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Peripheral Somatosensory Stimulation in the Treatment of Parkinson's Disease: A Preliminary Clinical Trial

LA Nussbaum[1], TM Janjua[1], J Pederson[2] and Eris S. Nussbaum[1*]

[1]Department of Neurosurgery, National Brain Aneurysm and Tumor Center, USA
[2]Department of Biostatistics, Superior Medical Editing, USA

Abstract

Objective: To evaluate the safety and efficacy of peripheral somatosensory stimulation (PSS) in patients with Parkinson's disease.

Methods: 8 patients with Parkinson's Disease (PD) underwent daily PSS therapy over a 4-week study period. Assessments were conducted at baseline and at 4 weeks, evaluating anxiety using the Generalized Anxiety Disorder Scale (GAD-7), depression using the Patient Health Questionnaire (PHQ-9), and PD symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS). Statistical analysis was performed using Wilcoxon signed-rank tests or paired t-tests. The odds of transitioning to an improved score for a given survey question were analyzed using cumulative link mixed models.

Results: Four men and four women completed the trial. Mean age was 74.6 years (range 65 to 84 years). No adverse events were described by the patients. Anxiety scores decreased significantly from a median of 7 (IQR: 3.25-13) to 3.5 (IQR: 0.25-6) by week 4 ($p=0.008$). Similarly, total depression significantly decreased, with median PHQ-9 scores dropping from 13 (IQR: 8–18.75) to 5.5 (1.5–7.75) by week 4 ($p=0.008$). Based on UPDRS results, patients had significantly improved symptoms from baseline to follow-up (51.5 ± 12.6 vs. 25.1 ± 17.6, $p<0.001$), as well as improved scores for all subdomains, including mentation, behavior, and mood (MBM: 6.4 ± 2.8 vs. 2.1 ± 1.4, $p<0.001$), activities of daily living (ADL: 21.6 ± 5.3 vs. 13.1 ± 6.9, $p<0.001$), and motor examination (ME: 23.5 ± 7.5 vs. 9.9 ± 11.4, $p<0.001$). The overall cumulative odds ratio (cOR) was 5.88 ($p<0.001$), suggesting that on average, the odds of moving from one score to an improved score at week 4 are approximately 6 times higher than moving to a neutral or worse score compared to baseline values. This finding held true for all UPDRS subdomains, with cOR values of 5.76, 4.02, and 12.07 for MBM, ADL, and ME, respectively (all $p<0.001$).

Conclusion: PSS stimulation appeared to have a significantly favorable effect on anxiety, depression, and primary Parkinson's disease symptoms in this group of patients. We suggest that further investigation into the potential usefulness of PSS therapy in patients with Parkinson's disease is warranted.

Keywords: Anxiety • Neuromodulation • Alzheimer's • Parkinson's disease • Somatosensory • Stimulation

Introduction

Parkinson's Disease (PD) is a degenerative disorder of the central nervous system that affects more than 1 million people in the United States with a total estimated economic cost exceeding 50 billion dollars [1-6]. Classic PD symptoms include tremor, rigidity, slowness of movement, postural instability, and gait difficulty as well as cognitive findings such as dementia, memory loss, and depression [7-10]. While medications are effective in ameliorating some of the symptoms of PD, serious side effects occur, and medication effectiveness often wanes in the later stages of the disease [7-12]. Surgical intervention may be useful in improving the motor symptoms of PD but requires invasive techniques that also carry risk [11,12]. Thus, there is a substantial need for other approaches in the treatment of PD. Peripheral Somatosensory Stimulation (PSS) therapy is a non-invasive technique which may be beneficial to patients with a variety of neurological disorders [13-17]. This report focuses on our experience with the impact of PSS therapy on symptoms in a group of patients with Parkinson's disease.

***Address for Correspondence:** Eris S. Nussbaum, Department of Neurosurgery, National Brain Aneurysm and Tumor Center, USA, Email: lnussbaum@comcast.net*

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Methods

Study description

NeuroGlove is a non-invasive device that provides PSS stimulation in the form of pneumatic puffs of air directed at the volar surface of the distal forearm, the palm, and the fingers. This study was designed as a prospective, single center trial enrolling eight patients to explore the effect of PSS therapy on symptoms and quality-of-life measures in patients with PD. Men and women between the ages of 18 years and 85 years with an active diagnosis of PD who were able to provide informed consent were considered eligible for trial enrollment. Patients who were unable to comprehend or follow instructions or unable to use the device due to physical limitations of the upper extremity including fracture, joint deformity, severe spasticity/contracture, or skin breakdown were excluded from participation.

Device use

Subjects were instructed to use the device at home for 2 hours of therapy per day (60 minutes for each hand) for 4 weeks. At the conclusion of the trial, compliance was determined based on patient reporting and using an internal computerized system that allowed the investigators to track device use during the course of the trial.

Statistical methods

The primary objective of this study was to evaluate the impact of 4 weeks of PSS therapy on the severity of anxiety, depression, and PD symptoms. The measures examined by the GAD-7, PHQ-9, and UPDRS scales are provided in Tables 1-3. Descriptive statistics were calculated for individual scores at each timepoint, including mean ± standard deviation (SD) or median and interquartile range (IQR). A composite score of all questions using the pooled mean or median value of patient-specific survey questions was also compared between patient visits.

Table 1. List of questions for GAD-7 anxiety surveys

Question	Description
Q1	Feeling nervous, anxious, or on edge
Q2	Not being able to stop or control worrying
Q3	Worrying too much about different things
Q4	Trouble relaxing
Q5	Being so restless that it is hard to sit still
Q6	Becoming easily annoyed or irritable
Q7	Feeling afraid as if something awful might happen
Note: Each question is rated on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). Total scores are calculated by summing individual responses, with the following severity categories: 0 (no symptoms), 1-4 (minimal), 5-9 (mild), 10-14 (moderate), and 15-21 (severe).	

Table 2. List of questions for PHQ-9 depression surveys

Question	Description
Q1	Little interest or pleasure in doing things
Q2	Feeling down, depressed, or hopeless
Q3	Trouble falling or staying asleep, or sleeping too much
Q4	Feeling tired or having little energy
Q5	Poor appetite or overeating
Q6	Feeling bad about yourself, or that you are a failure or have let yourself or your family down
Q7	Trouble concentrating on things, such as reading the newspaper or watching TV
Q8	Moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual
Q9	Thoughts that you would be better off dead, or hurting yourself
Note: Each question is rated on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). Total scores are calculated by summing individual responses, with the following severity categories: 0 (no symptoms), 1-4 (minimal), 5-9 (mild), 10-14 (moderate), and 15-21 (severe).	

Table 3. List of items on the Unified Parkinson's Disease Rating Scale (UPDRS).

Domain/Category
Mentation, Behavior and Mood
Intellectual Impairment
Thought Disorder
Depression
Motivation/Initiative
Activities of Daily Living
Speech (Related to Activities of Daily Living)
Salivation
Swallowing
Handwriting
Cutting Food and handling Utensils
Dressing
Hygiene
Turning in Bed and Adjusting Bed Clothes
Falling
Freezing when Walking
Walking
Tremor
Sensory Complaints Related to Parkinsonism
Motor Examination
Speech (Related to Motor Examination)
Facial Expression
Tremor at Rest
Action or Postural Tremor of Hands
Rigidity
Finger Taps
Hand Movements
Rapid Alternating Movement of Hands
Leg Agility
Arising from Chair
Posture
Gait
Postural Stability
Body Bradykinesia and Hypokinesia
Note: Each item for a given domain is scored on a 5-point ordinal scale: 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), 3 (severe symptoms), 4 (very severe symptoms).

We assessed changes in overall ordinal scores from GAD-7 and PHQ-9 patient-specific responses using non-parametric Wilcoxon signed-rank tests to determine if there were significant improvements from baseline to week 4. Effect sizes from Wilcoxon's signed rank tests were reported as the median of differences alongside approximates of the 95% Confidence Interval (CI). Since this nonparametric test is based on ranks, it is typically not possible to derive a CI with exactly 95% confidence. Instead, the closest approximate was calculated; for simplicity these are reported as 95% CIs in text. For comparisons of UPDRS results, the assumption of normality was validated using the Shapiro-Wilk test, and comparisons were made using a paired t-test.

To analyze overall cumulative probability of improved scores for GAD-7, PHQ-9, and UPDRS results across measurement times for a given item, we employed Cumulative Link Mixed Models (CLMMs) with logit link functions. The models were specified with the following formula using the clmm () function in the 'ordinal' package for R: Score ~ Visit + (1 | Subject). Where, 'Score' represents individual ordinal-scale responses, 'Visit' is the predictor variable of interest (baseline or week 4), and '(1 | Subject)' indicates the inclusion of random intercepts for individual subjects to account for within-subject variability. Laplace approximation was employed to estimate the model parameters. Predicted probabilities for each score at a given time point were extracted from the model. Overall effect sizes from the CLMM model are reported as cumulative odds ratios (cOR).

Line plots were generated to show patient-specific and group-averaged results across time points. Stacked bar plots were generated to show predicted probabilities of obtaining different survey scores for a given question at baseline and at the end of the study.

All analyses were conducted in RStudio (2024.04.2 Build 764), running on R version 4.4.1. CLMM analyses were performed using the 'ordinal' package (version 2023.12-4.3). Figures were generated using the 'ggplot2' package (version 3.5.1).

Results

Patients

Eight patients with a formal diagnosis and active symptoms of PD were consented and enrolled in the trial. Of these patients, 4 were female and 4 were male, with a mean age of 74.6 years ± 6.8 years, ranging from 65 to 84. All patients completed the trial. Compliance with device use was greater than 95% based on self-reporting and internal control checks at the conclusion of the trial. No patient reported an adverse event related to use of the device. Regarding anxiety symptoms, 3 had minimal (GAD-7 scores 0-4), 1 had mild (GAD-7 scores 5-9), 2 had moderate (GAD-7 scores 10-14), and 1 had severe anxiety (GAD-7 scores 15-21). Regarding depression symptoms, 4 patients were mild (PHQ-9 scores 5-9) and the remaining 4 had moderately severe symptoms (PHQ-9 scores 15-19). Regarding Parkinson's disease symptoms, the overall mean UPDRS scores was 51.5 ± 12.6. A summary of patient baseline characteristics is provided in Table 4.

Table 4. Patient baseline characteristics

Characteristic	Value
Age	74.6 ± 6.8
Sex	-
Male	4 (50%)
Female	4 (50%)
GAD-7	7 (3.25–13)
0–4 (minimal)	3 (37.5%)
5–9 (mild)	1 (12.5%)
10–14 (moderate)	2 (25%)
15–21 (severe)	1 (12.5%)
PHQ-9	13 (8–18.75)
0–4 (minimal)	0 (0%)
5–9 (mild)	4 (50%)
10–14 (moderate)	0 (0%)
15–19 (moderately severe)	4 (50%)
20–27 (severe)	0 (0%)
UPDRS	51.5 ± 12.6
Mentation, Behavior and Mood	6.4 ± 2.8
Activities of Daily Living	21.6 ± 5.3
Motor Examination	23.5 ± 7.5

Note: Data are expressed as event counts (percentage of total), mean ± standard deviation, or median (interquartile range).

GAD-7=Generalized Anxiety Disorder; 7-item survey; PHQ-9=Patient Health Questionnaire; 9-item survey; UPDRS=Unified Parkinson's Disease Rating Scale

Change in anxiety symptoms (GAD-7)

By week 4, all patients reported either minimal/resolved symptoms (n=4) or mild anxiety symptoms (n=4) based on GAD-7 survey questions. Patients were most improved regarding Q5 ("Being So Restless that it is Hard to Sit Still") and Q6 ("Becoming Easily Annoyed or Irritable"), with median scores of 1.5 (mild-moderate) at baseline and 0 (no symptoms) at the end of the study. Overall, total anxiety scores demonstrated a significant reduction, with the median composite score dropping from 7 (IQR: 3.25–13) at baseline to 3.5 (IQR: 0.25-6) by week 4, indicating a transition from typically mild symptoms at the outset to minimal or resolved symptoms by the end of the study (p=0.008) (Figure 1) (Table 5).

Table 5. Summary of survey responses for anxiety (GAD-7) and depression (PHQ-9), and Parkinson's symptoms at baseline and week 4

Survey	Baseline	Week 4	Effect Size (95% CI)	p-value
Total GAD-7 Score	7 (3.25–13)	3.5 (0.25–6)	-4 (-13; -2)	0.008
Score 0	22%	67%	7.51 (3.06–18.43)	<0.001
Score 1	60%	30%		
Score 2	11%	2%		
Score 3	8%	1%		
Total PHQ-9 Score	13 (8–18.75)	5.5 (1.5–7.75)	-8.25 (-14.0; -2.0)	0.008
Score 0	23%	61%	5.16 (2.60–10.25)	<0.001
Score 1	34%	26%		
Score 2	20%	7%		
Score 3	22%	5%		

Note: Individual summary data at baseline and week 4 are presented as median (interquartile range) or percentages (i.e., predicted probabilities). Effect sizes are reported as the median of differences or cumulative odds ratios.
GAD-7=Generalized Anxiety Disorder; 7-item survey; PHQ-9=Patient Health Questionnaire; 9-item survey.

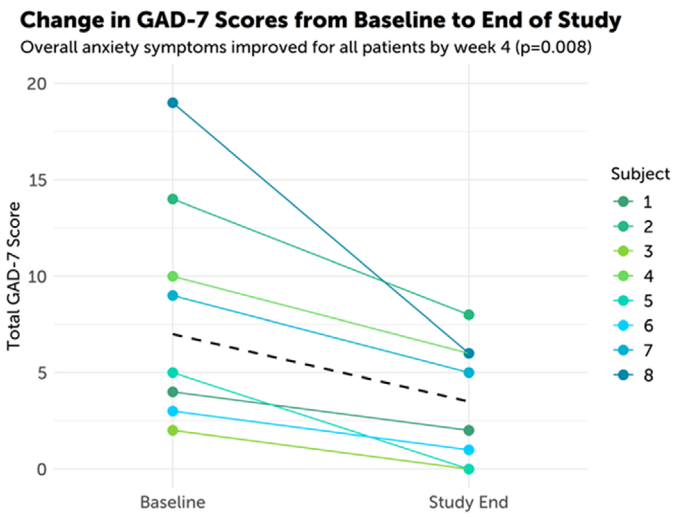

Figure 1. Change from baseline severity of anxiety symptoms based on GAD-7 survey results. Patient specific total scores are presented as colored lines, and the black dotted line represents the pooled median scores at baseline and week 4. GAD-7=Generalized Anxiety Disorder 7-item survey

Overall, the predicted probability of obtaining the best outcome for an individual question (score=0) was 22% at baseline vs. 67% by week 4. Conversely, the predicted probability of obtaining the worst outcome (score=3) was 8% at baseline vs. 1% at week 4 (Table 5). The overall cOR was 7.51 (p<0.001), suggesting that on average, the odds of moving from one score to a lower (improved) score at week 4 are 7.51 times higher than moving to a neutral or worse score compared to the baseline values.

Change in depression symptoms (PHQ-9)

After 4 weeks of therapy, patients reported either minimal (n=4), mild (n=3), or moderate depression symptoms (n=1). Patients were most improved regarding Q2 ("Feeling Down, Depressed, or Hopeless") and Q4 ("Feeling Tired or Having Little Energy"), with median scores of 2 (moderate) and 3 (severe) at baseline, and 0 (no symptoms) and 1 (mild) at the end of the study, respectively. Overall, total PHQ-9 scores demonstrated a significant reduction, with the median composite score dropping from 13 (IQR: 8–18.75) at baseline to 5.5 (IQR: 1.5–7.75) by week 4, indicating a transition from typically moderate symptoms at baseline to mild symptoms by the end of the study (p=0.008) (Figure 2) (Table 5).

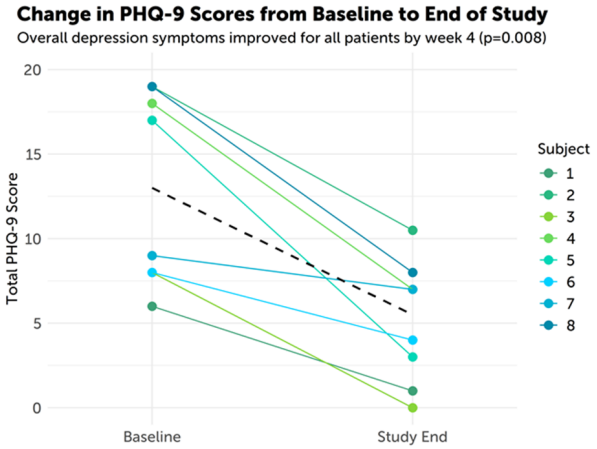

Figure 2. Change from baseline severity of depression symptoms based on PHQ-9 survey results. Patient specific total scores are presented as colored lines, and the black dotted line represents the pooled median scores at baseline and week 4. PHQ-9=Patient Health Questionnaire-9

Overall, the predicted probability of obtaining the best outcome for an individual question on the PHQ-9 survey (score=0) was 23% at baseline vs. 61% by week 4. Conversely, the predicted probability of obtaining the worst outcome (score=3) was 22% at baseline vs. 5% at week 4 (Table 5). The overall cOR was 5.16 (p<0.001).

Of interest, three patients spontaneously noted a significant improvement in their ability to fall asleep and stay asleep during the study period. Overall, 6 of the 8 described improvements in falling and/or staying asleep, while two patients had no change in sleep patterns.

Change in Parkinson's symptoms (UPDRS)

Patients showed significant improvement in mean UPDRS scores from baseline to follow-up (51.5 ± 12.6 vs. 25.1 ± 17.6, p<0.001), with all subdomains improving: Mentation, behavior, and mood (MBM: 6.4 ± 2.8 vs. 2.1 ± 1.4, p<0.001), activities of daily living (ADL: 21.6 ± 5.3 vs. 13.1 ± 6.9, p<0.001), and motor examination (ME: 23.5 ± 7.5 vs. 9.9 ± 11.4, p<0.001) (Figure 3) (Table 6). The cOR was 5.88 (p<0.001), indicating an approximately 6-fold greater likelihood of score improvement at week 4 compared to a neutral or worse outcome. Subdomain cOR values were 5.76 for MBM, 4.02 for ADL, and 12.07 for ME (all p<0.001). Predicted probabilities of achieving the best outcome (score=0) increased from baseline to follow-up: 12% to 44% overall, 22% to 62% for ADL, 11% to 34% for MBM, and 7% to 47% for ME.

Table 6. Summary of Unified Parkinson's Disease Rating Scale (UPDRS) scores at baseline and week 4

Survey	Baseline	Week 4	Effect Size (95% CI)	p-value
Total UPDRS Score	51.5 ± 12.6	25.1 ± 17.6	-26.4 (-34.1; -18.7)	<0.001
Score 0	12%	44%	5.88 (4.11–8.39)	<0.001
Score 1	33%	39%		
Score 2	34%	13%		
Score 3	20%	4%		
Score 4	1%	0%		
Total MBM Score	6.4 ± 2.8	2.1 ± 1.4	-4.3 (-6.0; -2.5)	<0.001
Score 0	22%	62%	5.76 (2.10–15.84)	<0.001
Score 1	29%	24%		
Score 2	17%	7%		
Score 3	29%	7%		
Score 4	2%	0%		
Total ADL Score	21.6 ± 5.3	13.1 ± 6.9	-8.6 (-12.1; -5.0)	<0.001

Score 0	11%	34%	4.02 (2.36–6.84)	<0.001
Score 1	31%	41%		
Score 2	39%	20%		
Score 3	17%	5%		
Score 4	2%	0%		
Total ME Score	23.5 ± 7.5	9.9 ± 11.4	-13.6 (-18.9; -8.3)	<0.001
Score 0	7%	47%	12.07 (6.61–22.04)	<0.001
Score 1	36%	43%		
Score 2	39%	8%		
Score 3	18%	2%		
Score 4	0%	0%		

Note: Individual summary data at baseline and week 4 are presented as mean ± standard deviation or percentages (i.e., predicted probabilities). Effect sizes are reported as the mean of differences or cumulative odds ratios.
ADL=Activities of Daily Living; MBM=Mentation, Behavior, and Mood; ME=Motor Examination; UPDRS=Unified Parkinson's Disease Rating Scale

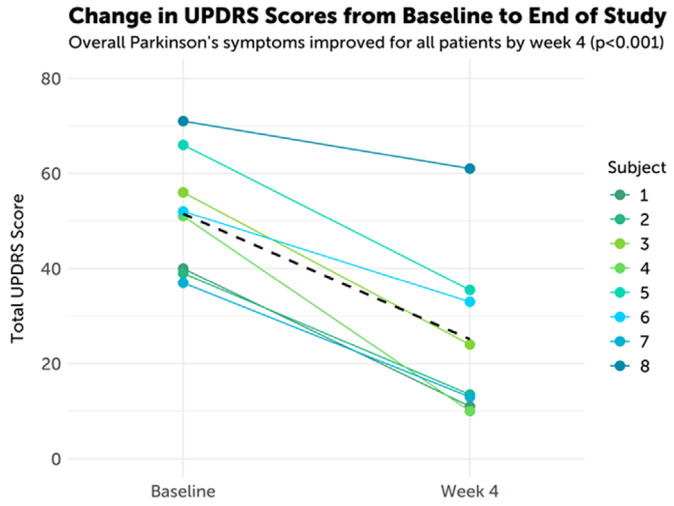

Figure 3. Change from baseline severity of Parkinson's symptoms based on UPDRS score results. Patient specific total scores are presented as colored lines, and the black dotted line represents the group-averaged results at baseline and week 4. UPDRS=Unified Parkinson's Disease Rating Scale

It is interesting to note that patients with refractory tremor including one individual who had undergone prior deep brain stimulation (DBS) therapy described improvement in both the frequency and intensity of their tremor during the trial period.

Discussion

PD is the second most common neuro-degenerative disorder affecting more than 2% of the population over the age of 65 years and resulting in significant disability and economic cost [1-6]. PD is associated with progressive loss of the dopaminergic neurons in the substantia nigra [7-10]. Although the cause of this cell death is unknown, recent studies indicate that it may be the result of abnormal synchronization within the cells of the dopaminergic brain circuits, specifically those of the sub-thalamic nucleus [18-26]. Medications have proven moderately effective in the treatment of PD; nevertheless, serious side effects occur, and medication effectiveness often wanes in the later stages of the disease. In addition, medications cycle in effectiveness during any 24-hour period, creating periods of "on" and "off" in the PD symptomatology [7-12]. Despite a variety of advances in the treatment of PD over the past two decades, there remains a substantial need for novel and preferably non-invasive approaches in the treatment of PD.

PSS is a non-invasive technique that provides somatosensory stimulation to the brain which may be beneficial to patients with a variety of neurological disorders. It has been shown in rodent models of stroke that early PSS significantly and reproducibly improves neurological outcomes following ischemic injury and may prevent injury entirely if applied early enough [27-28]. Potential suggested mechanisms for this protection and benefit may include the encouragement of collateral blood supply to the affected sensorimotor cortex which can improve regional cerebral perfusion and/or direct neuronal reorganization which may allow for better functional recovery [29]. Clinical experience in humans has suggested that such peripheral sensory stimulation can improve recovery and rehabilitation after stroke and may be similarly beneficial in a variety of conditions including traumatic brain injury and inflammatory, autoimmune conditions such as multiple sclerosis [30-35]. PSS has also been shown to improve symptoms in patients with post-traumatic stress disorder, anxiety, depression, and insomnia [36-39].

Recent studies have demonstrated the potential benefit of PSS in patients with PD and have suggested that vibrotactile stimulation may act to desynchronize the dopaminergic system that is affected in PD [18-26]. These studies have shown improvement in the motor symptoms associated with PD including gait and tremor with some patients experiencing dramatic symptomatic relief. The current study was undertaken to further evaluate the effect of daily PSS therapy on patients with PD, evaluating both motor symptoms and cognitive issues including the anxiety, depression, and insomnia that can be associated with PD.

In this preliminary study, we encountered a significant response to PSS treatment as evidenced by improvements in both motor symptoms as well as measures of anxiety and depression in patients with PD. Several patients with refractory tremor, including one patient who had previously undergone DBS surgery, noted improvement in both frequency and intensity of tremor during the trial. Prior to treatment, patients typically presented with mild anxiety and moderate depression, which improved to generally minimal or no anxiety and mild depression by the end of the study.

It is interesting to note that three patients spontaneously commented on an improvement in their sleep patterns, noting that they found it both easier to fall asleep and stay asleep during the study. As documented in the PHQ-9, 6 of the 8 patients experienced an improvement in their sleep patterns during the study with the greatest improvements identified in the patients who had the most sleep disruption at baseline. PSS has previously been shown to improve sleep in patients with anxiety and depression [39]. The scientific basis for such improvements is uncertain but may be related to the role played by abnormal sensory processing in anxiety, depression, and sleep disturbances [40].

Limitations

The primary limitations of our study are the small sample size and the

absence of an active control group. Data is also limited by self-reported survey questions that may not capture other clinically important outcomes. Data related to patient factors such as medication timing which can be important in PD symptoms, daily routines, and lifestyle changes may have also influenced patient outcomes. Nevertheless, this trial was meant primarily to evaluate the safety of PSS in this patient population and to gather preliminary evidence of the possible usefulness of PSS in the treatment of patients with PD, potentially forming the basis for a larger controlled study.

Conclusion

We describe the results of a clinical trial evaluating the impact of one month of treatment with PSS on symptoms in patients with a diagnosis of PD. All patients completed the trial and demonstrated varying degrees of benefit from the therapy. This clinical trial provides encouraging preliminary evidence of improved PD symptoms following 4 weeks of PSS therapy. By week 4, patients demonstrated statistically significant reductions in anxiety, depression, and motor PD symptoms. These findings show that patients across various stages of Parkinson's disease may benefit from PSS therapy. We suggest that further investigation into the potential use of PSS in the treatment of patients with PD is warranted.

Conflicts of Interest

Drs. Eric and Leslie Nussbaum are shareholders in NeuroGlove, LLC.

Study Approval

IRB#00014420-613-REG-1010

Clinicaltrials.gov Registration#NCT06578273

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