefore be indicative of convergent mechanisms of pain and neurostimulation, whereby patients with similar features of centrally mediated pain (e.g., secondary hyperalgesia and allodynia, augmented central pain processing, cortical reorganization, etc.) may have a comparable chance of achieving clinically significant improvement regardless of the anatomic location of the nerve.

Features of central sensitization have been identified in numerous pain conditions including many that are not typically considered neuropathic in origin, such as axial or mechanical back and neck pain, osteoarthritis, and pain following cancer. While neurostimulation has been historically considered largely for pain of neuropathic origin, PNS has demonstrated both peripheral and central mechanisms of pain relief and has been shown to reduce the features of central sensitization regardless of the presence of a neuropathic source (9,32-34). Accordingly, clinical studies have increasingly demonstrated consistent outcomes in PNS across both

neuropathic (e.g., postamputation pain, postoperative neuropathic pain, migraine, etc.) and nonneuropathic (e.g., hemiplegic shoulder pain, axial back pain, post-cancer pain, etc.) pain conditions and across multiple nerve targets throughout the extremities, trunk, and head and neck (1,2,35). These potential mechanistic commonalities underlying the disease state may contribute to the consistency in response to 60-day PNS across the range of nerve targets reported in the present study.

The present study defined responders as patients reporting ≥ 50% relief and/or quality of life improvement as measured by the PGIC. This is consistent with recent studies and society guidelines that have emphasized the value of holistic or multidomain assessment of patient outcomes to evaluate therapeutic benefit. All levels of improvement on the PGIC corresponded to clinically significant levels of pain relief – for example, patients reporting "Minimally Improved" on the PGIC averaged 37% pain relief at the end of treatment and patients reporting "Much Improved" and "Very Much Improved" averaged well over 50% mean pain relief (Fig. 3). Although percent pain relief and quality of life or functional improvements are not necessarily correlated for every patient, and there are subsets of patients for whom improvement in pain and quality of life are decoupled (28), in general these data suggest that patients reporting at least minimal clinically significant improvement in PGIC also reported clinically significant levels of pain relief, validating the chosen thresholds for responders in the present analysis.

A review of subject-level data from previously published prospective clinical studies of short-term percutaneous PNS found that 71% of patients in aggregate (122/172) reported ≥ 50% reductions in pain and/or pain interference at the end of treatment, and 58% (100/172) reported at least 50% pain relief alone (6-8,10,11,36-39). These rates are similar to the present study in which 71% of patients met the primary composite endpoint and 55% of patients had at least 50% pain relief through the end of the temporary PNS treatment period (Fig. 1; Table 2). While previous prospective studies have primarily reported pain interference as an assessment of function and pain-related quality of life, PGIC as used in the present study provides a similar assessment of the overall impact of pain and pain relief on quality of life and is also considered to be a core outcome measure by pain researchers (21,22,40). The overall similarity of the present real-world outcomes to published data provides support for the findings of prior clinical trials that short-term percutaneous PNS can provide significant reductions in pain and resulting improvements in quality of life.

Among the 71% of patients who were responders in the present study (Fig. 1), clinical and real-world evidence suggest that a majority are likely to achieve long-term pain relief beyond the 60-day treatment period (6,7,10,41). In patients who do not achieve significant pain relief or for whom pain returns soon after the end of 60-day treatment, a recent study by Naidu and colleagues (18) highlighted how a temporary 60-day PNS treatment may help obviate or validate the need for a permanent implant. Analysis of patient responsiveness throughout a 60-day PNS treatment period found that 38% of patients were defined as delayed responders or delayed nonresponders whose early responses in the first one to 2 weeks (i.e., when a typical conventional neurostimulation trial would seek to determine eligibility for a permanent implant) did not reliably predict whether the treatment would ultimately be considered successful at 60 days (18). This significant rate of delayed response suggests that in patients who do not achieve sustained relief, the length of the 60-day treatment period may be advantageous to improve appropriate patient identification prior to advancing to a permanently implanted system (18). For example, delayed responders may not have been afforded the opportunity to advance to permanent PNS implantation, when necessary, if they had undergone only a conventional length stimulation trial. Meanwhile, delayed nonresponders may have undergone a permanent neurostimulation system implantation based on the results of the conventional length trial and ultimately failed, potentially necessitating explant at additional cost, invasiveness, and risk (18). Based on these scenarios, a 60-day PNS treatment can provide patients with the potential for sustained long-term pain relief while also helping inform stepwise treatment strategies to optimize outcomes and improve cost-effectiveness by identifying optimal PNS candidates.

Limitations

The present study plays an important role in evaluating the efficacy of a 60-day PNS treatment in broad clinical practice and supplementing the findings of previous randomized controlled trials and other clinical trials. The major limitation of this study is that it is retrospective in nature and relies on a device manufacturer's database. Treatment-related and outcomes data were originally recorded by device field representatives

to inform patient support, such as patient education and compliance, technical troubleshooting, stimulation programming, and treatment optimization as part of routine use of the device. Secondary analyses of the data as in the present study are therefore subject to potential sources of bias in the collection of outcomes, though standardized instruments like average NRS-11 pain score, patient-reported percent pain relief, and PGIC were used to help minimize bias in administration.

Other limitations relate to the data analysis. Data collection was not compulsory, and patients were only included in the analysis if both baseline and EOT data were available. This evaluation of outcomes "as-observed" has the potential to overestimate response rates (42). However, based on the sensitivity analysis described above, even in a worst-case scenario where all those missing EOT data are imputed as nonresponders, the overall success rate would still be estimated at 58%; a reasonable approximation scenario based on the distribution of nerve targets in the missing data suggests consistency with the reported overall success rate of 71%.

An additional limitation is that standardized measures for pain medication usage and physical function are absent. Detailed demographic information is not available due to the nature of the database, which could enable deeper insights into the effectiveness of PNS treatment in specific subpopulations. While acknowledging these limitations, the present study nonetheless provides examples of how large real-world data sets, in combination with prospective studies and additional independent databases and analyses, can contribute to a complementary picture of the effectiveness, safety, and implementation of a 60-day PNS tratment in routine clinical practice.

Conclusions

The present real-world, retrospective review of patient outcomes evaluates the efficacy of 60-day PNS in 6,160 patients at the end of the PNS treatment period. Overall, 71% of patients reported ≥ 50% pain relief and/or improvement in quality of life, with consistent rates of treatment response across various nerve targets. This study represents the largest body of real-world evidence to date regarding patient outcomes during a 60-day treatment period, complementing the findings of published prospective clinical trials.

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