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Long-Term Treatment of Chronic Postamputation Pain With Bioelectric Nerve Block: Twelve-Month Results of the Randomized, Double-Blinded, Cross-Over QUEST Study

Leonardo Kapural, MD, PhD[1]; Billy Kim, MD[2]; John Eidt, MD[3]; Erika A. Petersen, MD[4]; Jason M. Schwalb, MD[5]; Konstantin V. Slavin, MD[6,7]; Nagy Mekhail, MD, PhD[8]

ABSTRACT

Objective: The multicenter, randomized, double-blinded, active-sham controlled trial (high-freQUEncy nerve block for poST amputation pain [QUEST]) was conducted to show the safety and efficacy of a novel, peripherally placed high-frequency nerve block (HFNB) system in treating chronic postamputation pain (PAP) in patients with lower limb amputations. The primary outcomes from QUEST were reported previously. This study presents the long-term, single–cross-over, secondary outcomes of on-demand HFNB treatment for chronic PAP.

Materials and Methods: After the three-month randomized period, subjects in the active-sham group were crossed over to receive therapy for 12 months. Subjects self-administered HFNB therapy as needed and reported their pain (numerical rating scale [NRS]; range, 1–10) before and 30 and 120 minutes after each treatment. Pain medication use was reported throughout the study. Pain-days per week and quality of life (QOL) were assessed using the Brief Pain Inventory (BPI). Adverse events (AEs) were recorded for all subjects implanted for 12 months.

Results: Of 180 subjects implanted in QUEST, 164 (91%) were included in the cross-over period, and 146 (82%) completed follow-up. By month 12, average NRS pain in the combined cohort was reduced by 2.3 ± 2.2 points (95% CI, 1.7–2.8; $p < 0.0001$) 30 minutes after treatment and 2.9 ± 2.4 points (95% CI, 2.2–3.6; $p < 0.0001$) 120 minutes after treatment. Mean pain-days per week were significantly reduced (−3.5 ± 2.7 days; $p < 0.001$), and subject daily opioid use was reduced by 6.7 ± 29.0 morphine equivalent dose from baseline to month 12 ($p = 0.013$). Mean BPI-interference scores (QOL) improved by 2.7 ± 2.7 points from baseline ($p < 0.001$). The incidence of nonserious AEs and serious AEs was 72% (130/180) and 42% (76/180), respectively; serious device-related AEs occurred in 15 of 180 subjects (8%).

Conclusion: Overall, HFNB delivered directly to the damaged peripheral nerve provided sustained, on-demand relief of acute PAP exacerbations, reduced opioid utilization, and improved QOL for patients with lower limb amputations with chronic PAP.

Keywords: High-frequency nerve block, neuropathic pain, peripheral nerve stimulation, phantom limb pain, postamputation pain

Address correspondence to: Leonardo Kapural, MD, PhD, Carolinas Pain Institute and Center for Clinical Research, 145 Kimel Park Drive #200, Winston-Salem, NC 27103, USA. Email: lkapuralmd@gmail.com

[1] Carolinas Pain Institute and Center for Clinical Research, Winston-Salem, NC, USA;
[2] Department of Vascular Surgery, The Surgical Clinic, Nashville, TN, USA;
[3] Department of Vascular Surgery, Baylor Scott and White Heart and Vascular Hospital Dallas, Dallas, TX, USA;
[4] Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA;
[5] Department of Neurosurgery, Henry Ford Medical Group, Detroit, MI, USA;
[6] Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, USA;
[7] Neurology Section, Jesse Brown VA Medical Center, Chicago, IL, USA; and
[8] Department of Pain Management, Cleveland Clinic, Cleveland, OH, USA

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INTRODUCTION

Approximately 160,000 lower limb amputations are performed annually in the USA, with 3.6 million Americans estimated to have amputated lower limbs by 2050.[1] In addition to significant functional[2] and socioeconomic[3] impacts, approximately 80% of patients with amputations experience chronic postamputation pain (PAP) in the form of phantom limb pain (PLP) (pain in the missing limb), residual limb pain (RLP) (pain in the remaining stump), or both.[4] Chronic PAP is emotionally debilitating, significantly increases anxiety, depression, and suicidal ideation, and impairs activities of daily living (ADL).[5]

The pathophysiology of PAP involves peripheral and central nervous system mechanisms.[4,6] After amputation, axons in the damaged peripheral nerve initiate regenerative sprouting, creating new connections and/or forming a neuroma. These axons increase voltage-gated sodium channels (VGSC) expression, causing spontaneous ectopic afferent (hyperexcitable) activity to the dorsal root ganglion (DRG).[7,8] The DRG contains the cell bodies of the sensory components of peripheral nerves and projects to dorsal horn interneurons in the spinal cord and to the brain (spinothalamic tract). DRG neurons undergo similar hyperexcitable changes to the damaged peripheral nerve, specifically increasing expression of VGSC and ectopic discharge activity.[9] Over time, repeated input from the periphery can induce lasting changes in central nervous system (CNS) plasticity, further strengthening the pain signal in a process called central sensitization.[10] In short, continuous abnormal signaling within the peripheral pain pathway increases the activity of excitatory N-methyl-D-aspartic acid and glutamate receptors in the spinal cord, leading to long-term potentiation of the pain signal to the cortex.[11] The increased signaling through ascending pain pathways is accompanied by a reduction of inhibitory descending pain pathways, further enhancing the painful signal.[10,12] These changes in the periphery and spinal cord can induce reorganization of the somatosensory cortex, further complicating ways the patient with amputation experiences pain.[13]

Providing effective, long-term pain relief for patients with chronic PAP remains a challenge. A recent attempt to establish expert global consensus for PAP proposed 37 different treatment modalities including noninvasive, pharmacologic, surgical, and neuromodulatory methods, with minimal consensus reached.[14] Peripheral nerve blocks with lidocaine or other VGSC blockers temporarily reduce PAP when injected at the site of amputation[15] or DRG[16]; however, evidence of long-term effectiveness is limited to case reports.[17] Numerous surgical options can address the peripheral mechanisms but with varying levels of success and high rates of pain recurrence.[17] Newer approaches, such as targeted muscle reinnervation, have shown promise in small studies, but differences in outcomes primary versus secondary to amputation are not well-known.[18] Pharmacologic therapies address the central mechanisms of PAP, even to the level of cortical reorganization,[19] but carry myriad side effects and risk of tolerance or abuse.[20] A Cochrane Review concluded that opioids and gabapentin provided short-term relief of PAP, despite conflicting results, but also described a lack of large, well-controlled studies.[21] Neuromodulation with spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS) is anchored on the Gate Control Theory,[22] which postulates that constant stimulation of large diameter Aβ-fibers induces inhibition of nociceptive Ad- and C-fiber response, thereby providing pain relief.[23] Both therapies have shown benefit in neuropathic pain but lack supportive large, randomized trials in chronic PAP and carry high rates of device explant.[24,25] Recent small studies have shown the benefit of PNS in reducing PAP out to one year ($N = 6$)[26] and SCS in reducing PAP and improving sensory feedback out to one month ($N = 3$).[27]

Previous studies indicated use of a high-frequency alternating current (HFAC) stimulus to produce nerve conduction block through inhibitory actions on VGSCs in multiple preclinical models,[28–30] and a subsequent small feasibility study confirmed reductions in chronic PAP on application of HFAC directly to damaged peripheral nerves of patients with amputations.[31] In this pilot study, seven of ten subjects treated with an implantable on-demand bioelectric nerve block system showed significant pain reduction at three months, which was sustained for 12 months.[31] From this finding, a 180-subject prospective, multicenter, randomized, double-blinded, active-sham controlled study (high-freQUEncy nerve block for poST amputation pain [QUEST]; NCT02221934) was designed.[32] The primary end points of the three-month randomized controlled period showed a significantly higher responder rate (≥50% pain reduction in ≥50% treatment sessions) in subjects receiving high-frequency nerve block (HFNB) than in active-sham 30 minutes after treatment (24.7% vs 7.1%; $p = 0.002$).[33] From this treatment effect, the number needed to treat (NNT) to achieve 50% pain reduction at 30 minutes was 5.7. Treatment effect increased over time at 120 minutes after treatment (46.8% vs 22.2%; $p = 0.001$; NNT = 3.9). Subjects with HFNB also had significant improvements in quality of life (QOL) ($p = 0.01$) and reduction in opioid use ($p = 0.157$) compared with subjects with active-sham.[33] At the end of the three-month randomized period, subjects with active-sham were crossed over to HFNB treatment (single crossover), and the entire cohort was observed for another nine months. In this study, we report the 12-month secondary end point results of the QUEST trial of chronic PAP.

MATERIALS AND METHODS

Study Population, Screening, and Study Flow

Previous publications have described the study design and methods of QUEST (ClinicalTrials.gov identifier: NCT02221934).[32,33] As reflected in the history on ClinicalTrials.gov, study end points were incompletely described in the original entry, and the registry was revised by an independent statistician after study enrollment commenced to provide additional detail; study outcomes were not changed after enrollment began. QUEST was a prospective, multicenter, double-blind, randomized, active-sham–controlled clinical trial that enrolled adult patients with amputations with chronic, severe PAP. Key inclusion criteria included unilateral lower limb amputation ≥12 months; chronic PAP (≥six months with exacerbations lasting ≥60 minutes with frequency of ≥four episodes per week with >5 on a numerical rating scale [NRS]); and stable drug regimen ≥four weeks. Patients were excluded for previously implanted active medical device; confounding source of pain that would interfere with reporting of limb pain; uncontrolled diabetes; untreated psychologic conditions; and conditions requiring magnetic resonance imaging studies after device implant. QUEST conformed to the US Code of Federal Regulations and the ethical guidelines/recommendations of the Declaration of Helsinki. The study was approved by the Western investigational review board and each site's institutional review board. Study participants provided informed consent.

The subjects enrolled underwent a month-long screening process to confirm adequate pain levels. The subjects were then required to show significant (>50%) pain relief after ultrasound-guided nerve block (15 mL of 2% lidocaine) proximal to the site of amputation and little-to-no (<30%) pain relief after sham (saline) injection at the same location, but away from the nerve.[32] On successful completion of screening, subjects were implanted with the investigational Altius® Direct Electrical Nerve Stimulation System (Neuros Medical, Inc, Aliso Viejo, CA).[32,33] The device comprises an implantable pulse generator (IPG) with an integrated rechargeable battery connected to one or two cuff electrodes of varying sizes wrapped around the target nerve(s)—typically the sciatic nerve for above-the-knee amputations and the tibial and common peroneal for below-the-knee amputations. The IPG was programmed to deliver the prespecified treatment program when the subjects initiated therapy with their patient controller.

Two weeks after implant, subjects returned to the clinic for device activation and programming. Subjects were randomized (1:1) to receive either the Treatment (HFNB) or Control (active sham) program for the three-month randomized study period. The Treatment group received 30 minutes of HFNB (5–10 kHz; 0V–16V; 0–20 mA) whereas the Control group received an ultralow frequency (0.1 Hz) subtherapeutic program. Randomization was stratified by the clinical sites using random permuted blocks with subjects, investigators, and site personnel blinded to randomization. Two weeks after programming, subjects began the randomized testing period and could activate their devices for pain management. After the three-month randomized study period ended, Control subjects crossed over to receive the Treatment program for the remainder of the 12-month study period. A single–cross-over design was used so as not to deprive subjects of treatment after the randomized testing was completed.

Data Collection and Outcomes

The subjects activated their HFNB system as needed for pain management. Therapy sessions lasted 30 minutes, followed by a 30-minute lockout for nerve recovery. The subjects were instructed to record their pain intensity using a 0-to-10 NRS score before and 30 and 120 minutes after therapy in their eDiary application (Axiom Real-Time Metrics, Toronto, Canada) on a study-provided, secure mobile phone (Samsung, Seoul, South Korea). Subjects also reported their daily current NRS pain score, past 24-hour average, least, and worst pain scores (Brief Pain Inventory [BPI]-Intensity scale), pain medications usage, and prosthesis use.[34] Subjects were instructed to continue taking medications as needed for pain management but were not given any formal opioid weaning protocol. Subjects completed the BPI-interference in ADL assessment at baseline, and at three-, six-, and 12-month visits.

The primary effectiveness and safety end points from the three-month randomized controlled period were described previously and compared Treatment with active-sham Control.[33] The secondary efficacy end points included in this analysis were pain relief 30 and 120 minutes after treatment (acute pain relief) and change from baseline over the 12-month period for pain-days per week (defined as NRS pain intensity score [BPI-intensity] ≥4 for worst daily pain); opioid medication use (reported as morphine equivalent dose [MED]); and QOL (BPI-interference in ADL summary score). Unless otherwise noted, data are presented for the combined cohort (Treatment + Control arms) as prespecified in the statistical analysis plan. The secondary safety end point was the incidence of all safety events, including nonserious adverse events (AEs) and adverse device events, serious adverse events (SAEs) and adverse device effects, and unanticipated adverse device events (UADEs) in all subjects implanted, from screening injection through 12 months. Clinical oversight included an expert independent physician adjudicator who adjudicated AEs (ie, deaths, device- or procedure-related SAEs, and SAEs associated with the target limb or implant site) and a data monitoring committee that monitored AE rates and provided safety and futility reviews throughout enrollment.

Daily hours of prosthetic leg use were an exploratory end point because prothesis use was not required for eligibility. To further investigate the long-term pain profiles of subjects, post hoc analyses evaluated end-of-day least, worst, and average pain intensity pain scores (BPI-intensity) over 12 months (Chronic Pain Relief).

Statistical Analysis

QUEST was statistically powered at 0.90, with a sample size of 180 according to the primary effectiveness end point.[33] All randomized subjects with documented device use who agreed to long-term follow-up were included in the secondary efficacy analyses. Safety analyses included all subjects who received an implant ($N = 180$); the baseline characteristics of the safety population have been previously described.[33] Descriptive statistics are presented for all variables. Acute pain relief at each reported time point was calculated as the average reduction from initiation of a treatment session to 30 or 120 minutes after treatment per patient across all sessions occurring within the previous month. A paired *t*-test at a two-sided significance level of $p \leq 0.05$ was used to assess change from initiation of a treatment session. Average total daily MED (for the total population and for each subject), mean change in BPI-intensity, and mean weekly hours of prosthetic use were calculated using the average across two weeks at each time point and compared with baseline using paired *t*-tests at a two-sided significance level of $p \leq 0.05$. BPI-interference scores at designated time points were compared with baseline using a paired *t*-test at a two-sided significance level of $p \leq 0.05$. Percentage change from baseline in BPI-interference scores was compared in the groups using a one-way, one-sided analysis-of-variance model with a one-sided significance level of 0.025. Average change in average, worst, and least pain at end of day were calculated per patient by subtracting the average end-of-day pain at baseline from the average end-of-day pain at six and 12 months. The average reduction was reported across patients, with a paired *t*-test used to assess significance at a two-sided significance level of 0.05. Data are presented as mean ± SD unless otherwise noted. Analyses used SAS® Software version 9.4 or R version 3.3.2 (SAS Institute Inc, Cary NC) or later.

RESULTS

Study Subjects

After the conclusion of the three-month randomized, double-blind portion of QUEST ($N = 180$ implanted subjects), 83 subjects initially randomized to the Control (sham treatment) arm were crossed over to the Treatment arm, producing 164 subjects (91%) included in the cross-over stage, with 146 subjects (82%) completing the 12-month follow-up (Fig. 1). Groups within the combined cohort were well matched regarding demographics, clinical history, amputation characteristics, and baseline pain (Table 1). Most subjects reported regularly experiencing both PLP and RLP, and pain was typically persistent in nature. During the

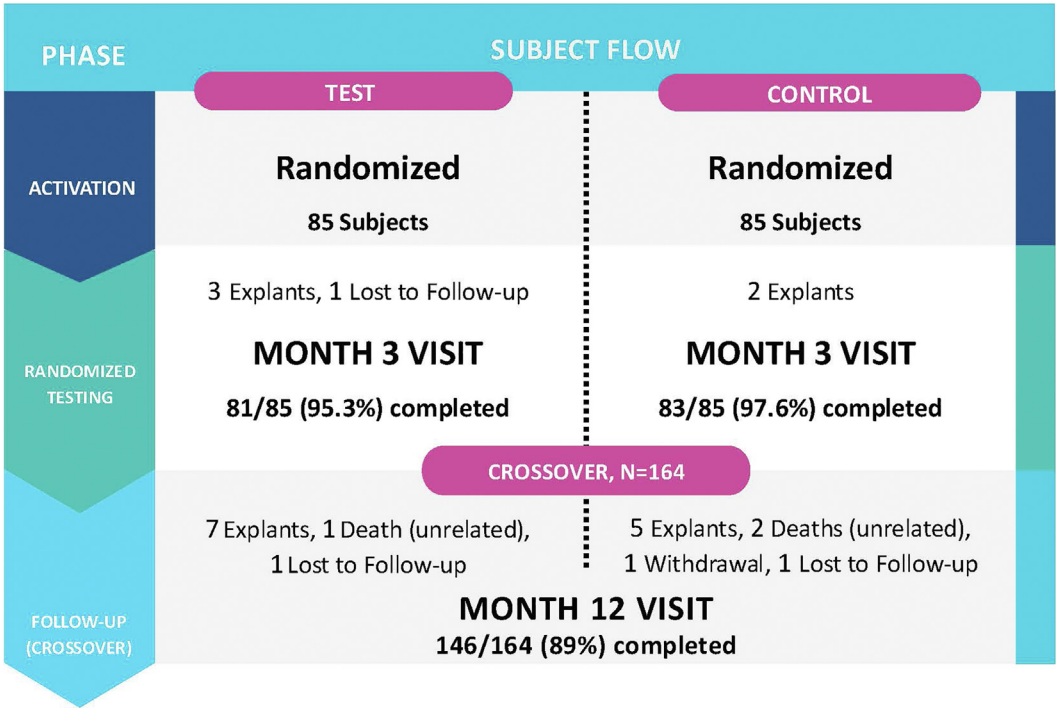

Figure 1. QUEST subject flow chart. Subject flow diagram for $N = 170$ subjects included in the three-month primary end point analysis. The number of possible subjects completing a particular milestone (eg, remaining subjects) is listed in the fraction denominator based on noted subject fall-out between milestones. Fraction numerators represent the number of subjects who completed each milestone. $n = 164$ subjects crossed over to the single-arm follow-up, with $n = 146$ of 149 possible subjects completing the month-12 visit.

eDiary screening process, the mean number of pain-days per week was 6.6 ± 0.6, and mean daily worst, average, and least NRS pain levels were 7.7 ± 1.2, 6.0 ± 1.5, and 4.5 ± 2.0, respectively.

Pain Outcomes

At month 12, acute pain reduction 30 minutes after therapy was 2.3 ± 2.2 points (95% CI, 1.7–2.8; $p < 0.0001$) (Fig. 2). This equated to an approximately 33% reduction (33.0%–35.3%) across the nine-month follow-up period. Further reductions in NRS pain scores were observed from 30 to 120 minutes after therapy. At 12 months, the reduction in NRS pain intensity 120 minutes after therapy was 2.9 ± 2.4 points (95% CI, 2.2–3.6; $p < 0.0001$), equating to an approximately 45% reduction (43.1%–47.1%) across the nine-month follow-up period. Subjects initially randomized to the Control arm showed immediate improvement in pain relief on crossover (upward slope from month 3 to month 4); by month 6, subjects in the Control arm had achieved approximately 80% of the pain reduction experienced by the Treatment group at both 30 minutes (change in NRS pain intensity vs baseline for Control: −1.9 ± 2.0 [95% CI, −2.3 to −1.4]; Treatment: −2.4 ± 2.3 [95% CI, −3.0 to −1.8]; $p < 0.0001$ for both) and 120 minutes (change in NRS pain intensity vs baseline for Control: −2.6 ± 2.2 [95% CI, −3.1 to −2.1]; Treatment: −3.2 ± 2.4 [95% CI, −3.8 to −2.5]; $p < 0.0001$ for both) after treatment. The number of pain-days per week was reduced relative to baseline by 2.4 ± 2.6 days at month 6 and 3.5 ± 2.7 days at month 12 ($p < 0.001$ for both).

Functional Outcomes

The population total daily MED for the combined cohort over time is presented in Figure 3a. Total daily MED at six months was reduced by 42% from baseline and by month 12 was reduced by 56% relative to baseline. The per subject mean change from baseline in average daily MED at six and 12 months was −7.0 ± 24.1 ($p < 0.001$) and −6.7 ± 29.0 ($p = 0.013$), respectively. Subject-level changes in opioid use for subjects who reported opioid use at baseline and provided medication data at 12 months are shown in Figure 3b. Over the 12-month study period, 30 of 37 subjects (81%) reported a reduction in opioid utilization, with 35% ($n = 13$) having a complete reduction in use.

At the end of the randomized trial period (month 3), subjects in the Treatment group showed stronger improvement in average QOL compared with baseline than did subjects in the Control group (BPI-interference difference vs baseline: Treatment, −2.3 ± 2.6 [37.7% improvement]; Control, −1.3 ± 2.4 points [23.4% improvement]; Fig. 4). After crossover to HFNB, subjects initially randomized to the Control group exhibited improvement in QOL but not to the magnitude of subjects initially randomized to Treatment. By month 12, change in BPI-interference scores relative to baseline was similar for participants initially randomized to the Treatment (−2.7 ± 2.7 points) and Control groups (−2.6 ± 2.8 points), representing 46% and 44.1% improvement, respectively ($p = 0.265$). The combined cohort reported an average 2.7 ± 2.7-point improvement in BPI-interference at 12 months ($p < 0.001$), representing a 45.1% improvement from baseline.

Safety Outcomes

Of 180 subjects implanted (safety population), 130 (72%) experienced ≥one nonserious AE; the most common nonserious AEs were falls (39/180; 22%), implant site infection (9/180; 5%), and back pain (7/180; 4%). A total of 76 of 180 subjects (42%)

Table 1. Subject Demographics, Comorbidities, Amputation Characteristics, and PAP.

Demographics and Comorbidities	Overall (N = 164)	Treatment (n = 81)	Control (n = 83)	p Value*
Age, y, mean ± SD	58.3 ± 12.1	58.6 ± 12.1	58.0 ± 12.7	0.732
Sex male, %	60.4	60.5	60.2	1.000
DM—current or previous, %	36.0	42.0	30.1	0.144
PVD—current or previous, %	32.3	30.9	33.7	0.739
Race, %				0.927
American Indian or Alaska Native	1.8	2.5	1.2	
Asian	0.0	0.0	0.0	
Black or African American	12.8	13.6	12.0	
Native Hawaiian or Other Pacific Islander	0.6	1.2	0.0	
White	80.5	77.8	83.1	
Multiple	1.8	2.5	1.2	
Not known	2.5	2.5	2.4	
Ethnicity, %				0.745
Hispanic or Latino	0.0	0.0	0.0	
Not Hispanic or Latino	98.8	98.8	98.8	
Not reported	0.6	1.2	0.0	
Not known	0.6	0.0	1.2	
Amputation Characteristics				
Location, N				0.752
AKA	70	36	34	
BKA	94	45	49	
Cause, %				0.955
Vascular	42.7	43.2	42.2	
Trauma	41.5	42.0	41.0	
Other	15.9	14.8	16.9	
Prosthetic use, N	135	66	69	
Prosthetic use, h/wk, mean ± SD†	64.6 ± 36.2	56.9 ± 34.3	72.0 ± 36.7	0.152
Pain characteristics				
Location of pain, %				0.606
Phantom only	8.6	10.0	7.3	
Residual limb only	4.9	6.3	3.7	
Both phantom and residual	86.4	83.8	89.0	
Duration of pain, %				0.872
Persistent	64.4	63.8	65.1	
Episodic	35.6	36.3	34.9	
Pain d/wk, mean ± SD	6.6 ± 0.6	6.6 ± 0.7	6.6 ± 0.5	0.771
Daily worst pain	7.7 ± 1.2	7.7 ± 1.2	7.7 ± 1.2	0.555
Daily average pain	6.0 ± 1.5	6.1 ± 1.5	6.1 ± 1.5	1.000
Daily least pain	4.5 ± 2.0	4.6 ± 2.0	4.5 ± 1.2	0.945
BPI-interference to ADL, mean ± SD	5.9 ± 2.0	6.1 ± 2.1	5.8 ± 1.9	0.555

AKA, above-the-knee amputation; BKA, below-the-knee amputation; DM, diabetes mellitus; PVD, peripheral vascular disease.
*Statistical comparisons of treatment groups for categorical variables are performed using two-sided Fisher's exact test. Significance is evaluated at the 0.05 level. Statistical comparisons of treatment groups for continuous variables are performed using the two-sided two sample t-test. Significance is evaluated at the 0.05 level. Daily limb pain scores are taken from daily end-of-day reports from eDiary at baseline.
†Of subjects who reported prosthetic use at baseline.

experienced SAEs. No individual SAEs were reported by >3% of subjects; the most common SAEs were infections (37/180; 20%) and complications due to procedures or injury (15/180; 8%). Procedure-related SAEs occurred in 18 subjects (10%), and device-related SAEs occurred in 15 subjects (8%). No UADEs were observed. There were three deaths during the study period, all unrelated to device or procedure.

There were 22 randomized subjects (12%) with explants. None of the explants occurred within 30 days of implant; nine explants occurred before the end of the three-month randomized testing period, and 13 occurred between months 3 and 12. The most common reason for explant was implant site infection (n = 8). Notably, subject request for explant was rarely due to lack of therapy or device discomfort (n = 2); in both cases, the device was functional at the time of explant.

Exploratory Outcome

Prosthetic use in the combined cohort (exploratory end point) steadily increased throughout the study period, but increases did not reach statistical significance relative to baseline (mean hours/week at three months: 60.9 ± 40.4; six months: 63.3 ± 40.3; 12 months: 68.6 ± 40.8; $p \geq 0.112$ for all).

Post Hoc Analyses

Post hoc evaluation of daily pain levels reported by subjects showed significant changes in chronic pain profiles. Self-reported

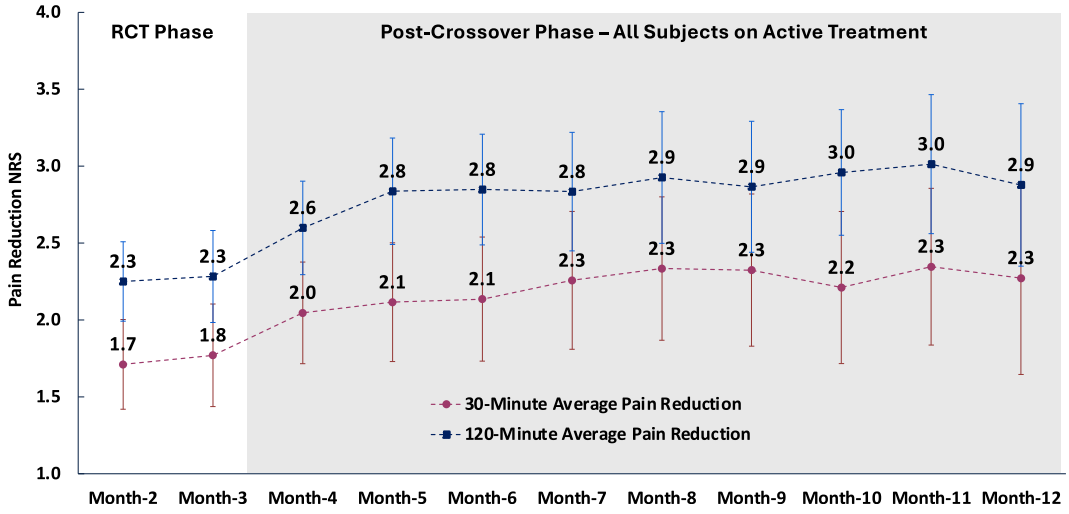

Figure 2. Average pain reduction at 30 minutes and 120 minutes after therapy through 12-month follow-up in full combined cohort. Average change (reduction) in self-reported NRS pain levels 30 minutes (red line) and 120 minutes (blue line) by month through follow-up. Data are presented as average change across all subjects remaining in QUEST during the month noted, regardless of initial randomization assignment. The shaded area depicts the post–cross-over long-term follow-up portion of the study, during which all subjects were receiving HFNB Treatment. Error bars represent ± 95% CI. RCT, randomized controlled trial.

worst, least, and average pain levels over the past 24 hours steadily decreased over the follow-up period (Fig. 5). At 12 months, the mean daily worst pain level was 5.4 ± 2.7 points (mean difference vs baseline, −2.3 ± 2.58 [95% CI, −2.8 to −1.8]; $p < 0.0001$) representing a 30% reduction from baseline. Mean daily average pain intensity was 3.7 ± 2.4 (mean difference vs baseline, −2.2 ± 2.2 points [95% CI, −2.7 to −1.8]; $p < 0.0001$), representing a 38% reduction from baseline, and mean least pain intensity was 2.4 ± 2.2 points (mean difference vs baseline, −2.0 ± 2.23 points [95% CI, −2.5 to −1.6]; $p < 0.0001$), representing a 47% reduction from baseline by month 12.

DISCUSSION

The secondary end point results of the QUEST study indicate the long-term ability of HFNB to provide relief from chronic PAP exacerbations within 30 minutes of initiating therapy and lasting for ≥two hours. Importantly, device effectiveness regarding reported pain did not diminish with use but rather increased over six to eight months of use before stabilizing over the remainder of the 12-month follow-up period. Although individual time points varied, clinically meaningful reductions (>two points[35]) from baseline in self-reported daily pain levels were observed by six to

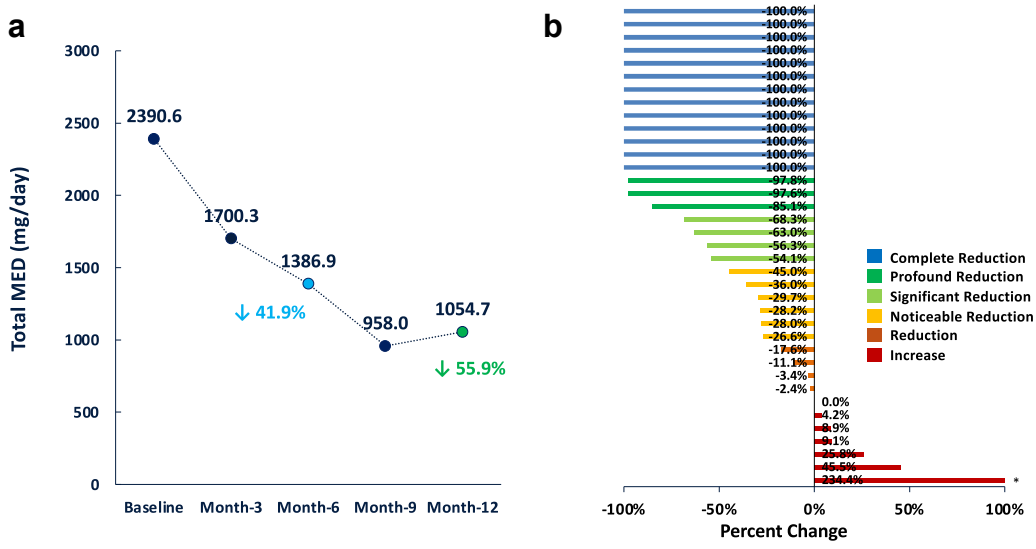

Figure 3. Average MED change relative to baseline. a. Cumulative daily total MED (mg/d) for all subjects, regardless of initial randomization assignment. Percentage changes noted at month 6 and month 12 were calculated relative to baseline. b. Tornado plot of the mean percentage change of average daily MED for subjects taking opioids to manage pain at baseline, with data reported at month12 ($N = 37$). Colors indicate degree of reduction or increase: complete reduction = 100% from baseline; profound reduction = ≥90% to <100% from baseline; significant reduction = ≥50% to <90% from baseline; noticeable reduction = ≥20% to <50% from baseline; reduction = <20% from baseline. Reduction is indicated as negative (–) percentage change, an increase as a positive percentage change. *The x-axis has been truncated owing to a single subject with >100% increase in daily MED at 12 months.

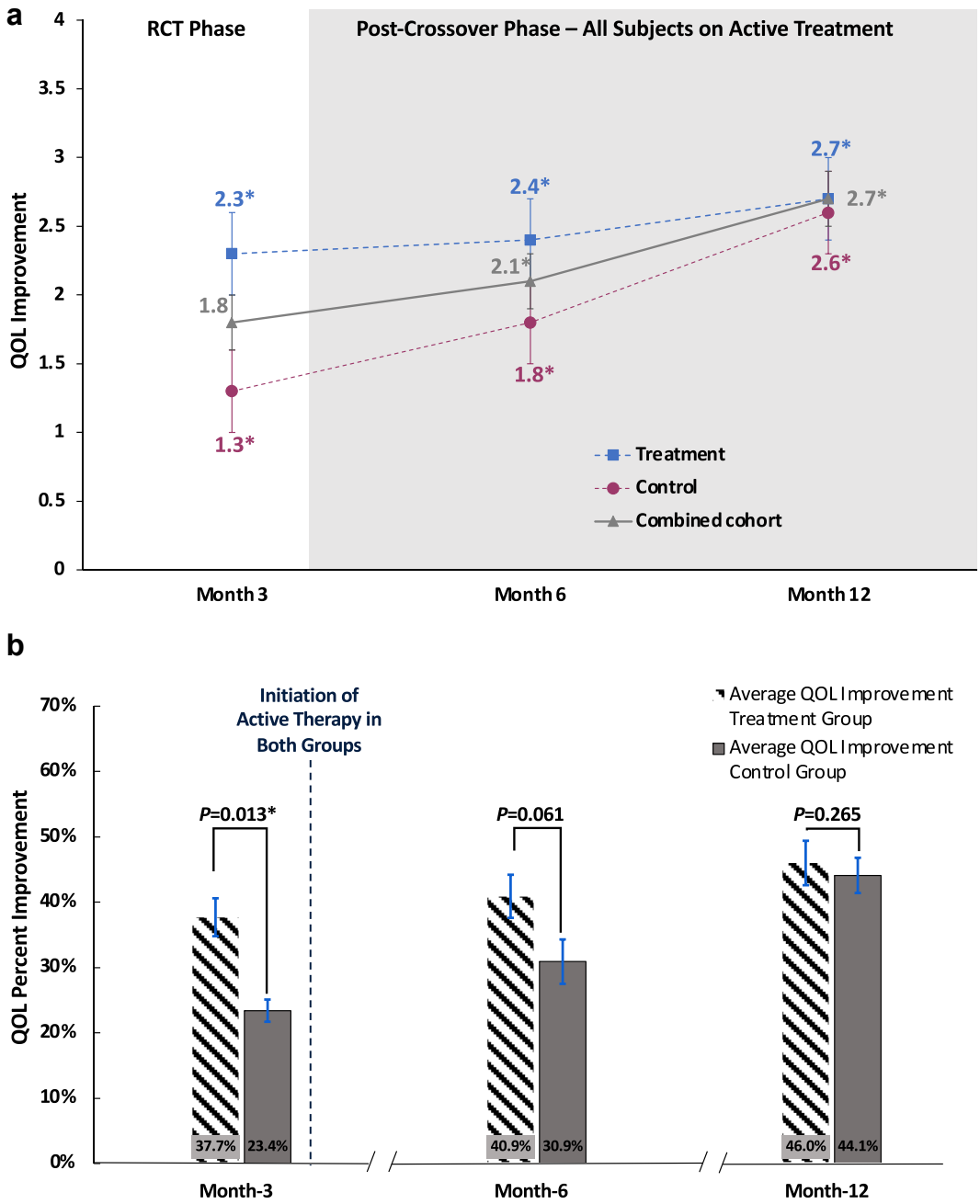

Figure 4. a. Improvement in BPI pain interference score through 12 months for subjects initially randomized to the Treatment (blue squares) and Control (red circles) arms and the combined cohort (gray triangles). Data are presented as the absolute value of reductions in BPI-interference scores. Error bars represent SE. *p <0.001 compared with baseline; the combined cohort was not compared with baseline at the three-month time point. b. Percentage change in self-reported QOL, generated by a composite score of pain interference in ADL of daily living through BPI. Average individual percentage improvements calculated at month 3, month 6, and month 12 compared with baseline. Checkered bars represent average change in subjects initially randomized to Treatment group; solid bars represent average change in subjects initially randomized to Control group. Significance values refer to the difference in percentage improvement between Treatment and Control. Dotted line denotes crossover of all subjects to receive therapy. Error bars represent ± 95% CI.

eight months and sustained through 12 months, indicating lasting changes in overall pain profiles. In addition to reductions in acute and chronic pain, subjects reached nearly 50% QOL improvement, with a significant reduction in opioid medication usage from baseline. These results build on the successful primary findings of the randomized, double-blind QUEST study and support the use of HFNB to help relieve pain and QOL burden for patients with lower limb amputations with chronic PAP.[33]

The current device produces pain relief by delivering an HFAC waveform capable of preventing painful signals originating in the periphery from reaching the CNS. The mechanism of the system inactivates VGSCs at the damaged nerve ending that are

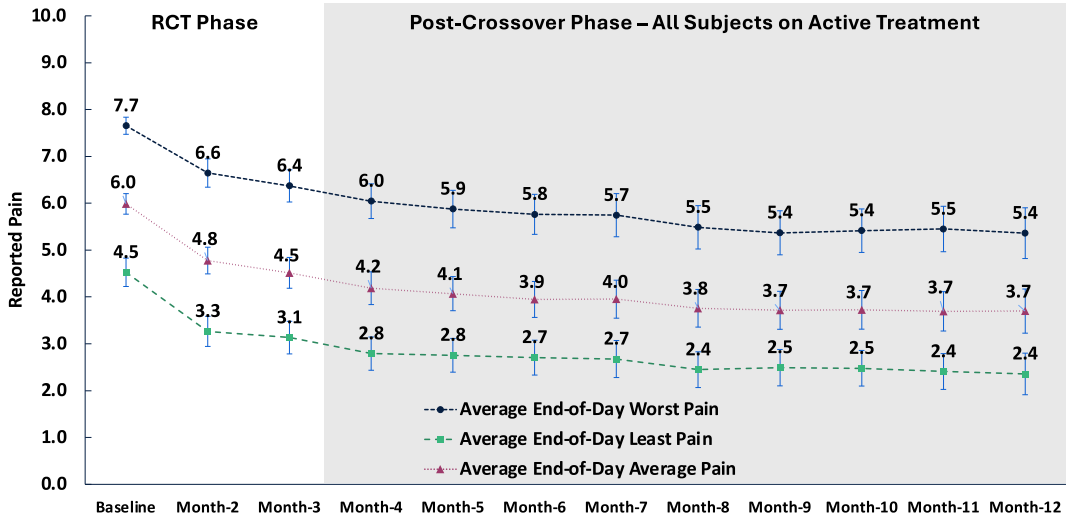

Figure 5. Average end-of-day pain levels through 12-month follow-up in full combined cohort. Average worst (blue line), least (green line), and average (red line) NRS pain levels over the previous 24-hour period reported daily from baseline through 12 months. Data are presented as an average change across all subjects remaining in QUEST during the month noted, regardless of initial randomization assignment. The shaded area depicts the post–cross-over long-term follow-up portion of the study during which all subjects were receiving HFNB treatment. Error bars represent ± 95% CI.

characteristically overexpressed after an amputation,[7] providing a direct and immediate electrical nerve conduction block. In the present study, this conduction block produced an average approximately 33% reduction in pain within 30 minutes of initiating therapy, which increased to approximately 45% pain reduction within two hours. These results underscore the importance of reducing aberrant peripheral activity to effectively treat PAP exacerbations. Central mechanisms also are at play in chronic PAP, and repeated painful input into the CNS has been shown to induce maladaptive CNS plasticity or central sensitization leading to an increased pain response.[10,11] Interestingly, we observed a central desensitization whereby repeated blocking of these painful inputs into the CNS over time caused relief of daily pain. Subjects reported >two-point reductions in daily worst, average, and least pain, representing an average 30%, 38%, and 47% reduction, respectively, over the 12-month study. The ability of a therapy to effectively and reproducibly block acute pain while also decreasing chronic PAP has, to our knowledge, not been previously documented. Injectable nerve blocks address the peripheral mechanisms of PAP through blockade of VGSCs, but their effects are too short-lived to affect CNS plasticity. Conversely, opioids and other analgesics address the central mechanisms of PAP but do not directly target the peripheral source of pain. Neuromodulation devices indirectly address central mechanisms of PAP by applying a constant low-frequency (Hz range) stimulation based on the classical Gate Control Theory mechanisms. Although this approach has been shown to be effective in treating intractable back pain, it may not be ideally suited for treating chronic PAP in which reducing peripheral hyperactivity is critical. Continual stimulation by these devices also can produce CNS accommodation causing therapeutic fatigue and high rates of explant.[36,37] In contrast to these low-frequency, low-amplitude field stimulation systems, the system evaluated here used intermittent (patient-initiated), high-frequency (5–10 kHz), high-amplitude (up to 20 mA) stimulus delivered circumferentially to the damaged peripheral nerve over a relatively short (30-minute) period. The unique stimulation parameters delivered through a nonconventional "wrapped cuff" electrode array in this study were associated with reductions in acute pain that were sustained through 12 months. Moreover, the low rates of device-related AEs observed over the follow-up period suggest a favorable safety profile in this population with substantial incidence of diabetes mellitus and peripheral vascular disease.

Subjects collectively experienced significant functional improvements in addition to pain reduction. Amputations have a much larger impact on a patient than just pain, including severe emotional, physical, and socioeconomic effects. We measured ways pain interferes with ADL (including general activity, mood, walking ability, ability to work, interpersonal relations, sleep, and enjoyment of life) to generate a composite QOL score based on the average interference scores across all questions (Fig. 4). This study revealed an average 2.7-point improvement in BPI-interference, representing a 45% improvement in QOL over 12 months. We also observed a significant reduction in use of opioid pain medication (Fig. 3), presumably because subjects found effective treatment of acute pain and reduction in daily pain levels with HFNB therapy. Accordingly, the NNT for 50% acute pain reduction calculated here was 3.9 at two hours after therapy, which exceeds the NNT of gabapentin (7.2) and strong opioids (4.3) for treating chronic neuropathic pain.[38] Opioid use was not the primary focus of this study; thus, not all subjects reported taking opioids at baseline, and groups were not evenly matched. Despite no formal weaning protocol provided, more than half of subjects taking opioids reported ≥50% reduction in use by 12 months, with >one-third of subjects reporting complete cessation of opioids (Fig. 3b). Considering a recent review of eight years of CMS data revealed more than half of amputees take opioids in the perioperative period, with approximately 45% reporting prolonged use,[20] the organic reduction in opioid utilization shown here warrants future studies.

Numerous features of the QUEST study design and execution deserve attention and consideration when designing future chronic pain studies. Double-blinded, active-sham controlled designs, considered the gold standard, have been previously performed in the chronic pain space. To our knowledge, this is the first of those

studies to use a longitudinal, repeated-measures design to study daily changes in chronic pain and consistency of therapeutic response to treatment. Requiring subjects to report at least daily allowed dynamic changes in pain throughout the course of the study to be observed, which may have otherwise been missed in a typical study design with binary time points (eg, end of study compared with baseline pain).[32–34] We believe this repeated-measure approach adds significant value to tracking patients with intermittent pain.

QUEST used a diagnostic screen to identify subjects who would be appropriate candidates for HFNB therapy. Most payers require a "trial" for SCS and PNS, when a temporary system is implanted for a week or longer to determine whether the patient will benefit from the therapy before full surgical implant. Although temporary, electrode implantation in SCS/PNS trial periods is associated with typical surgical risks (eg, bleeding and infection) and has not been shown to be associated with superior patient outcomes.[39] In contrast, the trial for QUEST was based on subject response to lidocaine, which has the same molecular targets as HFNB (VGSCs). This minimally invasive diagnostic screen addresses the magnitude of VGSC overexpression that contributes to chronic PAP. The use of lidocaine injection response to predict therapeutic response obviates the need for a stimulation trial, representing a significant advantage.

This study had several limitations. First, QUEST used a single–cross-over design,[33] which prohibited further evaluation of duration of therapy effectiveness. Although it would have been academically interesting to investigate whether the effects of treatment wear off, we did not think it was in the best interest of the patients to relinquish much-needed therapy. Second, the use of pain medication was not controlled for between groups. The unequal use of opioids at baseline precluded between-group comparisons after the three-month primary end point, but the full cohort changes and individual subject data presented here support overall reductions in opioid use and warrant further investigation. In addition, study eligibility criteria may reduce real-world applicability. Specifically, subjects with uncontrolled diabetes (hemoglobin A1C >8.0 without medication) were excluded despite diabetes being common in patients with amputations. Nevertheless, approximately one-third of subjects reported diabetes, which was consistent with the approximately 40% of patients with vascular amputations enrolled. Finally, our reporting did not differentiate by pain type. The therapy was intended to treat all PAP, including both PLP and RLP; thus, the severity (and not the source) of the pain was the clinical focus. Importantly, >86% of subjects reported regularly experiencing both PLP and RLP, which is highly representative of the population with amputations.[40] In addition, there was significant improvement in QOL measures, which is the real goal of any neuromodulatory therapy.

CONCLUSIONS

The long-term, single–cross-over, secondary end point analyses of the QUEST study showed that use of HFNB provides significant improvement in pain and functional outcomes in patients with amputations experiencing chronic PAP. This on-demand therapy provided effective relief from painful episodes without the risks of opioids or need for repeated office visits to receive therapy. The increasing magnitude of acute pain relief coupled with an overall reduction in daily pain levels over time suggest HFNB may represent an effective treatment option for intractable PAP.

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Authorship Statements

Leonardo Kapural contributed to the design and implementation of the study. Leonardo Kapural, Billy Kim, John Eidt, Erika A. Petersen, Jason M. Schwalb, Konstantin V. Slavin, and Nagy Mekhail participated equally in data collection, analysis and interpretation of the results, and preparation of the manuscript. All authors approved the final manuscript.

Conflict of Interest

Leonardo Kapural reports grants and/or personal fees from Biotronik, Medtronic, Nevro, Presidio, Saluda Medical, Nalu Medical, and Gimer Medical. Erika A. Petersen reports grants and/or personal fees from Biotronik, Medtronic Neuromodulation, Nevro, Presidio Medical, Saluda, and SPR, outside the submitted work. Jason M. Schwalb reports grants from Medtronic, SetPoint, Nevro, MeiraGTX; and salary support for role as codirector of the Michigan Spine Surgery Improvement Collaborative, paid directly to employer from Blue Cross Blue Shield of Michigan, outside the submitted work. Konstantin V. Slavin reports institutional research and education grants from Medtronic, Abbott, Boston Scientific, Neuros, and Stryker; personal and institutional support from Abbott, Biotronik, Integer, Medtronic, Saluda, Stimwave, Synergia, Thermaquil, and WISE; and participation on a Data Safety Monitoring Board for Abbott and Nurami. The remaining authors reported no conflict of interest.

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COMMENT

This pivotal study on chronic PAP among patients with lower limb amputations, conducted through the multicenter QUEST trial, stands as a significant contribution to the neuromodulation literature. Briefly, this secondary analysis of the 12-month outcomes from the previously published sham-controlled, double-blinded randomized controlled trial provides crucial insights into the long-term efficacy of a novel, peripherally placed HFNB system. Given the notoriously difficult nature of treating chronic PAP, these findings are particularly valuable, especially because even advanced interventions such as SCS often fail in this population. The data from the QUEST trial highlight that HFNB therapy offers substantial on-demand pain relief, with an average reduction of 30% within 30 minutes and 47% within two hours of treatment. Over the 12-month follow-up period, participants reported statistically significant decreases in worst, average, and least daily pain levels, although the modest-to-moderate clinical significance of these reductions may warrant future trials to be conducted to confirm this therapeutic effect. Moreover, the study revealed a 45% improvement in quality of life and a remarkable 56% reduction in opioid use among the participants. These outcomes underscore the potential of HFNB as an effective treatment option for chronic PAP. By providing consistent pain relief, enhancing quality of life, and reducing dependence on opioids, HFNB may offer a promising nonopioid therapeutic alternative. This study not only advances our understanding of neuromodulation but also highlights the importance of developing innovative treatments for chronic pain conditions that are resistant to conventional therapies.

Ryan D'Souza, MD
Rochester, MN, USA