MANAGING PARKINSON'S DISEASE WITH A MULTIDISCIPLINARY PERSPECTIVE

EDITED BY: Daniel Martinez-Ramirez, Adolfo Ramirez-Zamora, Mayela Rodríguez-Violante and Seyed-Mohammad Fereshtehnejad

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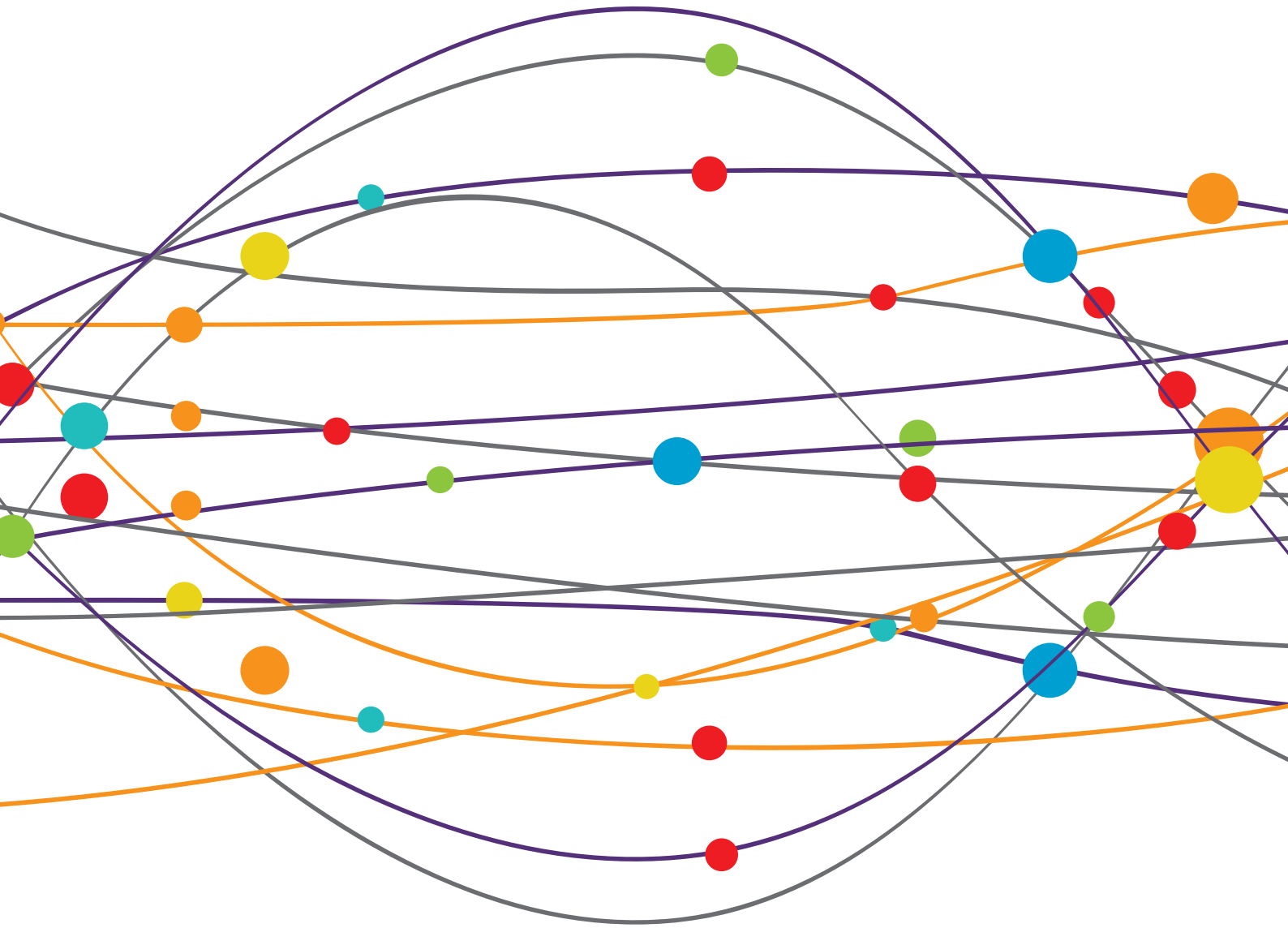

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MANAGING PARKINSON'S DISEASE WITH A MULTIDISCIPLINARY PERSPECTIVE

Topic Editors:
Daniel Martinez-Ramirez, Escuela de Medicina y Ciencias de la Salud Tec Salud, Tecnológico de Monterrey, Mexico
Adolfo Ramirez-Zamora, University of Florida Health, United States
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico
Seyed-Mohammad Fereshtehnejad, Division of Neurology, Department of Medicine, Ottawa Hospital, Canada

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EDITORIAL
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Editorial: Managing Parkinson's Disease With a Multidisciplinary Perspective

Seyed-Mohammad Fereshtehnejad[1,2]*, *Mayela Rodríguez-Violante*[3], *Daniel Martinez-Ramirez*[4] and *Adolfo Ramirez-Zamora*[5]

[1] Division of Neurology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada, [2] Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden, [3] Movement Disorders Clinic, Clinical Neurodegenerative Research Unit, Mexico City, Mexico, [4] Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico, [5] Department of Neurology, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, United States

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Editorial on the Research Topic

Managing Parkinson's Disease With a Multidisciplinary Perspective

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***Correspondence:**
Seyed-Mohammad Fereshtehnejad
sm.fereshtehnejad@ki.se

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Parkinson's Disease (PD) is a complex and heterogeneous disorder from prodromal to advanced stages, with a wide range of motor and non-motor symptoms from bradykinesia and rigidity to dysautonomia, sleep disturbances, and cognitive impairment (1). Such a clinical diversity necessitates the involvement of healthcare professionals from different disciplines for an optimal management plan. Clinical guidelines recommend that all persons with PD should have access to a broad range of medical and allied health professionals for personalized, integrative, and multidisciplinary care (2, 3). This is supported by growing evidence showing the effects of integrated multidisciplinary interventions on improving quality of life and disease progression in people with PD (4–6).

Apart from symptomatic management and clinical care, other aspects of PD also warrant a multidisciplinary approach with a wide variety of expertise being involved from discovery of its pathophysiology and early prodromal stage to progression of parkinsonian features as medications' side effects. Roiter et al. analyzed the prevalence of parkinsonian symptoms in patients with severe mental illnesses admitted to a monocentric inpatient psychiatry ward. Parkinsonian (previously referred to as extrapyramidal) symptoms were quite common in this population (50.5%), with tremor (33%) being the most common manifestation. Only a minority of patients met the criteria for possible PD, which were significantly older, had more medical comorbidities with a larger number of medications including antipsychotics, and slightly more than half of them had reduced striatal dopamine transporter binding in ^{123}I-FP-CIT SPECT. Whether antipsychotic medications unmask underlying neurodegenerative pathology by quickening the progression of the prodromal stage is not yet clear (7).

Gastrointestinal problems such as constipation are increasingly appreciated as another non-motor prodromal feature (1) and/or risk factor for developing PD (8), integrating another discipline into the diagnosis, and care of, people with PD. In their longitudinal study on *de novo* PD patients, Palacios et al. showed that Levodopa, as the mainstay of PD symptomatic therapy, did not

change the gut microbiota composition after 3 months of initiation. Nevertheless, they observed a marginally lower abundance of *Clostridium* group IV in PD patients with a good response to Levodopa, which needs further investigation in the future.

Multidisciplinary diagnostic approaches such as neuroimaging techniques and other biomarkers are helpful to analyze overlapping movement disorders syndromes. There is evidence suggesting that patients diagnosed with essential tremor (ET) are at increased risk of developing PD (9). This relationship has been controversial as both disorders are common with significant clinical overlap between them. In this special article, Wang et al. reviewed the evidence on the application of neuroimaging [i.e., transcranial sonography (TCS), voxel-based morphometry, diffusion tensor imaging, proton MR spectroscopy], and potential multidisciplinary clinical biomarkers (i.e., non-motor symptoms and heart rate variability) suggestive of prodromal PD in ET. Current evidence suggests that patients with ET have an increased risk of developing PD, especially those with substantia nigra hyperechogenicity in TCS and in ET patients with specific tremor features, non-motor, genetic, and autonomic characteristics.

One very well-appreciated multidisciplinary aspect of PD is the caring and management practices beyond the routine protocols. There is an increasing interest in assessing the benefits of different physiotherapy and exercise interventions in patients with PD. Multiple mobility and rehabilitative strategies have been recognized as part of a multidisciplinary approach to PD management. As such the roles of allied health care members, namely physiotherapists and occupational therapists, in the multidisciplinary care of PD have been well-recognized (10). In a small, open-label, prospective study (Kotani et al.) aimed to investigate whether core exercise complemented with a hybrid assistive limb for lumbar support may improve the motor function in PD patients. The authors reported significant improvement in standard, validated motor measures at the end of the trial (after 3 months) with adequate safety. In a randomized controlled clinical trial, Segura et al. assessed the impact of a high-intensity tandem bicycle program on symptoms severity. They noted significant improvement in motor function clinically and in biochemical and functional neuroimaging variables. Giménez-Llort et al. proposed the "PasoDoble," as a novel dance/music patient-caregiver intervention in PD patients. In this methods article, they reviewed the rationale on evidence-based therapeutic benefits of dance/music therapy and highlighted the potential benefit of this specific multidisciplinary technique.

Complementary medicine involves health care practices not considered as part of standard care that are used along with conventional medicine; when these practices are combined in a coordinated and standardized manner the result is integrative medicine (11). Huang et al. performed a systematic review on the effectiveness of acupuncture using the AMSTAR-2 and GRADE criteria. Overall, acupuncture was safe and improved some axial parkinsonian symptoms. However, the more striking finding was that most studies were rated as very low to low quality thus highlighting the need for better-designed studies in the future. Sharpe et al. reviewed non-pharmacological interventions in the context of axial and cognitive symptoms in early PD. The effect of balance, posture, speech, swallowing, and cognitive interventions proved to be of value highlighting the role of a unified multidisciplinary plan with an individualized approach.

Advanced management in PD, as another aspect of multidisciplinary care, is usually needed when oral or transdermal medications fall short in controlling the motor and non-motor fluctuations and accompanying complications such as dyskinesia with a large impact on quality of life and daily life activities (12). These advanced therapies include deep brain stimulation (DBS), continuous levodopa-carbidopa intestinal gel, and continuous subcutaneous apomorphine infusion. Qi et al. reported motor outcomes at 1 year in 40 individuals with PD who underwent subthalamic nucleus DBS. DBS improved motor function in all patients with various indexes of progression, yet the fast-progression group had less improvement. The slightly different outcome depending on the preoperative progression index might be a useful indicator for the multidisciplinary team involved in this type of management.

Aye et al. conducted a review with the objective of presenting current evidence and gaps in knowledge of multidisciplinary management and provision of community care of people with PD. The authors described their 14-year experience based on the Partners Community Care Program in Singapore that provides care for people with PD in the community and at their homes. The authors argued that although there is scarce experimental evidence supporting the use of multidisciplinary management, probably due to the great heterogeneity of the interventions and the need to individualize treatment, multidisciplinary management in PD should be recommended. Interdisciplinary or transdisciplinary support, as well as remote support with tools such as telemedicine, are feasible methods to provide and achieve the ideal patient-centric management. In their perspective article, Göttgens et al. discussed the impact of "sex" and "gender" in the multidisciplinary management of patients with PD. For motor symptoms such as imbalance and dyskinesias, authors propose possible sex- and gender-sensitive interventions such as balance training and DBS. Regarding non-motor symptoms, a reduction or discontinuation of dopaminergic therapies, cognitive behavioral therapy, referrals for training coping skills, and social support interventions were suggested. With respect to lifestyle, authors recommend self-monitoring of weight and dietetic plan for men and physical exercise and motivational interventions in women. Finally, in terms of social support, they suggest proactively identifying patients' social networks and referral to social support groups as well as regular evaluations to identify caregiver strain and improve their education about PD. It is crucial to identify these sex- and gender-related differences in knowledge and care provision to optimize the multidisciplinary management plan for people with PD.

Capitalizing on the importance of managing PD with a multidisciplinary approach, one must consider its potentially prohibitive cost by involving a broad range of medical and allied

health professionals. One way to overcome its financial burden is innovative virtual or in-person platforms such as online health communities or patients' networks where professionals and patients can meet online in a secured environment to share their experiences (10).

AUTHOR CONTRIBUTIONS

This editorial was written by S-MF, MR-V, DM-R, and AR-Z and edited by S-MF. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Biofeedback Core Exercise Using Hybrid Assistive Limb for Physical Frailty Patients With or Without Parkinson's Disease

Naoya Kotani[1,2], *Takashi Morishita*[1]*, *Aya Yatsugi*[1,2], *Shinsuke Fujioka*[3], *Satoshi Kamada*[2], *Etsuji Shiota*[2], *Yoshio Tsuboi*[3] *and Tooru Inoue*[1]

[1] Department of Neurosurgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan, [2] Department of Rehabilitation Medicine, Fukuoka University Hospital, Fukuoka, Japan, [3] Department of Neurology, Fukuoka University Faculty of Medicine, Fukuoka, Japan

Introduction: Elderly people often exhibit "frailty," and motor dysfunction occurs. Several studies have reported about the relationship between motor dysfunction and frailty in Parkinson's disease (PD). This study aimed to test whether the core exercise using the hybrid assistive limb lumbar type for care support (HAL-CB02) may improve the motor functions in frailty patients with or without PD and to explore the optimal patient selection from the frailty cohort.

Materials and Methods: We recruited 16 frailty patients (PD = 8; non-PD = 8). The participants performed core exercise and squats using HAL-CB02 for five sessions a week. Outcome measures were 10-m walking test, step length, timed up-and-go test, 30-s chair stand test, and visual analog scale. Evaluation was conducted at baseline, post-exercise, and 1- and 3-month follow-ups.

Results: Both PD and non-PD patients showed significant improvement in all evaluation items post-exercise. Moreover, no significant difference was found in the improvement value between the two groups.

Conclusions: Our results suggest that biofeedback exercise with HAL-CB02 is a safe and promising treatment for frailty patients. Motor dysfunction in PD patients may be partly due to physical frailty, and biofeedback exercise with HAL-CB02 is proposed as a treatment option.

Keywords: arthrogenic muscle inhibition, biofeedback, central pattern generator, frailty, hybrid assistive limb, Parkinson's disease

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Daniel Martinez-Ramirez, Tecnológico de Monterrey, Mexico

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Izabella Uchmanowicz, Wroclaw Medical University, Poland
Jinyoung Youn, Sungkyunkwan University School of Medicine, South Korea

***Correspondence:**
Takashi Morishita
tmorishita@fukuoka-u.ac.jp

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INTRODUCTION

The proportion of elderly people aged 65 years or older has exceeded 15% in developed countries, and it is expected to exceed 30% in 2050 (1). Physiological performance gradually decreases with aging, and frailty would be a severe burden in this population. Frailty affects activities of daily living (ADLs) and quality of life, resulting in frequent falls and walking problems. In addition, frailty is associated with mental and psychological problems, such as cognitive dysfunction and depression (2, 3). In recent years, several studies have reported on the relationship between motor dysfunction

and frailty in Parkinson's disease (PD) (4–7). PD patients are likely to have frailty, and such patients are more prone to gait and balance problems than normal PD patients (5, 6).

Gait disturbance is a common problem among PD patients, and physical frailty is potentially attributable to the gait problem in PD. Atrophy and disability of erector spinae muscles have been reported to cause gait disturbance (7, 8). Trunk muscle activity plays an important role in stabilizing gait. In particular, the strength of the erector spinae muscles is highly correlated with physical activity levels (9). When the trunk leans forward during walking, a decrease in step length and an increase in cadence are observed (10). In addition, the strength of the erector spinae muscles is reduced in the leaning posture, resulting in reduced walking speed and a wide base of walking (11).

Chronic muscle disuse in physical frailty is associated with neuromuscular disorders including PD, especially in the elderly population. In contrast, resistance training is effective, but these active adaptations could not be achieved with neuromuscular electrical stimulation or traditional rehabilitation efforts alone (6, 12); thus, establishment of new treatment methods has been expected.

In the field of neurorehabilitation, the hybrid assistive limb (HAL; Cyberdyne Inc., Tsukuba, Japan) has been receiving growing attention. HAL is a robotic exoskeleton designed to facilitate movements and was developed based on the "interactive biofeedback" (iBF) hypothesis (13). Specifically, the movement of the robot is triggered by bioelectric signals (BESs) detected by surface electrodes, supporting spontaneous movement of impaired muscles generating sensory feedback. Several studies have demonstrated the efficacy and feasibility of HAL and single-joint HAL for select neurological disorders (13, 14). In this study, we used a model called HAL lumbar type for care support (HAL-CB02).

HAL-CB02 is designed to mitigate risks of back pain by reducing the stress that will be applied on the back. HAL-CB02 consists of an exoskeleton frame and a power unit. The exoskeleton frame is composed of molds and belts for attachment to the lower back and the thigh and incorporates a three-axis accelerometer for measuring the absolute angle of the torso of the wearer. The power unit is composed of angle sensors and actuators of both hip joints. BES is detected from the surface electrode affixed to the erector spinae muscles; when the hip joints shift from flexion to extension, the actuator generates torque in accordance with the activity of the erector spinae muscles. The generated torque is transmitted to the wearer through the exoskeleton frame and supports standing, lifting operation, etc. By adjusting the assistance level, HAL-CB02 provides support according to the difficulty level of the movement, and the burden on the lumbar is reduced. HAL-CB02 is lightweight, as it weighs 3.1 kg including its battery, and it is easy to assemble and operate. An overview of HAL-CB02 is shown in **Figure 1**.

In a study using HAL for lumbar support (prototype of HAL-CB02), stress on the lumbar intervertebral disc during weight lifting was reduced (15). In addition, when HAL-CB02 was worn for lifting movements and snow shoveling, lumbar fatigue was significantly reduced and working efficiency was significantly improved (16, 17). In this context, we hypothesized that exercise with the assistance of HAL-CB02 would enable repetitive movements of core muscles under a reduced load and thus improve motor dysfunction associated with walking ability in frailty patients. We also considered that frailty patients would have muscle disuse and loss of muscle coordination in common regardless of coexistence of neurodegenerative diseases, and therefore, a robot-assisted core exercise regimen may be applied for patients with advanced PD that is often complicated with frailty. To address this hypothesis, we considered that comparing the response to the robot-assisted rehabilitation between frailty patients with and without PD is important to shed light on the relationship between frailty and PD. In this study, we aimed to test whether the core exercise and squats using the HAL-CB02 may improve the motor functions of the lower limb in frailty patients and to explore the optimal patient selection from the frailty cohort.

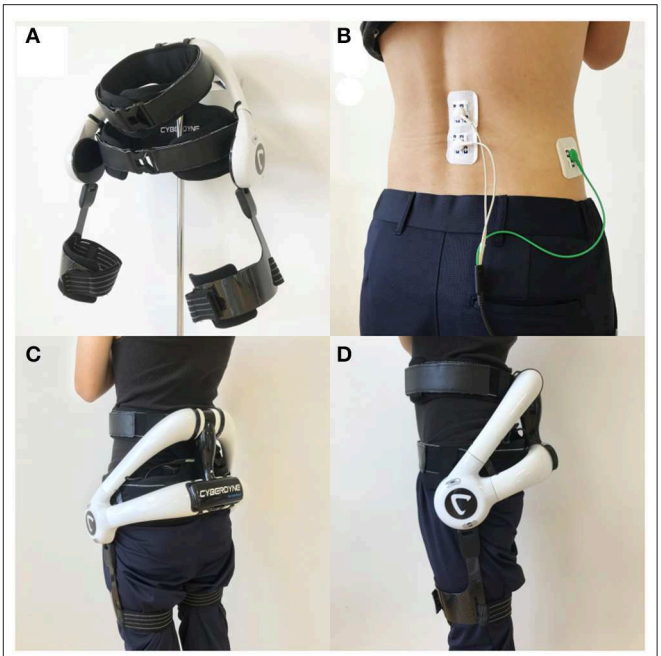

FIGURE 1 | Overview of HAL-CB02. **(A)** Overall picture of HAL-CB02. **(B)** The location of electrode detecting BES from the erector spinae muscles (dual white code), and the reference electrode is at the side (single green code). **(C,D)** Back and side views of the HAL-CB02 when fully attached. BES, bioelectric signals.

MATERIALS AND METHODS

Study Design

We included elderly frailty patients with or without PD who experienced walking disability from the period between June 2017 and September 2019. In this study, frailty was diagnosed based on the definition of Fried et al. (**Table 1**). Frailty is diagnosed when three or more conditions in the criteria are met, while pre-frailty meets one or two conditions. In this study, we made diagnosis of the walking disability based on

TABLE 1 | Frailty-defining criteria.

Criteria	Measurement
Weight loss	Lost >5 kg unintentionally in prior 12 months
Exhaustion	Felt exhausted for no reason in last week (self-report)
Low physical activity	Activity scale Male: <383 kcal/week Female: <270 kcal/week
Slowness	Time >10 s to walk 10 m at usual pace
Weakness	Grip strength Male: <26 kg Female: <18 kg

Frailty: three or more criteria present.
Pre-frailty: one or two criteria present.
Robust: no criteria present.

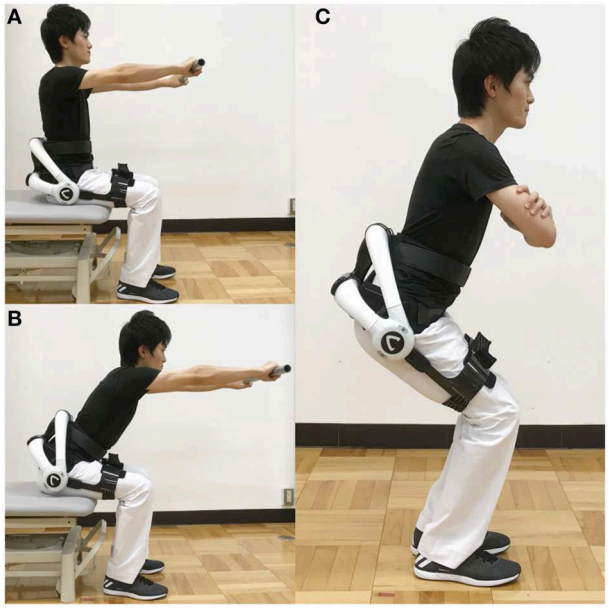

FIGURE 2 | HAL-assisted exercise. **(A,B)** In the core exercise, patients were instructed to repeat bend over **(B)** and upright **(A)** positions, with the upper body in a sitting position with a pole held by extended arms. **(C)** Squat exercise with the HAL. He is a staff of our hospital, and written informed consent was obtained for publication of this study and accompanying images. HAL, hybrid assistive limb.

the self-report and the 10-m walking test (10 MWT) results showing approximately 10 s or longer. For the non-PD cohort, we included patients with frailty associated with lumbar spine problems such as lumbar canal stenosis and compression fracture. For the PD cohort, we included advanced PD patients at Hoehn and Yahr (H&Y) Stages III and IV in the on-medication state. All PD patients had been diagnosed and followed by movement disorders specialists (SF and YT). We excluded patients with severe dementia, acute bone fracture, spine problems requiring surgical treatment, severe cardiopulmonary diseases, and a physique to which the robot does not fit. We also excluded PD patients at H&Y Stage V and with severe dyskinesia.

This prospective study was approved by our institutional review board, and informed consent was obtained from study subjects. Since this is the first report to test the feasibility of rehabilitation program using the HAL-CB02 for frailty cohorts, we included only limited numbers of patients.

All patients performed five sessions of exercise using HAL-CB02. Exercise for PD patients was performed with "on" medication. The exercise time was 20–30 min per session, and participants took a rest as needed. As core exercises, pelvic tilt and forward reach were performed 30 times each. Exercises involved awareness of the anteversion of the pelvis at the sitting position and stimulation of the erector spinae muscles. In the squat method, the feet were spread apart according to the width of the shoulder, and the angle from the heel to the feet was approximately 30°. Then, the participants slowly bend their knees so that the buttocks protrude backwards, being careful that the knees are within the toe level. The knee flexion angle is targeted for a half squat (90°), and if there is knee pain, quarter squats (45°) are allowed. Then, the participants slowly extend their knees and return to the standing position. The assist level of HAL-CB02 was adjusted according to the physical state of the participants. We allowed participants with low physical function to use handrails. The number of squats was not specified, and participants were allowed to perform squats until exhaustion. The states of exercises are shown in **Figure 2**.

To evaluate the efficacy of the exercise, we measured physical functions using the 10 MWT, step length, timed up-and-go (TUG) test, and 30 s chair stand test (CST-30), at four time points: baseline, following five exercise sessions, 1-, and 3-month follow-up. During gait evaluation, physical therapists support the patients to prevent falls as needed. In CST-30, the participants performed sit-to-stand movements from a chair completed with arms crossed over the chest and as many times as possible within 30 s. We measured pain levels using the visual analog scale (VAS) and assess whether pain does not occur with exercise. Participants performed core exercises and squats using HAL-CB02 for five sessions within 1 week. All PD patients were also evaluated "on" medication. Adverse events associated with robot rehabilitation were also recorded such as skin problems, exacerbation of pain, and muscle damage.

Statistical Analysis

Scores at baseline, immediately after HAL-assisted exercise, and at 1- and 3-month follow-up were compared using Friedman's test and Wilcoxon signed-rank test for intragroup comparisons. For intergroup comparisons, the Mann–Whitney U test was used to compare the improvement rate from baseline. Values are presented as mean ± standard deviation. SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A $p < 0.05$ was considered significant. We also performed Friedman's test to test the null hypothesis of no change in the number of squats during the training period.

RESULTS

We recruited 16 frailty patients including eight non-PD and eight PD patients. Baseline demographics are summarized in **Tables 2**, **3**. No significant differences in any demographic features were found between the two groups. All non-PD patients had a history of some chronic spine problems inclusive of lumbar canal stenosis ($n = 5$), vertebral compression fracture ($n = 2$), and spina bifida ($n = 1$). Peak dose dyskinesia potentially affecting robot-assisted exercise program was not observed in all PD participants. In the PD group, 1- and 3-month follow-up data could only be evaluated in five and four patients, respectively, due to accessibility to the follow-up clinic. All participants completed the HAL-assisted exercise successfully, without any adverse events, and the squat frequency increased significantly with each session ($p < 0.001$) (**Figure 3**).

Physical evaluations showed significant improvements. The measured median and interquartile range values (p-values compared with baseline) from the evaluation items of the non-PD group at baseline, post-HAL, and 1- and 3- month follow-up were as follows: 10 MWT values were 23.3 [13.5, 46.3] s at baseline, 15.9 [10.8, 30.2] s ($p = 0.012$) post-HAL, 16.3 [10.2, 25.3] s ($p = 0.012$) at 1-month follow-up, and 18.5 [10.3, 34.6] s ($p = 0.012$) at 3-month follow-up. Step length values were 0.38 [0.19, 0.43] m at baseline, 0.43 [0.26, 0.49] m ($p = 0.012$) post-HAL, 0.46 [0.32, 0.53] m ($p = 0.012$) at 1-month follow-up, and 0.41 [0.24, 0.49] m ($p = 0.012$) at 3-month follow-up. TUG values were 30.1 [17.5, 47.0] s at baseline, 18.3 [11.3, 28.8] s ($p = 0.012$) post-HAL, 20.5 [11.0, 31.6] s ($p = 0.012$) at 1-month follow-up, and 27.1 [13.1, 42.6] s ($p = 0.093$) at 3-month follow-up. CST-30 values were 4.5 [0.0, 7.3] times at baseline, 6.0 [3.8, 8.3] times ($p = 0.017$) post-HAL, 6.0 [3.8, 9.5] times ($p = 0.011$) at 1-month follow-up, and 7.5 [3.8, 8.8] times ($p = 0.024$) at 3-month follow-up (**Figure 4** and **Table 4**). In addition, three participants with frailty at baseline improved to pre-frailty at 1-month follow-up, and two of them were able to keep up even at 3-month follow-up. Also, two of the five participants with pre-frailty at baseline were "robust" at 1-month follow-up, and they maintained this state even at 3-month follow-up.

The measured median and interquartile range values (p-values compared with baseline) from the evaluation items of the PD group at baseline, post-HAL, and 1- and 3- month follow-ups were as follows: 10 MWT values were 15.3 [10.6, 26.7] s at

TABLE 2 | Baseline demographics of two cohorts.

	Non-PD	PD	*p*-values
N	8	8	
Age (years)	73.8 ± 13.2	68.6 ± 8.3	0.161
Sex	Male 3 (37.5%)	Male 4 (50.0%)	0.614
	Female 5 (62.5%)	Female 4 (50.0%)	
Disease duration (PD, years)	N/A	10.9 ± 7.1	
H&Y stage (PD)	N/A	III 3 (37.5%) IV 5 (62.5%)	
Weight (kg)	58.0 ± 9.1	56.3 ± 13.8	0.959
Height (cm)	158.3 ± 8.9	159.9 ± 13.0	1.000
BMI	23.1 ± 2.4	21.8 ± 4.0	0.279
10 MWT (s)	35.5 ± 31.1	20.3 ± 13.3	0.328
Step length (m)	0.33 ± 0.13	0.38 ± 0.16	0.645
TUG (s)	37.9 ± 30.9	19.5 ± 8.5	0.279
CST-30 (times)	4.0 ± 3.7	3.3 ± 2.2	0.645

10 MWT, 10 m walking test; BMI, body mass index; CST-30, 30 s chair stand test; H&Y stage, Hoehn and Yahr Stage; PD, Parkinson's disease; TUG, timed up and go test. Measured values are presented as means ± standard deviation.

TABLE 3 | Patient characteristics.

Non-PD group					PD group					
Case	**Age**	**Sex**	**Frailty**	**Comorbid spine problems**	**Case**	**Age**	**Sex**	**Frailty**	**Comorbid spine problems**	**H&Y stage (on/off)**
1	84	F	Frailty	Mild LCS	1	75	F	Frailty	Lumbar spondylosis (L4,5)	III/IV
2	79	M	Pre-frailty	LCS s/p laminectomy	2	63	F	Pre-frailty	None	IV/IV
3	87	F	Frailty	LCS s/p PLIF	3	65	F	Pre-frailty	None	III/III
4	46	F	Pre-frailty	Spina bifida	4	61	M	Pre-frailty	None	IV/IV
5	73	F	Frailty	Mild LCS	5	60	M	Pre-frailty	None	IV/IV
6	67	M	Pre-frailty	Vertebral compression fx (L2)	6	66	M	Pre-frailty	Mild LCS	IV/IV
7	83	F	Pre-frailty	Vertebral compression fx (L5)	7	76	F	Frailty	None	IV/IV
8	71	M	Pre-frailty	LCS s/p PLIF	8	83	M	Frailty	Mild LCS	III/III
	73.8 ± 13.2	3 males 5 females				68.6 ± 8.3	4 males 4 females			

fx, fracture; H&Y stage, Hoehn and Yahr stage; LCS, lumbar canal stenosis; PD, Parkinson's disease; PLIF, posterior lumbar interbody fusion; s/p, status post.

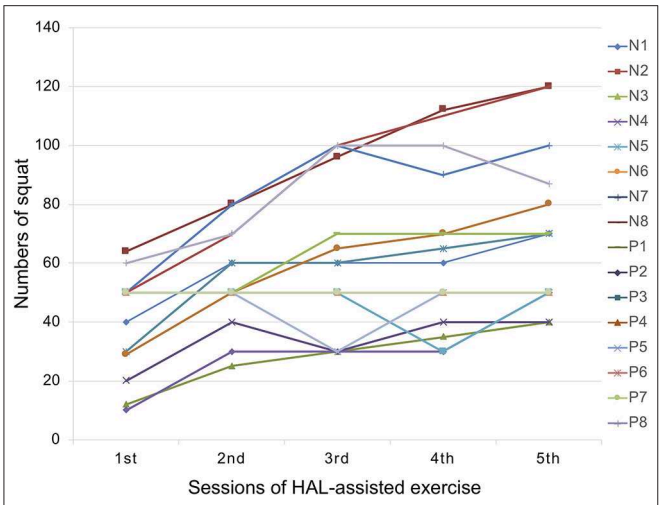

FIGURE 3 | Transition graph showing number of squats at each session. HAL, hybrid assistive limb; N, non-Parkinson's disease; P, Parkinson's disease.

baseline, 9.6 [8.5, 13.3] s ($p < 0.001$) post-HAL, 12.0 [9.4, 13.8] s ($p = 0.001$) at 1-month follow-up, and 10.4 [10.1, 10.9] s ($p = 0.006$) at 3-month follow-up. Step length values were 0.37 [0.28, 0.47] m at baseline, 0.51 [0.42, 0.60] m ($p < 0.001$) post-HAL, 0.42 [0.40, 0.48] m ($p = 0.001$) at 1-month follow-up, and 0.52 [0.47, 0.57] m ($p = 0.003$) at 3-month follow-up. TUG values were 17.7 [12.9, 22.7] s at baseline, 14.0 [10.1, 20.2] s ($p < 0.001$) post-HAL, 14.6 [11.5, 17.8] s ($p = 0.002$) at 1-month follow-up, and 11.7 [11.5, 18.3] s ($p = 0.136$) at 3-month follow-up. CST-30 values were 4.0 [2.3, 4.3] times at baseline, 6.5 [5.8, 8.3] times ($p = 0.001$) post-HAL, 7.0 [7.0, 9.0] times ($p = 0.001$) at 1-month follow-up, and 9.0 [6.8, 11.8] times ($p = 0.006$) at 3-month follow-up (**Figure 5** and **Table 4**). In addition, two participants with frailty at baseline improved to pre-frailty at 1-month follow-up, and one of them was able to keep up even at 3-month follow-up. Also, two of the six participants with pre-frailty at baseline were "robust" at 1-month follow-up, and one of them maintained this state even at 3-month follow-up.

Moreover, the improvement values from the baseline of each evaluation item in the non-PD group and PD group were compared. In all evaluation items, significant differences between the two groups at all time points were not observed (**Figure 6**).

Pain levels were reduced with HAL-assisted exercise. All patients in the non-PD group had low back pain, but post-HAL, the pain was significantly reduced and the effect persisted even after 1-month follow-up; however, at 3-month follow-up, a statistically significant difference was not observed, even if the measured value was higher than the baseline. In the PD group, no patients complained of low back pain, and pain related to HAL-assisted exercise was not reported. In the non-PD group, measured median and interquartile range values (p-values compared with baseline) of VAS score at rest and in motion at baseline, post-HAL, at 1- and 3-month follow-up were as follows: VAS scores at rest were 35.5 [23.3, 48.5] at baseline, 8.0 [3.8, 16.3] ($p = 0.036$) post-HAL, 10.5 [1.5, 14.0] ($p = 0.012$) at 1-month follow-up, and 23.0 [17.8, 28.5] ($p = 0.233$) at 3-month follow-up. VAS scores in motion were 49.0 [19.5, 55.3] at baseline, 9.5 [4.5, 18.5] ($p = 0.017$) post-HAL, 11.0 [5.8, 17.8] ($p = 0.028$) at 1-month follow-up, and 24.0 [10.8, 31.8] ($p = 0.176$) at 3-month follow-up (**Figure 4** and **Table 4**).

DISCUSSION

To the best of our knowledge, this study is the first to use HAL-CB02 in frailty and PD patients. HAL-CB02 may improve motor function. This result has the potential to improve frailty from a long-term perspective and clarified the feasibility of HAL-assisted exercise. One advantage of the robot rehabilitation is that the robot enables repeated performance of the same movements that are usually difficult to assist manually. We speculate that robot rehabilitation improves motor coordination by controlling axial muscles.

There are several reports of robot-assisted gait training (RAGT) for PD. Cappecci et al. reported that RAGT significantly improved endurance, gait capacity, motor symptoms, quality of life, and freezing gait (18). In addition, Alwardat et al.'s meta-analysis reported that RAGT showed better outcomes than conventional interventions in some motor aspects of PD (19). Robot-assisted rehabilitation enables standardized treatment regardless of the therapists' experience and repetitive exercise without patient's fatigue as shown in our results. Most of the reported RAGTs are based on gait assist robots, but we anticipate that HAL-CB02, as a treatment with core exercise and squats, can be performed more easily and safely. Concerning the similar improvements in two cohorts in our study, there are several explanations.

In this study, both PD and non-PD patients showed significantly improved motor function. In addition, since no significant difference was found between these two groups in terms of the improvement rate, it is expected that patients with physical frailty may have the same motor dysfunction regardless of the presence or absence of PD. From the standing point, we consider that the disturbance of the central pattern generator (CPG) in the spinal cord exists in common among frailty patients. Repetitive sensory feedback from HAL training may activate the central nervous system (CNS) and possibly induce neuroplasticity in the spinal cord level to facilitate functional recovery in the disused neuronal networks (20) (**Figure 7**).

Although there may be common factors for improvement among non-PD and PD cohorts, another factor may contribute to the improvement differently. We speculate that arthrogenic muscle inhibition (AMI) may be also related as a cause of failure of conventional rehabilitation of frailty patients, especially in a non-PD cohort with back pain. AMI is defined as the suppression of motor neurons due to trauma and the associated pain, resulting in decreasing muscle function. It is thought that abnormality of proprioceptive receptors due to swelling, inflammation, pain, and joint laxity causes AMI (21, 22). AMI is a reflexive response that acts as a protective mechanism to prevent further damage to the joint (23). AMI is the result of many different joint receptor activities. It acts on inhibitory

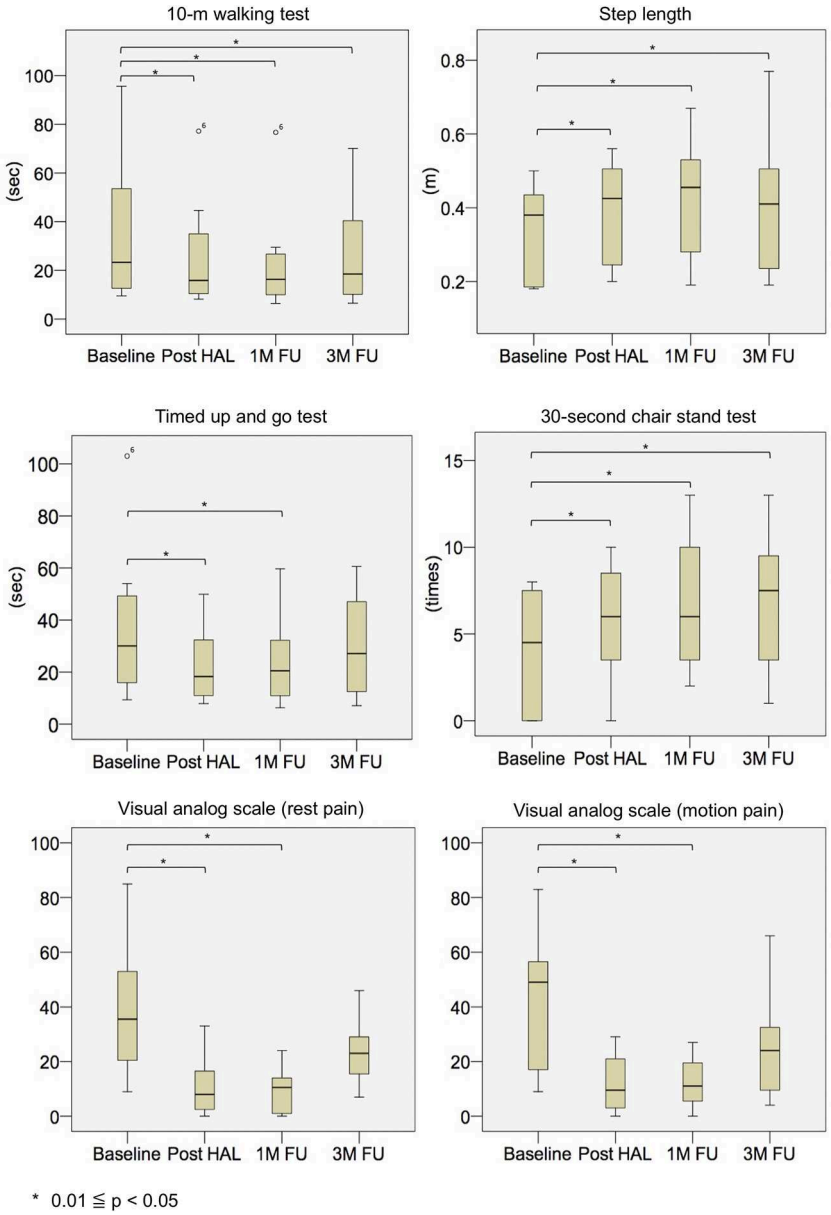

FIGURE 4 | Box plots depicting outcome measures in the non-PD group at baseline, post-HAL, and at 1- and 3-month follow-ups. FU, follow-up; HAL, hybrid assistive limb; PD, Parkinson's disease.

interneurons that form synapses in the motor neuron pool of articular muscle tissue (24). Rice et al. proposed three spinal reflex pathways related to AMI: the group I non-reciprocal (Ib) inhibitory pathway, flexion reflex, and gamma (γ)-loop. When abnormality occurs in the peripheral joints and changes the afferent discharge from proprioceptive receptors, these spinal reflex pathways are impaired (21). Furthermore, joint afferents are susceptible to changes in discharge (25, 26), and the spinal descending pathway may strongly influence interneurons and motor neurons at the spinal level (27–29). Several studies have described the relationship between spinal reflex and AMI (21, 30), and proprioceptive sensory feedback is related to reflex inhibition (31, 32). Although AMI was reported to be related to lower-limb functions in many cases, Russo et al. reported that AMI of paravertebral muscles was easily affected by damage to the lumbar region (33). As described above, it is speculated that physical frailty patients easily develop neuromuscular disorders and are prone to dysfunction of the erector spinae muscles, and they are likely to have AMI.

An effective treatment for AMI includes biofeedback therapy (34, 35). Most of the reports are based on electromyographic biofeedback, which measures the electrical activity of the muscle from the electrodes attached to the skin surface and feeds back the magnitude of the muscle activity visually and auditorily (36–41).

TABLE 4 | Details of clinical outcomes.

	Non-PD group				PD group			
	Baseline	**Post HAL**	**1 M follow-up**	**3 M follow-up**	**Baseline**	**Post HAL**	**1 M follow-up**	**3 M follow-up**
10 MWT (s)	23.3 [13.5, 46.3]	15.9 [10.8, 30.2] (0.012)	16.3 [10.2, 25.3] (0.012)	18.5 [10.3, 34.6] (0.012)	15.3 [10.6, 26.7]	9.6 [8.5, 13.3] (<0.001)	12.0 [9.4, 13.8] (0.001)	10.4 [10.1, 10.9] (0.006)
Step length (m)	0.38 [0.19, 0.43]	0.43 [0.26, 0.49] (0.012)	0.46 [0.32, 0.53] (0.012)	0.41 [0.24, 0.49] (0.012)	0.37 [0.28, 0.47]	0.51 [0.42, 0.60] (<0.001)	0.42 [0.40, 0.48] (0.001)	0.52 [0.47, 0.57] (0.003)
TUG (s)	30.1 [17.5, 47.0]	18.3 [11.3, 28.8] (0.012)	20.5 [11.0, 31.6] (0.012)	27.1 [13.1, 42.6] (0.093)	17.7 [12.9, 22.7]	14.0 [10.1, 20.2] (<0.001)	14.6 [11.5, 17.8] (0.002)	11.7 [11.5, 18.3] (0.136)
CST-30 (times)	4.5 [0.0, 7.3]	6.0 [3.8, 8.3] (0.017)	6.0 [3.8, 9.5] (0.011)	7.5 [3.8, 8.8] (0.024)	4.0 [2.3, 4.3]	6.5 [5.8, 8.3] (0.001)	7.0 [7.0, 9.0] (0.001)	9.0 [6.8, 11.8] (0.006)
VAS at rest	35.5 [23.3, 48.5]	8.0 [3.8, 16.3] (0.036)	10.5 [1.5, 14.0] (0.012)	23.0 [17.8, 28.5] (0.233)				
VAS in motion	49.0 [19.5, 55.3]	9.5 [4.5, 18.5] (0.017)	11.0 [5.8, 17.8] (0.028)	24.0 [10.8, 31.8] (0.176)				

10 MWT, 10 m walking test; CST-30, 30 s chair stand test; HAL, hybrid assistive limb; PD, Parkinson's disease; TUG, timed up-and-go test; VAS, visual analog scale. Measured values are presented as median [interquartile range] and (p-values compared to baseline).

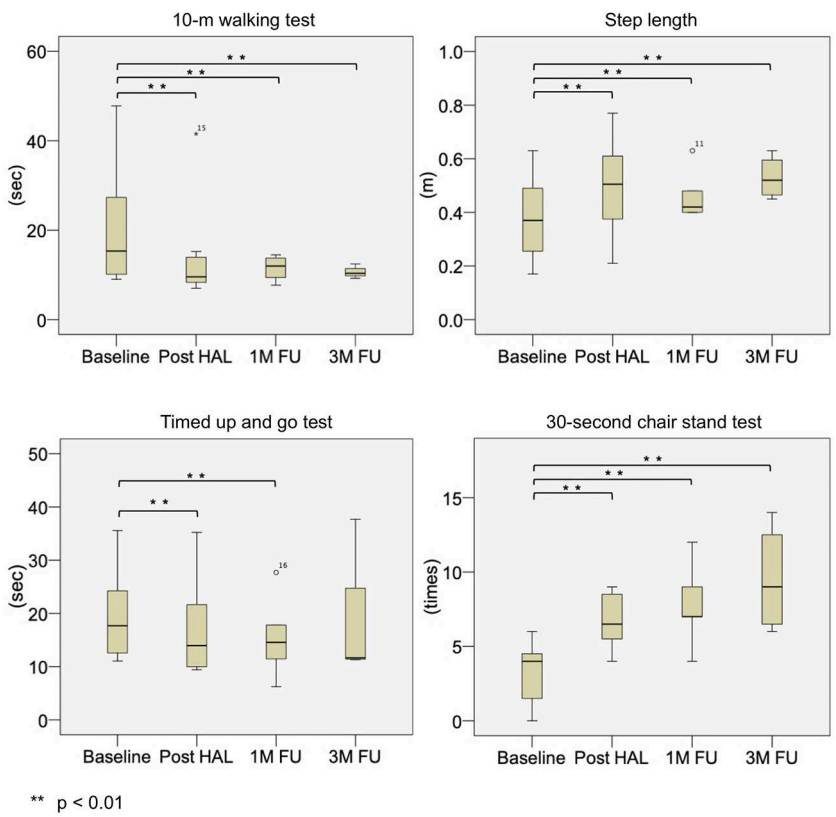

FIGURE 5 | Box plots depicting outcome measures in the PD group at baseline, post-HAL, and at 1- and 3-month follow-ups. FU, follow-up; HAL, hybrid assistive limb; PD, Parkinson's disease.

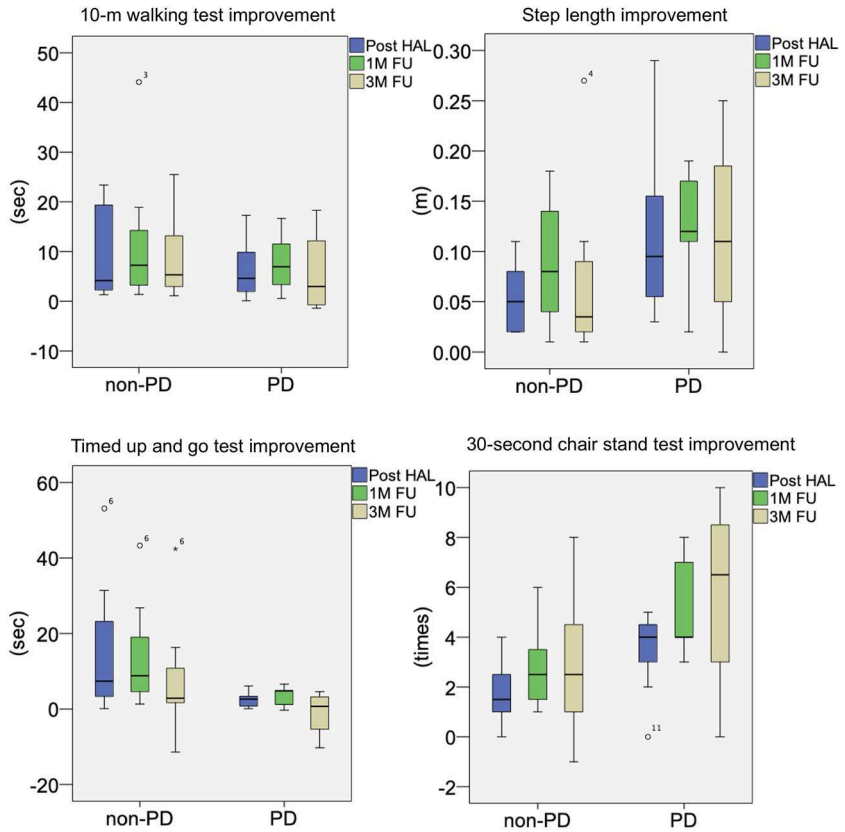

FIGURE 6 | Box plots of intergroup comparison of improvement rates from baseline for non-PD and PD groups. FU, follow-up; HAL, hybrid assistive limb; PD, Parkinson's disease.

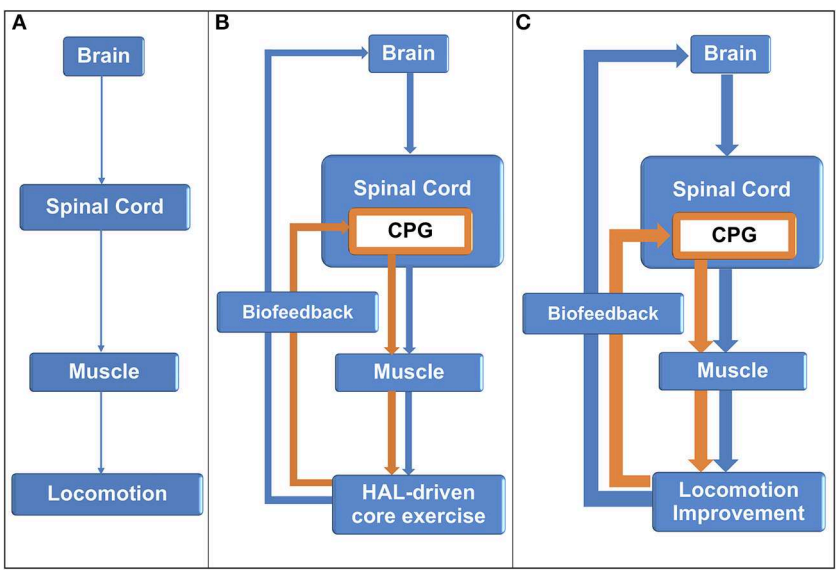

FIGURE 7 | Central nervous system activation by sensory feedback from hybrid assistive limb-assisted training. **(A)** Central nervous system (CNS) lesion resulted in gait disability. **(B)** The hybrid assistive limb (HAL) assisted core function, and sensory input was sent back to the CNS levels to activate the brain and the central pattern generator in the spinal cord. **(C)** In turn, the damaged CNS generated improved descending signals to the muscle for better locomotion.

Similarly, in this study, we consider that biofeedback with HAL-CB02 had improved AMI. We considered that HAL-assisted exercise stimulates proper proprioceptive receptors by repeatedly feeding back correct motion at low load and suppresses abnormal spinal reflexes. Actually, our group has shown the possibility of AMI improvement by HAL-assisted exercise in patients who underwent total knee arthroplasty (42, 43). Similarly, our non-PD patients showed significant pain reduction following HAL-assisted exercise, and this may partly contribute to the improvement in motor functions.

As limitations of this study, we did not evaluate ADL, quality of life, and objective measures such as electromyograms, so we could not identify the clinical impact and cause of improvement. Since the subjects with only exercise without HAL-CB02 were not recruited as control, we could not measure the efficacy of the robot-assisted exercise. Furthermore, the sample size was small, and several patients in the PD group were unable to complete follow-up evaluation. Future investigation on these issues with an increased number of cases is necessary to confirm our findings.

CONCLUSIONS

Our results suggest that biofeedback therapy with HAL-CB02 may be a safe and promising treatment for patients with physical frailty even complicated with spine problems. In addition, motor dysfunction in PD patients may be partly due to physical frailty, and biofeedback therapy with HAL-CB02 is proposed as a treatment option. Immediate and sustained effects on patients who were refractory to conventional rehabilitation could provide evidence that changes in input to specific receptors by HAL-CB02 contribute to activation of disused neuronal networks and amelioration of AMI. Further long-term follow-up studies with an increased number and control cohort of conventional rehabilitation are warranted.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fukuoka university institutional review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NK, TM, and TI: concept and design. TM, SF, and YT: acquisition of subjects. NK and AY: acquisition of data. NK, TM, SK, and ES: interpretation of data. NK, TM, SF, SK, ES, YT, and TI: preparation of manuscript.

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Patient-Centric Care for Parkinson's Disease: From Hospital to the Community

Yin Minn Aye[1,2,3†], *Sylvia Liew*[4†], *Shermyn Xiumin Neo*[1,2], *Wei Li*[1,2,4], *Hwee-Lan Ng*[1,2], *Shu-Ting Chua*[1,2], *Wen-Tao Zhou*[1,2], *Wing-Lok Au*[1,2], *Eng-King Tan*[1,2], *Kay-Yaw Tay*[1,2,4], *Louis Chew-Seng Tan*[1,2,4‡] *and Zheyu Xu*[1,2,4*‡]

[1] Department of Neurology, National Neuroscience Institute, Singapore, Singapore, [2] Parkinson Disease and Movement Disorders Centre, Parkinson Foundation Centre of Excellence, National Neuroscience Institute, Singapore, Singapore, [3] Department of Neurology, Yangon General Hospital, Yangon, Myanmar, [4] Parkinson Society Singapore, Singapore, Singapore

Parkinson's disease (PD) is a chronic neurodegenerative disease with complex motor and non-motor symptoms often leading to significant caregiver burden. An integrated, multidisciplinary care setup involving different healthcare professionals is the mainstay in the holistic management of PD. Many challenges in delivering multidisciplinary team (MDT) care exist, such as insufficient expertise among different healthcare professionals, poor interdisciplinary collaboration, and communication. The need to attend different clinics, incurring additional traveling and waiting time for allied health therapies can also make MDT care more burdensome. By shifting MDT care to local community settings and into patients' homes, patient-centered care can be achieved. In Singapore, the National Neuroscience Institute created the Community Care Partners Programme in 2007 to bring the allied MDT team to the community and nurse-led Integrated Community Care Programme for Parkinson's Disease in 2012 to provide care in community and at patient's home. However, attaining MDT care in the community setting is difficult to achieve where there is a shortage of PD-trained professionals. As such, interdisciplinary and transdisciplinary management would be other best practice options to deliver patient-centric care in PD. Telemedicine could be another viable option to bring the MDT closer to the patient.

Keywords: Parkinson's disease, multidisciplinary approach, community care, telemedicine, Singapore model of care

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***Correspondence:**
Zheyu Xu
xu.zhe.yu@singhealth.com.sg

†*These authors share first authorship*

‡*These authors share senior authorship*

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INTRODUCTION

In Parkinson's disease (PD), multidisciplinary care is widely practiced in hospital settings to manage the multiple symptomatology of this complex disorder. However, the provision of multidisciplinary care in the hospital setting can be challenging in resource-tight healthcare systems, resulting in delays and reactive rather than proactive care. One of the ways to provide patient-centered care is to bring care directly to the patients in the local community setting or straight into the home environment.

Patient-centric care has been defined as "providing care that is respectful of, and responsive to, individual patient's needs and preferences" (1). A recent review of delivering patient-centered care in PD highlighted the importance of patient education and multidisciplinary care, along with the

use of patient-centered outcomes to better capture the patient experience and improve the delivery of individualized therapy (1).

This review aims to present the current evidence and knowledge gaps in multidisciplinary care and provision of community care in the PD and review the evidence for telemedicine use. We showcase how our model of community care in PD that includes delivery of allied health interventions in the community, provision of physiotherapy (PT) through group exercises with a non-governmental organization (NGO), and home care services was implemented to supplement specialist, hospital-based PD care within a public health setting in Singapore. We also highlight the recent applications of telemedicine in the field that could assist in improving delivery care models in PD.

ROLE AND EVIDENCE FOR MULTIDISCIPLINARY CARE IN PD

PD is a chronic, degenerative neurological disorder with a complex and heterogeneous phenotype. As disease progresses, patients show motor symptoms and non-motor symptoms that do not always respond to pharmacological therapies. Thus, an integrated, multidisciplinary approach that assembles different healthcare professionals is necessary to achieve holistic care (2). There has been an increasing drive toward providing patient-centered rather than physician-centered care (3).

In recognition that collaboration may improve patient care, healthcare professionals are increasingly required to work together to share expertise, knowledge, and skills. In transdisciplinary care, team members work jointly using a shared conceptual framework that draws together concepts, theories, and approaches from multiple disciplines in order to define, address, and resolve complex real-world problems, whereas in the interdisciplinary approach, they are working together but from individual disciplinary perspectives to address a common problem (4). Multidisciplinary care, on the other hand, is working in parallel or sequentially from disciplinary-specific frames to address common problems (4). The preferred care model will vary depending on the patient and disease profile and the local healthcare infrastructure. Multidisciplinary care is currently the most established model of care for PD.

Components of a PD multidisciplinary team (MDT) vary significantly according to the local practices and the availability of allied healthcare professionals. The MDT team is typically tertiary hospital-based to be able to assemble a diverse range of allied healthcare professionals (5). More ambitious models involving medical professionals from other less traditional fields of vascular medicine, urology, gastroenterology, geriatric medicine, and palliative care have been proposed (6).

Because of the heterogeneity of interventions and outcomes used, the evidence on multidisciplinary rehabilitation in PD remains limited and fail to reveal consistent long-term benefits particularly for objectively motor outcomes (2, 7). In contrast, subjective outcome measures have generally yielded positive results, but the placebo effect of dedicated allied health interventions within a clinical trial setting cannot be ignored. However, it can also be argued that MDT interventions are not amenable to testing in experimental settings unlike other single interventions in medical research. van der Marck et al. studied the effects of MDT care in Canada as a single-blind randomized controlled trial (RCT) and showed improvements in quality of life, motor function, depression, and social function scores after 8 months (8). However, van der Marck et al. later published the landmark IMPACT study in the Netherlands comparing community with integrated care interventions with those that gave usual care: small benefits were achieved in disability scores and quality of life, which had disappeared when corrected for baseline disease severity (9). Similarly, a UK study showed that although MDT intervention improved psychological well-being, this required ongoing care to maintain long-term benefits. Ferrazoli et al. in Italy studied the effects of a 4-weeks intensive hospital-based therapy: at 3 months, only PDQ-39 showed improvement, but not other objective motor outcome measures (10).

Potential limitations to the implementation of effective MDT intervention are distance, insufficient expertise among the different health professionals, poor interdisciplinary collaboration, and high costs. Furthermore, MDT care often requires patients to traverse between different clinic settings, incurring additional waiting and traveling time for routine follow-up appointments or allied health therapies.

There has been an increasing push to deliver more patient-centered care: two approaches that have been explored in recent years include bringing models of care to the community and providing care via telemedicine (6).

COMMUNITY CARE: SHIFTING CARE TO THE COMMUNITY

Even at the early disease, PD patients report physical limitations and early rehabilitation is vital in maintaining function (11). However, in one large RCT, personalized home PT interventions did not reduce fall rates (12). Subgroup analyses showed that only patients with milder disease benefitted.

Community-based group balance exercises classes in patients with early PD can lead to self-reported improvements in balance control while also meeting their social and emotional needs (11), which may improve adherence. In a UK 2-arm RCT with blinded assessment, a minimally supported community exercise intervention delivering twice weekly 30-min aerobic and 30-min resistance training over 6 months, both gait speed and MDS-UPDRS Part III scores improved (13).

Additionally, community-based care may allow for care to be provided at lower cost. Using a Discrete Event Simulation model applied to the National Health Service in the UK, shifting patients with PD from hospital to community services allowed reductions in hospital visits by a quarter and reduction in hospital manpower by one-third. Hospital-based treatment costs were estimated to decrease by 26%, leading to 10% overall savings in the total cost of treating PD patients (14).

One of the most successful and established model of regional care is the ParkinsonNet model in the Netherlands (15), where medical and allied health interventions are delivered within integrated regional community networks dispersed throughout the country by PD-specific therapists with specialized training who manage high caseloads (16). Better quality of care, fewer PD-related complications, lower mortality risk, and lower total healthcare costs were achieved compared to usual care (17, 18), and the use of specialized occupational therapy delivered in the community setting resulted in an improvement in self-perceived daily functioning (19).

While ParkinsonNet has been introduced to other European countries (20), its applicability has limited generalization across other healthcare systems. Singapore has been instead working toward an interdisciplinary approach for community care that allows the healthcare professionals to adopt some roles of the other professionals.

OVERVIEW OF THE SINGAPORE MODEL OF CARE

PD is the second most common neurodegenerative disease in Singapore with an estimated 6,000 patients. The National Neuroscience Institute (NNI), which is one of the designated Parkinson centers of Excellence (PCOE), looks after approximately two-thirds of the patients in the public health setting in specialized tertiary movement disorders clinics staffed by movement disorder neurologists and supported by specialist allied health professionals who deliver PD-specific care. Within our catchment area, we have an approximate ratio of movement disorder neurologists to PD patients of 1:500. However, despite Singapore's small geographic size (721.5 km^2), patients in advanced disease remain dependent on caregivers or on private ambulance services to access in-hospital care. Allied health reviews are scheduled with their twice-yearly medical appointments where possible, but this is logistically challenging to achieve when multiple MDT input is required. A substantial proportion of our patients thus chose to forgo allied health visits.

As medical costs are still partially borne by patients who are means-tested, with each patient paying according to his/her ability, affordability of care is important. In 2007, we brought the allied MDT team to the community by establishing the Community Care Partners Programme (CCPP), which was funded by an initial grant from the Parkinson Foundation but subsequently with costs borne by the patient as a sustainable model of care. This limited, low-cost service delivery model was based on the ParkinsonNet model, training nurses and allied health professionals, particularly physiotherapists, occupational therapists, and speech therapists, in PD-specific care through our annual education program. This half-day program is taught by the medical, nursing, and allied health professionals based at the PCOE, consisting of a short series of lectures and innovative small group teaching model in the form of practical stations to teach PD-specific skills, such as PT interventions to manage freezing of gait, walking stability and balance, bed transfers of patients, and mobility of patients from a vehicle. This interdisciplinary education class allows our allied health partners to be upskilled in the care of PD patients.

In our model, patients with complex rehabilitation issues will continue to have their allied health reviews at the tertiary hospital. For patients with less complex issues, they are referred to allied health partners in the community, chosen for their proximity to the patient's home to allow greater access and encourage compliance to allied health interventions. The majority of our program is focused on delivering PT or speech therapy interventions, which can be carried out in individual or group settings. Delivery of allied health interventions in group settings has been one of the ways to maintain affordability of care and increase patient interactions.

The NNI oversees the training competency of our community partners in the form of yearly hands-on educational seminars conducted by our hospital-based MDT team. Our community partners are also invited to attend, at reduced costs, a symposium organized biennially where the most up-to-date advances in PD care are presented by an international and local faculty. Community care partners who have met our standards of care are acknowledged during our biennial symposiums and are invited to join our CCPP. In the past 13 years, we have established a network of 27 community partners with more than 400 allied healthcare providers trained to deliver specialist PD care in the community, thus freeing up hospital-based resources for patients requiring the most complex care.

Since 2014, we have also established a working collaboration with the Parkinson Society Singapore, an NGO, to support PD patients and their carers through the provision of allied health interventions as well as other social or wellness activities. Exercise programs include group PT exercises, non-contact boxing, and Tai chi classes. The organization has also collaborated with a large community care partner, St Luke's Eldercare, to train physiotherapists from 16 of their Day Rehabilitation Centers to conduct PT group classes. These centers allow greater access to specialized rehabilitation facilities in the community to ensure high standards of care.

Another aspect of providing community care is through the Integrated Community Care Programme for Parkinson's Disease (ICCP). This is a nurse-led service that was established in 2012 with funding from the Ministry of Health and the Tote Board Community Health Care Fund, and specifically targeted patients with more severe motor impairment or those without caregivers. Patients were visited by a specialist PD nurse who could refer them onwards to relevant community services if required. A training component was subsequently added to this model of care that allowed a larger network of 19 nurses from various homecare service providers from non-profit organizations to provide homecare. By 2018, 295 patients benefitted from this program.

As such, we are currently in the process of expanding the ICCP programme by (1) establishing a 3-months program of interprofessional training to community care partners; (2) providing patient-centered care by delivering care through community care partners, including joint consultations at the patient's home with movement disorders neurologists and the provision of care delivered by telemedicine; and (3) providing ongoing training in the form of monthly interprofessional

learning, yearly access to our training programs, and biennial access to our symposium.

TELEHEALTH IN PD

Telemedicine refers to the remote delivery of healthcare using telecommunications technology (21). Telemedicine for PD typically involves the use of videoconferencing platforms, as well as the remote use of devices, such as motion sensors to measure symptoms outside clinical settings (22). However, the spectrum of telemedicine is wide and includes telephone consults asynchronous communications via emails or text messaging (AMA). The progressive nature of PD makes it an ideal chronic condition to be managed via telemedicine, as patients and their caregivers often find it difficult to access care (23).

Telemedicine's feasibility has been established, particularly in large countries where greater time savings can be achieved. In a large RCT carried out in the US, telemedicine as an adjunct to usual care was shown to be feasible, with care standards comparable to in-person care (24). Another study was able to achieve an average of 3 h of time savings and reduce travel distance of up to 100 miles (25). However, patients generally preferred telemedicine to be combined with in-person visits rather than standalone telemedicine visits (26), and video quality is generally inadequate to allow accurate motor scoring (27). The UPDRS can be performed remotely with the exception of rigidity and postural instability testing (28).

The uptake of telemedicine in neurology has been slow. However, at the time of writing, we are experiencing a global pandemic of a novel coronavirus, Covid-19. This unprecedented event accelerated the adoption of tele-neurology, with loosening of policy and administrative restrictions (29). Implementation requires changes in legislation, reimbursement policies, and hospital workflows, including scheduling, billing, and prescribing practices (29). In addition, special attention needs to be paid to cybersecurity to safeguard patients' privacy. Many organizations, including the American Academy of Neurology and the International Parkinson and Movement Disorder Society, have issued guidelines on telemedicine use (30, 31).

At our institution, telephone and asynchronous consults via emails and text messaging have been in use for the last 5 years, to allow access to our specialist nurses. Our nurses have been empowered to troubleshoot disease-related complaints and adjust medications. This service is particularly reassuring for our deep brain stimulation patients who are in the initial programming phase and may help reduce clinic or emergency room visits.

We initiated our video consultation service in March 2019, choosing our primary service platform due to its reduced requirement for bandwidth without compromising on audiovisual performance. Additionally, the chosen service platform company already had a contractual service agreement in place to comply with our country's personal data protection act. Our operations team has worked closely with the primary service platform to improve the experience of video consultation, including requiring password authentication for meetings, having a waiting room feature to allow identity verification, and limiting content sharing to the provider.

Patient selection is vital with the service limited to those with stable neurological disorders, with at least one in-person consultation in the past year, who are able to cooperate or have a caregiver to assist. Written consent is obtained prior to the video consultation. Staff training in the form of hands-on training by IT support staff and e-learning modules are provided.

Telerehabilitation has been explored as a means of delivering allied health interventions remotely to improve balance (32) and deliver a web-based aerobic-based exercise program (33). Telerehabilitation has been successfully used to deliver speech therapy interventions, which are typically very time-intensive (34). At our center, we are in the process of implementing telerehabilitation for speech therapy and PT interventions. In the future, there are plans to collaborate with our homecare nursing teams to use telemedicine to optimize the care of homebound patients.

While there is great potential for telemedicine in the care of PD patients, it must be borne in mind that published studies in telemedicine have largely originated from developed countries with good infrastructure. Physicians generally rated telemedicine less favorably than patients, with technical problems in the software and inability to perform a detailed motor examination as the main caveats hindering more widespread adaptation of the technology (35).

Although there has been an explosion of studies exploring the use of sensors and smartphone applications that allow for data collection outside clinic settings to augment patient care, significant challenges persist in the form of non-compatible technology platforms and limited real-world clinical applications; hence, the Movement Disorders Society Task Force on Technology was convened in 2016 to set the direction of future research in this rapidly developing field (22).

TABLE 1 | Quality and outcome measures for Parkinson's disease (PD).

AAN Set (2015) (37)	International Consortium Set (2017) (38)
1. Annual PD diagnosis review	1. Cognitive and psychiatric symptoms/functioning
2. Avoidance of dopamine-blocking medications	2. Non-motor functioning
3. Psychiatric symptoms assessment	3. Motor functioning
4. Cognitive impairment or dysfunction assessment	4. Additional health outcomes
5. Querying about symptoms of autonomic dysfunction	a. Ability to work
6. Querying about sleep disturbance	b. Hospital admissions
7. Falls outcome	c. PD-related health status
8. PD rehabilitative therapy options	d. Falls
9. Counseling about regular exercise regimen	
10. Querying about PD medication-related motor complications	
11. Advanced care planning	

CLINICAL INDICATORS

Clinical indicators may be defined as measures that assess a particular healthcare process or outcome; quantitative measures to monitor and evaluate the quality of important management, clinical, and support functions that affect patient outcomes; or measurement tools, screens, or flags that are used as guides to monitor, evaluate, and improve the quality of patient care (36). Two PD groups have proposed their sets of quality measurement indicators in hospital-based settings, as summarized in **Table 1** (37, 38).

Many of these measurements may also be applied to telemedicine consults. More efforts are needed to derive a specific set of clinical indicators for PD community care. Meanwhile, we propose that emphasis should be given to falls outcomes, provision of rehabilitation therapy options, counseling about regular exercise, and assessment of quality of life health status.

CONCLUSIONS

We present the Singapore model of community care that has been sustainable over 14 years. Although there is a low level of evidence for MDT interventions in PD, largely due to the heterogeneous nature of the interventions and the need for personalization that makes it difficult to study trial settings, MDT care in PD is widely practiced internationally and recommended in several guidelines (39). However, the formation of a MDT is uncommon in the community settings where there is a shortage of professionals with PD-specific expertise. Interdisciplinary and transdisciplinary management would be another feasible method to tap on the lean manpower where the professionals are cross trained to deliver community care (29). In addition, patient-centric care is less fragmented when all professionals' boundaries are blurred unlike in the traditional multidisciplinary approach. New care models based on recent technological developments that combine remote monitoring and self-monitoring may allow for a decrease in hospital care and allow truly patient-centric care to be achieved (40).

AUTHOR CONTRIBUTIONS

YA, SL, and SN: conception and design, and writing of the first draft of the manuscript. WL, H-LN, S-TC, W-TZ, W-LA, E-KT, and K-YT: review and critique of the manuscript. LT and ZX: conception and design, writing, review, and critique of the manuscript.

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BRIEF RESEARCH REPORT
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Parkinson's Disease Caregiver Strain in Singapore

Siok-Bee Tan[1], *Allison F. Williams*[2,3], *Eng-King Tan*[4], *Richard B. Clark*[5] *and Meg E. Morris*[5]*

[1] Nursing Division, Singapore General Hospital, Singapore, Singapore, [2] School Health Sciences, The University of Melbourne, Melbourne, VIC, Australia, [3] School of Nursing and Midwifery, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia, [4] Department of Neurology, National Neuroscience Institute (Singapore General Hospital Campus), Singapore, Singapore, [5] Victorian Rehabilitation Centre, Healthscope ARCH and La Trobe Centre for Sport and Exercise Medicine Research, La Trobe University, Melbourne, VIC, Australia

Background: Caregiver strain is recognized globally with Parkinson's disease (PD). Comparatively little is understood about caregiver burden and strain in Asia.

Objective: To investigate caregiver strain for families living with PD in Singapore, in light of international data.

Methods: Ninety-four caregivers were recruited via people living with idiopathic PD in Singapore. Caregiver strain was assessed using the Zarit Burden Interview (ZBI); health status was assessing using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). PD disability measures were the Unified Parkinson's Disease Rating Scale (UPDRS) and modified Hoehn and Yahr (1967) Scale.

Results: Primary caregivers of people living with PD in Singapore were mostly cohabiting spouses, partners or offspring. Around half employed foreign domestic helpers. Mean caregiving duration was 5.9 years with an average of eight hours per day spent in caregiving roles. Most care providers were comparatively healthy. Caregivers reported significant levels of strain which increased with greater level of disability ($r = 0.36$, $n = 94$, $p < 0.001$). Associations were significant between caregiver strain and scores on the UPDRS mentation, behavior, and mood subscales [$r = 0.46$, $n = 94$, $p < 0.001$, 95% CI (0.28, 0.60)]. High scores on the UPDRS activities of daily living subscale were associated with caregiver strain [$r = 0.50$, $n = 94$, $p < 0.001$, CI (0.33, 0.64)].

Conclusion: Most caregivers in this Singapore sample reported high levels of strain, despite comparatively good physical function. Caregiver strain in PD spans geopolitical and cultural boundaries and correlates with disease severity. These results support the need for better early recognition, education, and support for caregivers of people living with PD.

Keywords: caregiver, carer, Parkinson's disease, well-being, quality of life, rehabilitation

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***Correspondence:**
Meg E. Morris
m.morris@latrobe.edu.au

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INTRODUCTION

Parkinson's disease (PD) is a debilitating and progressive condition that impacts the lives of individuals and their families (1). Although caregiver burden associated with PD is well-documented for Europe (2–7) and North America (8–11), there is a lack of published data for the south-east Asia region. Most elderly people with PD in countries such as Singapore live at home

(12, 13). It is important to understand how PD affects their caregivers because the prevalence of PD in South-East Asia ranges from 79 to 193 per 100,000 population (14). More than six million people will be living with PD in Asia by 2030 due to rapid population aging and lifestyle factors (15). People with PD experience movement disorders, falls, and non-motor symptoms that can reduce mobility and quality of life (1, 16). As the disease progresses, it can place a heavy burden on primary caregivers (17, 18). The individual and societal costs of PD are substantial (8, 19–23), yet are not fully understood for Asia.

With PD progression, caregiving can sometimes be perceived as the main role of some family members (24, 25). Studies in Australia (19, 26), Europe (6), and the USA (8) have reported considerable caregiver burden associated with PD. Caregiver burden refers to the negative physical, mental, and socioeconomic sequelae associated with caring for a person living with a disability (27). Martinez-et al. (28) and Kelly et al. (29) reported associations between PD caregiver burden and caregiver health-related quality of life (HRQoL). Caregiver HRQoL as measured on the EuroQoL has also been shown to correlate with burden, as measured on the Zarit Carer Burden Inventory (ZBI) ($r = -0.33$ to -0.49, $p < 0.01$) (28). Studies in western societies have also reported that psychological aspects of caregiver strain are associated with the level of PD disability (3). For example, disability in PD measured by the Barthel Index was associated with increased caregiver burden ($r = 0.46$–0.53, $p < 0.01$) (17). Many of the studies in the literature have focused on US and European populations with comparatively low ethnic and cultural diversity (30). The results for PD caregivers and care recipients might not be generalizable to south-east Asia, where there are geographical, cultural, and geopolitical differences. For example, Tan et al. (31) found that overall PD incidence rates were comparable between Singapore and the West, yet there were significance differences in the inter-ethnic incidence rates of PD between Chinese, Malays, and Indians.

The current study aimed to increase understanding of the dimensions of caregiver strain and burden in Singapore and to consider the findings in the context of global reports. We also aimed to determine the factors associated with strain in caregivers of this sample of people living with this progressive neurological condition.

METHOD

We conducted a cross-sectional survey with a convenience sample of 94 caregivers of individuals with PD. Patient data was also collected through associated caregivers. Recruitment was via a neurology specialist outpatient clinic at an acute tertiary hospital and a PD society in Singapore. For a 2-tailed bivariate analysis test with power of 0.80 and statistical significance at 0.05, a sample size of 85 care providers was required to detect a moderately strong relationship between variables (32). Criteria for the selection of caregiver participants included: (i) above 21 years of age; (ii) primary caregiver of a patient (care recipient) diagnosed with idiopathic PD by a neurologist; (iii) providing at least 3 h of daily care for 6 months or more; (iv) able to understand spoken English. The research protocol was approved by institutional review boards of The University of Melbourne (Ethics ID: 0719562) and Singapore General Hospital (Ethics ID: 2008/122/A). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

TABLE 1 | Hoehn and Yahr (33) stage when functioning at best.

	Number	Percent
Stage I Unilateral disease	19	20.2
Stage II Bilateral disease, without impairment of balance	8	8.5
Stage III Mild-moderate bilateral disease with some postural instability; physical independence	42	44.7
Stage IV Severe disability; still able to walk or stand unassisted	12	12.8
Stage V Wheelchair bound or bedridden unless aided	13	13.8

A structured questionnaire was administered to the caregiver participants. It contained items on (i) care recipient and caregiver sociodemographic characteristics; (ii) health information about the care recipients, measured using the modified Hoehn and Yahr Scale (HY) (33), and the Unified Parkinson's Disease Rating Scale (UPDRS) (34); (iii) information on the burden and health status of the caregivers quantified by the ZBI (35) as well as the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (36).

The ZBI has 22 items relating to the impact of care-recipient disabilities on caregiver physical and emotional health, and social, and financial distress. The ZBI score sums individual items (range 0–88), with a higher score indicating greater caregiver personal strain or role strain (35). The maximum possible scores are 24 (six items) for personal strain and 48 (12 items) for role strain. The ZBI has previously been shown to be a valid and reliable instrument for caregivers with dementia in Singapore (37). We also used the CIRS-G to estimate medical and psychiatric multi-morbidity burden in care providers (38). This scale rates the severity of problems as mild (1), moderate (2), severe (3), or extremely severe (4) (36).

When applicable, Spearman's rank correlation coefficients (r) were calculated to assess the direction and magnitude of the associations between variables. The strength of the relationships was interpreted following Cohen's guidelines (39); relationships were deemed as small where correlations ranged from $r = 0.10$–0.29; medium when $r = 0.30$–0.49 to large $r = 0.50$–1.00. Multiple regression analyses were used to explore the relationships between caregiver coping and well-being with sociodemographic, caregiving, and disease severity variables. Data were entered and analyzed using Predictive Analytics Software (PASW) Statistics 18. All reported p-values were 2-tailed with alpha set at 0.05.

We also conducted a comprehensive literature search of global PD caregiver burden on PubMed (1 April 2020) using the terms "Caregiver burden/strain AND Parkinson's disease" where studies included both caregivers and PD participants. Initially, the titles were screened by two people for keywords. The abstracts were then screened to ensure that studies were conducted on PD

TABLE 2 | Caregiver demographics and characteristics of caregiving.

Caregiving characteristics		
Demographics/ characteristics	***n***	**%**
Gender (%)		
Female	74	78.7
Relationship with care recipient		
Spouse/Partner	44	46.8
Sibling	4	4.3
Daughter	29	30.9
Son	9	9.6
Friend	3	3.2
Other	5	5.3
Living with care recipient		
Yes	79	84.0
No	15	16.0
Domestic helper		
Yes	43	45.7
No	51	54.3
Other helpers		
Yes	57	60.6
No	37	39.4
Who assists?[a]		
Spouse/partner	9	15.5
Sibling	22	37.9
Daughter	6	10.3
Son	12	20.7
Other	9	15.5
Resources other than family/friends for support		
Yes	19	20.2
No	75	79.8
Caregiver education and support group		
Yes	25	26.6
No	69	73.4
Hours of caregiver education		
0 h	79	84
>1 h	15	16
Hours of support group		
0 h	74	78.7
>1 h	20	21.3

[a]*n = 58 (a = caregivers who received assistance from others beside the domestic helpers).*

and caregiver strain or burden. Full-text articles 2018-2020 were reviewed to extract data on caregiver burden inventory utilized, caregiver demographics/duration, and descriptive statistics (e.g., mean, median) reported for the caregiver burden inventory utilized in the studies.

RESULTS

Parkinson's Disease Care Recipient Profile

Of the 94 Singaporean care recipients, 60 (64%) were male. The majority of the care recipients with PD were 51 years or older ($n = 88$, 93.6%). Six were aged 31–50 years. The age at which the care recipients were diagnosed with PD ranged from 33 to 89 years ($M = 61.8$, $SD = 11.8$). The mean duration of PD was 6.9 years (SD 5.6). Their mean UPDRS mentation, behavior and mood score was 3.4 (SD 2.9). The mean UPDRS ADL score was 15.4 ($SD = 9.5$). People living with PD had a range of levels of disease severity when functioning at their best (**Table 1**). It is notable that despite being rated five on the modified Hoehn and Yahr scale, 14% people with PD in the sample were being cared for at home.

TABLE 3 | Zarit burden interview mean scores.

	Mean	**SD**	**Minimum**	**Maximum**	**Median**
Personal strain	13.0	6.8	0.0	37.0	13.5
Role strain	5.3	4.4	0.0	18.0	4.0
Total score	23.0	13.2	1.0	71.0	21.5

Caregiver Profile

Most caregivers were females ($n = 74$, 78.7%). They were mainly spouses, partners, or daughters who lived with the people who had PD. The mean number of caregiving years was 5.9 years (range 0.25–25, SD 5.2). The care providers dedicated a mean of 8 h per day ($SD = 7.0$) in their PD caregiving roles. As shown in **Table 2**, foreign domestic helpers were often engaged to assist with personal care, rehabilitation, social engagement, and mobility (30). Notwithstanding, 58% of carers preferred help from family and friends, who were mainly siblings and sons, and daughters of care recipients. Approximately a quarter of the caregivers attended caregiver education or support groups to obtain more information about caring and rehabilitation for individuals with PD. Only a small percentage of caregivers attended more than 1 h of caregiver education and support.

Caregiver Strain in Singapore

Caregivers in this Singapore sample reported a mean ZBI score of 23 out of 88. The personal strain and role strain domains are shown in **Table 3**. In order to interpret the relative intensity of burden experienced by caregivers of people living with PD, the following cut-off values were used: 0–20 little strain; 21–40 mild to moderate strain; 41–60 moderate to severe strain; 61–88 severe strain (35). Some caregivers ($n = 45$, 47.9%) reported little burden; 37 caregivers (39.4%) had mild to moderate burden and 11 caregivers (12.8%) reported moderate to severe levels of burden.

Caregiver Multi-Morbidities

Most care providers were older women who were comparatively healthy, although some reported a range of health problems and multi-morbidities of mild to moderate severity as measured by the CIRS-G. The mean score for CIRS-G was 2 ($SD = 2$) and the CIRS-G Severity Index mean was 0.12 ($SD = 0.15$). In this sample, there were more healthy caregivers than those with multi-morbidity.

TABLE 4 | Summary data from key recent international PD studies of caregiver strain.

Lead author, year	Country	Key findings	Caregiver	Caregiver scales and values			
			n Sex Age (yrs), Mean (*SD*)	Questionnaire/index and domain	Mean (*SD*)	Median/ IQR/ Range	Correlations *r*
Balash, 2019	Israel	Progression of PD can affect male and female CG differently; some females experienced more stress	*n* = 122	Multi-dimensional Caregiver Strain Total Physical strain	24.2 (14.9), *f* 15.4 (15.4), *m*	NR	NR
Bartolomei, 2018	Italy	Sleep quality in PD was associated with caregiver burden and quality of life	*n*= 57 21 *m*, 36 *f* 62.0 (12.0)	Caregiver Burden Inventory	9.0 (12.5)	NR	NR
Carrilho, 2018	Brazil	Optimization of available treatment, with better control of PD severity, can decrease burden among caregivers	*n* = 21 80% *f* 53 (12.4)	Zarit Burden Interview UPDRS	28		0.48 (p = 0.026)
Crespo-Burillo, 2018	Spain	Deep brain stimulation was not associated with lower caregiver burden. Apathy in PD was associated with caregiver overload	*n* = 11 66.0 (9.9)	Zarit Caregiver Burden Inventory	48.6 ± 17.8	NR	ZBI and UPDRS-III 0.46
Dahodwala, 2018	USA	Caregiver strain was related to PD severity	*n* = NR	Multidimensional Caregiver Strain Index	19.9 (16.7), Men 16.4 (15.1), Women	NR	MCSI & co-morbidity 0.33
Drexel, 2019	Germany	Caregiver burden was noted for some dystonia patients. A small proportion of caregivers had burden	*n* = 93 34 *f* 61.6 (13.5)	Caregiver Burden Inventory and Hours of Caregiving	8.6 (9.6)	0-48	Caregiving hours per day (r = 0.409, p = 0.001)
Genç, 2019	Turkey	Almost half of caregivers showed burden. No significant differences between burden experienced in caregivers of early-stage and late-stage PD.	*n* = 74 (G1 40 G2 34) G1 *f* 25 (62.5%) G2 *f* 26 (76.5%) G1 6.65 (15.75) G2 49.41 (14.32)	Zarit Caregiver Burden Inventory	Little or no burden, G1 = 21 (52.5) G2 = 18 (52.9) Mild to moderate burden G1 = 15 (37.5) G2 =12 (35.3) Moderate to severe burden G1 =2 (5.0) G2 =3 (8.8) Severe burden G1 =2 (5.0) G2 = 1 (2.9)	NR	NR
Henry, 2020	USA	Difficulties with mobility, emotional well-being, and non-motor symptoms of PD were predictors of reduced caregiver QOL.	*n* = 181 77.9% *f* 64.04 (10.50)	PDQ-Carer	CG QOL items	NR	
					Self-care		0.76
					Anxiety/depression		0.78
					Activities		0.80
					Mobility		0.40
					ADL		0.39
					Emotions		0.38
					Cognition		0.36
					Bodily discomfort		0.25
					Non-motor		0.42

(Continued)

TABLE 4 | Continued

Lead author, year	Country	Key findings	Caregiver	Caregiver scales and values			
			n **Sex** **Age (yrs), Mean (*SD*)**	**Questionnaire/index and domain**	**Mean (*SD*)**	**Median/ IQR/ Range**	**Correlations *r***
Karlstedt, 2019	Sweden	Cognitive decline and poor ADL in PD was associated with CG burden	*n* = 22 *f* 70.7 (9.3)	Caregiver burden scale	42.5 (15.8)	NR	NR
Klietz, 2020	Germany	Motor UPDRS scores and patient's attentional symptoms were associated with caregiver burden	*n* = 78 64.8 ± 11.0	German version Parkinson's disease caregiver burden questionnaire	36.5 (27.1)	Range 0–100	PDQ-8 (*p* 0.064) and UPDRS part III (*p* 0.086) showed a trend toward association with caregiver burden
Kumar, 2019	Pakistan	Overall 62.8% caregivers were stressed; increasing stress and depression was related to PD progression. Most (86.7%) of the stressed caregivers were female ($p < 0.0001$)	*n* = 156 49 (31.4%) *f* 47.75 (11.98)	Caregiver Burden Inventory	NR	NR	NR
Lee, 2019	Korea	CB associated with higher daily time in caregiving. Better understanding of PD in spouses correlated with less burden	*n* = 142 72 *m*, 70 *f* 59.4 (14.4)	Caregiver Burden Inventory	52.0 (19.9)	49.0 (range 25.0–111.0)	CBI and: daily care time: 0.41 ($p = 0.000$) Care duration: 0.19 ($p = 0.024$)
Macchi, 2020	USA	Patient quality of life, anxiety and depression, and caregiver spiritual well-being contribute to caregiver burden	175 131 *f* (73%) 66 (11)	Zarit Burden Interview PDQ-39 PD QOL-AD Caregiver Reported HADS Anxiety Depression FACIT-SP spiritual well-being of caregivers	17.4 (7.9) 58.1 ± 28.4 33.8 ± 6.0 7.4 ± 3.6 4.3 ± 3.1 33.5 ± 8.7	NR	0.161 ($p = 0.0001$) 0.088 ($p = 0.0001$) 0.062 ($p = 0.0014$) 0.024 ($p = 0.038$)
Mosley, 2018	Australia	Caregiver burden was unchanged after subthalamic deep brain stimulation	*n* = 64 48 *f*, 16 *m* 58.3 (8.4)	Zarit Burden Inventory	21.4 (13.7)	21	NR
Rajiah, 2017	Malaysia	QoL domains such as "stigma" and "emotional well-being" in PD were associated with caregiver burden	*n* = 132 43 *m*, 87 *f* 45.1 (10.2)	Zarit Burden Interview	55.0 (19.2), mobility 39.0 (18.6), ADL 61.0 (17.4), emotional well-being 66 (16.8), stigma	NR	0.41
Smith et al., 2019	Mexico and America	Showed associations between PD-related impairments, caregiver burden, and caregiver mental health. Caregiver burden mediated the relation between PD-related impairments and caregiver mental health	*n* = 253 68.6% *f* USA group 76.4% *f* Mexico group 68.73 (8:36)	Short version Zarit Burden Inventory	NR	NR	NR
Tan, 2019	Singapore	Caregiver burden was associated with more prolonged disease, higher levodopa doses and motor fluctuations	*n* = 104	Zarit Burden Inventory	24.6 (15.3)	NR	NR

(Continued)

TABLE 4 | Continued

Lead author, year	Country	Key findings	Caregiver	Caregiver scales and values			
			n Sex Age (yrs), Mean (*SD*)	Questionnaire/index and domain	Mean (*SD*)	Median/ IQR/ Range	Correlations *r*
Tan, 2020 (this paper)	Singapore	Caregiver burden associated with PD disability, UPDRS mentation, behavior and mood subscale, and high scores on UPDRS ADL subscale	*N* = 94 caregiver-PwPD dyads caregivers: 74 f	Zarit Burden Inventory	23.0 (13.2)	NR	ZBI and HY 0.34 (at best) 0.35 (at worst) ZBI and UPDRS 0.38 (mood) 0.50 (ADL)
Trapp et al. 2018	Mexico	Caregiver burden mediated the relationship between family cohesion and quality of life	*n* = 95 78 *f* 51.1 (13.9)	Zarit Burden Interview	Family cohesion 24.26 (14.62)	0–70	−0.38
Tessitore, 2018	Italy	Statistically significant predictors of CB were caregiver need to change work and judgement of QoL. CB lower when treated with levodopa/carbidopa intestinal gel than continuous subcutaneous apomorphine or usual care	*n* = 126 57.9 (12.9)	Zarit Burden Inventory	LCIG−29.6 (14.4)		Work change: 23.6, 95%CI 10.4–36.8; *P* = 0.001
Torny, 2018	France	The severity of non-motor signs, patients' and caregivers' mood, and motor disease severity are the main determinants of caregiver burden	38 84% *f* 67.8 (9)	Zarit Burden Inventory PDQ-8 PD NMSS (total) HADS Depression	14.4 (12.7) 8.5 (6) 38 (41.6) 7.2 (4) 3.4 (4.2)		0.27 (p = 0.007) 0.46 (P < 0.0001) 0.16 (p < 0.0125) 0.35 (p < 0.0001)
Vatter et al. 2018	United Kingdom	Factor analysis revealed five burden dimensions (factors): 1. social & psychological constraints, 2. personal strain, 3. personal life, 4. concerns about future and 5. guilt. Factors were associated with lower relationship satisfaction, mental health, resilience, stress, anxiety, depression, resentment, negative strain, and PD motor severity.	*n* = 127 85.3% *f* 69.44 (7.62)	Zarit Burden Interview	35.51 (15.4)	35.00 2-74	factors 1 and 2 (r = 0.67), factors 2 and 3 (r =.67), factors 1 and 3 (r =.64) factors 3 and 4 (r =.62)
Yang, 2019	China	Caregiver self-efficacy mediated caregiver burden, caregiver anxiety and depression. Caregiver burden was related to poor cognition and poor motor function in people with PD.	*n* = 112 66 (58.9%) *f* 52.33 (13.43)	Chinese version of Zarit Burden Interview	19.58 ± 13.09	18.0 (0,59)	Caregiver burden & PD cognition −0.412 PD motor function 0.334

f, female; m, male; NR, not reported; CG, caregiver; PD, Parkinson's disease; PwPD, People living with PD; LCIG, levodopa/carbidopa intestinal gel; ADL, Activities of Daily Living; G, group.

Instruments: PDQ-39, Parkinson's Disease Questionnaire; MCSI, Multidimensional Caregiver Strain Index; CSI, Caregiver Strain Index; CBI, Caregiver Burden Inventory; ZBI, Zarit Burden Interview/Zarit Caregiver Burden Inventory; CSI, Caregiver Strain Index; PDCB, Parkinson's Disease Caregiver Burden Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; HY; modified Hoehn & Yahr Scale; MMSE, Mini-Mental State Examination; (HR)QoL, (Health-related) Quality of Life.

Relationships Between Care Recipient Disease Severity and Caregiver Strain

There was a statistically significant, moderately strong positive correlation between modified HY scores, and caregiver burden when the people with PD functioned at their best (r_s = 0.36, n = 94, p < 0.001). Statistically significant moderate positive correlations were also obtained between the HY scores and caregiver burden when the people with PD functioned at their worst (r_s = 0.38, n = 94, p < 0.001, 95% CI [0.19, 0.54]). This was particularly notable for the UPDRS Mentation, Behavior, Mood score (r_s = 0.46, n = 94, p < 0.001, 95% CI [0.28, 0.60]). The relationship between UPDRS Activities of Daily Living score and caregiver burden also showed a strong positive correlation (r_s = 0.50, n = 94, p < 0.001, CI [0.33, 0.64]). The personal strain and role strain for care providers increased with PD severity.

Global Analysis of Caregiver Strain

Table 4 summarizes data from our evaluation of key recent international studies of PD caregiver strain. The results show world-wide data demonstrating that care-giver strain is challenging and common, with many shared features between south-east Asia and other regions of the globe, as seen in the world-wide literature (40–79).

DISCUSSION

Regardless of geographical, cultural, and geopolitical differences, caregiver strain in PD is a major problem world-wide and correlates with disease severity (40–79). Our study showed that most south-east Asian PD caregivers are family members. Although many received support from domestic workers, they often experienced high levels of burden and strain. Both role strain and physical strain were reported, warranting consideration of systems to be put in place for early recognition, education, and support for caregiver strain.

Our results are consistent with European (8) and American literature [eg., (28, 40, 41)] showing more female than male PD care providers, given that Parkinsonism more often affects men. Previous studies have also shown close relationships between disability and quality of life in people with PD and the level of burden in caregivers (42). Caregiver strain is particularly associated with immobility in PD care recipients and the severity of non-motor symptoms associated with PD (7, 43). A Malaysian study by Razali et al. also found that patient age, stage and severity of illness were significantly associated with feelings of burden in caregivers (44). However, caregiver burden in this Malaysian study was not related to social status, kinship or duration of care (44).

Approximately one quarter of the care providers in our study attended caregiver education or support groups to obtain more information on how best to support people living with PD. This was rarely more than an hour in duration. The small amount of PD education concurs with the findings of Mehta et al. who reported that caregivers who lived in Singapore often did not receive very much formal training to care for people living with PD (45).

The caregivers in our sample reported more personal strain than role strain. Overall, they exercised a reasonable level of control over their caregiving roles even though it sometimes affected their personal health and social life. This was consistent with regional studies showing associations between caregiving and perceived burden (23, 43, 46). For example, a Singapore qualitative analysis (47) reported that many caregivers experienced lifestyle restrictions and felt physically and emotionally drained. Others (24, 48–50) reported that increased involvement in caring can sometimes be perceived to disrupt a caregiver's personal life and roles. Mehta noted that some (but not all) Singaporean caregivers interpreted their role to be obligatory "having no choice (but to care for the patient)" (45).

The results of our investigation also showed that caregiver burden had a moderately strong positive relationship with PD disease stage (**Table 4**). It also escalated with severe disability. This finding is consistent with global reports (**Table 4**). Of interest, a Malaysian study reported that respite in the form of caregiver support group or day care attendance for patients can reduce caregiver burden (44). Thommessen et al. (51) and Schrag et al. (43) found that only the mental health of care recipients was associated with caregiver burden. In contrast, we found that both poor mental health and activities of daily living were associated with caregiver strain.

There was no correlation between caregiver multimorbidity and perceived caregiver burden in our sample. This was in contrast to Martinez-Martin et al. (2) who found that Spanish caregivers tended to be less physically and mentally healthy compared to the general population. The care recipients in our study had a higher disease severity than counterparts in Spain (12). Differences in race, culture, and healthcare systems might also have contributed to the disparate results.

Although this is the largest PD caregiver study undertaken in the Asia-Pacific region to have identified critical elements in caring, it is not known whether the Singapore results generalize to other locations in Asia such as Indonesia, Malaysia, Vietnam, Thailand, Cambodia, or China. The sample mainly included men with PD and caregivers who were women. Further clarification of gender issues in caregiving is warranted. The sample size for each ethnic group also did not allow for critical analysis of differences in caregiving as a result from race, ethnicity, and culture that could have affected caregiving experiences. In addition, variations in treatment options for different countries could affect caregiver burden and strain. Longitudinal changes in caregiver burden and coping strategies were not examined. Further trials are needed to better understand how caregiver strain varies according to the stage of progression of Parkinsonism as well as the effects of different interventions to improve health, well-being and quality of life in care providers and care-recipients.

CONCLUSION

As with international data, care providers of people living with PD in Singapore often had raised levels of personal strain and role strain that were associated with the level of PD disability. The caregivers in our sample provided care for an average of 8 h per day for 6 years or more. Although foreign employed workers often gave assistance, around 80% of care providers were family members. Many care providers were elderly spouses. In Singapore, as for throughout the world, there is a need for systems to reduce caregiver burden that are responsive to the progressive trajectory of this common and chronic neurological disease.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the research protocol was approved by institutional review boards of The University of Melbourne (Ethics ID: 0719562) and Singapore General Hospital (Ethics ID: 2008/122/A). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-BT, AW, E-KT, and MM: contributed to research project conception and design. S-BT: original concept and research project organization and execution, data collection, statistical analysis, design and execution, and manuscript writing. AW: statistical analysis design, review, and critique. E-KT: statistical analysis review and critique, and manuscript: review and critique. MM: research project conception and design, and statistical analysis review and critique, and manuscript: review and critique. All authors contributed to manuscript revision, read and approved the submitted version.

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frontiers in Neurology

BRIEF RESEARCH REPORT
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Effect of a High-Intensity Tandem Bicycle Exercise Program on Clinical Severity, Functional Magnetic Resonance Imaging, and Plasma Biomarkers in Parkinson's Disease

Carolina Segura[1], Mauricio Eraso[1,2], Javier Bonilla[2], Carlos O. Mendivil[3,4], Giselle Santiago[5], Nicolás Useche[5], Oscar Bernal-Pacheco[6], Guillermo Monsalve[7], Laura Sanchez[2], Enrique Hernández[2], Maria José Peláez-Jaramillo[3] and Allison Cárdenas-Mojica[3]*

[1] Vida Activa, Department of Internal Medicine, Fundación Santa Fe de Bogotá, Bogota, Colombia, [2] School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia, [3] School of Medicine, Universidad de los Andes, Bogota, Colombia, [4] Endocrinology Section, Department of Internal Medicine, Fundación Santa Fe de Bogotá, Bogota, Colombia, [5] Radiology and Diagnostic Imaging Department, Fundación Santa Fe de Bogotá, Bogota, Colombia, [6] Neurology Department, Fundación Santa Fe de Bogotá, Bogota, Colombia, [7] Neurosurgery Section, Department of Surgery, Fundación Santa Fe de Bogotá, Bogota, Colombia

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***Correspondence:**
Carolina Segura
carolinasegura2015@gmail.com

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Rationale: The optimal modality, intensity, duration, frequency, and dose–response of exercise as a therapy for Parkinson's Disease (PD) are insufficiently understood.

Objective: To assess the impact of a high-intensity tandem bicycle program on clinical severity, biomarkers, and functional MRI (fMRI) in PD.

Methods: A single-center, parallel-group clinical trial was conducted. Thirteen PD patients aged 65 or younger were divided in two groups: a control group and an intervention group that incorporated a cycling program at 80% of each individual's maximum heart rate (HR) (≥80 rpm), three times a week, for 16 weeks. Both groups continued their conventional medications for PD. At baseline and at the end of follow-up, we determined in all participants the Unified Parkinson's Disease Rating Scale, anthropometry, VO_2max, PD biomarkers, and fMRI.

Results: VO_2max improved in the intervention group (IG) (+5.7 ml/kg/min), while it slightly deteriorated in the control group (CG) (−1.6 ml/kg/min) (p = 0.041). Mean Unified Parkinson's Disease Rating Scale (UPDRS) went down by 5.7 points in the IG and showed a small 0.9-point increase in the CG (p = 0.11). fMRI showed activation of the right fusiform gyrus during the motor task and functional connectivity between the cingulum and areas of the frontal cortex, and between the cerebellar vermis and the thalamus and posterior temporal gyrus. Plasma brain-derived neurotrophic factor (BDNF) levels increased more than 10-fold in the IG and decreased in the CG (p = 0.028). Larger increases in plasma BDNF correlated with greater decreases in UPDRS (r = −0.58, p = 0.04).

Conclusions: Our findings suggest that high-intensity tandem bicycle improves motor function and biochemical and functional neuroimaging variables in PD patients.

Trial registration number: ISRCTN 13047118, Registered on February 8, 2018.

Keywords: Parkinson disease, exercise, tandem bicycle, magnetic resonance imaging, biomarkers

INTRODUCTION

Parkinson's disease (PD) has a prevalence rate of 1–2 per 1,000 of the population worldwide (1). Despite L-DOPA treatment and optimal medication, around 36–50% of patients with PD will present motor complications such as dyskinesia and motor fluctuations (2, 3), and 78% will eventually develop dementia (4), leading to various degrees of disability and reduced quality of life. In working-age adults, PD also affects their economic productivity (5). All these issues have motivated an intense search for effective adjuvant therapies to complement current medications and improve management of PD. Exercise has been proven to improve motor function and mobility (6, 7) and enhance clinical functions including strength, gait, and balance (8). It also has a positive impact on cognitive function (9), patient-reported quality of life, and mental health (7, 10). The postulated mechanisms reported include enhanced cerebral oxygenation (11), improved plasticity of cortical striatum (12), release of humoral factors and neurotransmitters (7, 13, 14), and stimulation of dopaminergic neurons still functioning (15). More specific studies suggested that high-speed, complex goal-directed exercise such as cycling (high velocity, complexity, and repetition) can induce activity-dependent neuroplasticity (6, 16). High-cadence tandem cycling has shown to reduce PD symptoms in both upper and lower extremities and to increase brain activation as measured by functional MRI (fMRI) (6, 17–19).

A tandem bicycle has a drive train that mechanically links the pedals through a timing chain. When one of the riders is a PD patient, the higher cadence and consistency in pedaling that a healthy partner may deliver aids to achieve and maintain a pedaling rate that is greater than the former's preferred voluntary rate. Forcing the pace facilitates mechanically augmented moderate- and high-intensity aerobic exercise and provides sensory motor input possibly impacting motor speed and control via neurophysiological mechanisms. Some literature has shown that forced (tandem) cycling at a high cadence improves motor function and promotes functional improvement in PD. However, the mechanisms that underline those benefits are still being debated (6).

Abbreviations: PD, Parkinson's disease; IG, intervention group; CG, control group; UPDRS, Unified Parkinson's Disease Rating Scale; VO_2max, maximal oxygen consumption; fMRI, functional magnetic resonance imaging; BDNF, brain-derived neurotrophic factor; L-DOPA, L-3,4 dihydroxyphenylalanine; RANTES, regulated on activation, normal T expressed and secreted; MPO, myeloperoxidase; NCAM, neural cell-adhesion molecule; PDGF, platelet-derived growth factor isotype BB-BB; MP-RAGE, 3D magnetization-prepared rapid gradient echo; DPARSF, data processing assistant for resting-state fMRI; sICAM-1, intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; nM-EDL, non-motor aspects of experiences of daily living; M-EDL, motor aspects of experiences of daily living.

Low-intensity progressive cycling training can improve motor function in PD, especially akinesia (20).

However, the mechanisms underlying the improvement of motor function in PD patients after cycling are not known.

Several blood-borne molecules have been involved in mediating the effects of exercise on PD. One of them is brain-derived neurotrophic factor (BDNF), a protein with a potent effect on dopaminergic neuron survival and morphology (21, 22). Other potential mediators include regulated on activation, normal T expressed and secreted (RANTES), a chemokine correlated with motor involvement in PD patients (23); cathepsin D, a protease whose activity has been related to cell death in primate models of PD (24); myeloperoxidase (MPO), an enzyme with neurotoxic effects in a rodent model of PD (25); neural cell-adhesion molecule (NCAM) (26), a potential neurotrophic mediator; and platelet-derived growth factor isotype BB (PDGF-BB), whose regenerative properties have been demonstrated in a rat model of PD (27).

These mechanisms of action of exercise at the molecular and cellular level should also be reflected by changes in patterns of brain activation in functional neuroimaging studies. fMRI has revealed signature alterations in PD, including hyperactivation of cerebellar (28, 29) and primary motor cortex (30, 31). Recently, accelerated loss of hippocampal volume (32), gray matter atrophy of posterior cingulate cortex (33), and reduced connectivity in the prefrontal-limbic network (34) have also been linked to mild cognitive impairment and depressive symptoms in PD. Some studies have shown increased exercise-induced activity in the ventral striatum and increased repetitive transcranial magnetic stimulation-evoked dopamine release in the caudate nucleus (17). Nonetheless, the influence of highly challenging exercise therapy on fMRI features of PD is insufficiently known.

Despite abundant evidence addressing the clinical impact of exercise on PD, the optimal modality, frequency, and intensity of exercise practice as an adjuvant therapy in PD have not been established. The same can be said about the mechanistic pathways that result in the reported improvements.

Some of the heterogeneity of results regarding benefits of exercise in PD may arise from the fact that voluntary and self-paced exercise elicit distinct neural responses and may yield different outcomes (35). Animal and human trials with forced exercise (i.e., practiced above the intensity preferred by the subject) have shown positive results (36, 37). Furthermore, a prior trial proved a tandem bicycle intervention to be feasible in PD and to improve general physical performance measures (37).

With this context, we aimed to assess the impact of a high-intensity exercise program based on tandem bicycle training and on diverse aspects of PD including standardized scales of clinical symptoms, biochemical markers, and functional neuroimaging.

MATERIALS AND METHODS

Participants

Thirteen patients with idiopathic PD confirmed by a neurologist specializing in movement disorders according to the Movement Disorder Society Clinical Diagnostic Criteria (38) accepted to participate in the study. Inclusion criteria were a PD Hoehn and Yahr stage 1–3, age 65 or less, stable dopaminergic oral therapy, negative exercise stress test, and no contraindications to exercise. Exclusions were surgery for PD, cancer, joint diseases, coronary disease, hyperthyroidism, chronic obstructive pulmonary disease, asthma, hypertension, vision defects, history of stroke, anemia, anticoagulant use, pacemaker, insulin pumps, mini-mental score below 24, or the presence of any contraindication for magnetic resonance imaging.

Study Design

A single-center, parallel-group clinical trial was conducted. Participants were divided in two groups: a control group (CG) and an intervention group (IG) that incorporated high-intensity exercise. Both groups continued with their conventional pharmacological anti-PD medications. Motor function, anthropometric measurements (weight, height, body mass index, waist circumference, percent body fat, percent lean body mass measured by bioelectrical impedance analysis), estimated maximal oxygen consumption (VO_2max), biomarkers, and functional neuroimaging were assessed before and after complete the intervention in both groups.

The study was conducted at the indoor facilities of the "Vida Activa" wellness center of Fundación Santa Fe University Hospital. VO_2max and Unified Parkinson's Disease Rating Scale (UPDRS) were measured while individuals were "on" anti-Parkinson's medications. The physicians who took all measurements were blinded to patient group.

Intervention

The exercise protocol included a conditioning phase of 8 weeks as a progressive adaptation process to exercise. The conditioning phase was intended to allow participants to learn how to ride a tandem bicycle as none of them had used it before, to understand each participant's individual physical needs related to the exercise and to improve the equipment based on individual needs in order to provide greater comfort during exercise and allow some time for its progressive adaptation to the body.

The conditioning phase consisted of session of 30–40 min length, one session per week for the first 4 weeks and two sessions per week for the last 4 weeks. Each session began with 5 min of warmup (low resistance pedaling at 30–40 rpm), followed by 20 min of cycling at 50–60% of their individual's maximum heart rate (HR) (40–60 rpm) and ended with a cool down period of 5 min of cycling at 30–40 rpm. Participants performed 10 min of stretching exercise after each session. Rating of perceived exertion (on the Borg scale) and HR (speed and cadence) were monitored by a general practitioner physician during each session.

We considered the conditioning phase to be very important in order to improve patient engagement, increase patient's confidence and self-efficacy, and build a social network among patients and their families that increases adherence to the intervention and helps prevent exercise-related injury.

After the conditioning phase, patients participated in a high-intensity forced cycling program on a stationary tandem bicycle, three times a week for 16 weeks. Each training session consisted of a 10-min warm-up (low resistance pedaling at 30–40 rpm), followed by 20 min cycling at 80% of each individual's maximum HR while pedaling at 80 rpm or faster and ended with a cool down period of 5 min of cycling at 30–40 rpm. Participants performed 10 min of stretching exercise after each session. To rate perceived exertion (on the Borg scale) and HR, speed and cadence were monitored by a general practitioner during each session. HR was collected with a Polar^{TM} heart rate monitor worn on the chest; pedaling variables were measured using a bicycle speedometer and odometer. Healthy physical educators partnered with each patient to provide motivation and to assist individuals to keep the pace and cadence to reach 80% of their individual's maximum HR during each session. All participants successfully completed each exercise session.

Clinical Assessment

We measured in all participants at study start and end the UPDRS, estimated maximal oxygen consumption (VO_2max), and anthropometry.

Functional Magnetic Resonance Imaging

Subjects were scanned on a General Electric Signa Excite 1.5 T scanner at a University Hospital. T1 images were acquired using 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequence, repetition time (TR) = 13.12 ms, echo time (TE) = 4.2 ms, flip angle = 15°, field of view (FOV) = 240 × 240 mm, voxel size = 1 mm isotropic. Resting and task fMRI data were acquired using gradient-echo echoplanar imaging (EPI) sequence, with TR = 3,000 ms, TE = 60 ms, flip angle = 90°, FOV = 240 × 240 mm, voxel size = 3.75 × 3.75 × 7 mm. Each run of resting fMRI scan lasted 6 min, producing 180 volumes of 3D images. For the hand motor task, subjects were required to tap with the index fingers for periods of 30 s alternating with 30 s of rest.

Data were analyzed using the package SPM12, Department of Imaging Neuroscience Group, London, UK. The images were realigned spatially to the first series of each subject to correct the head movement; slice timing correction ascending (39), and slice 10 was taken as a reference. Functional images were normalized to standard stereotaxic space Atlas Montreal Neurological Institute (MNI). Finally, images were spatially smoothed with a three-dimensional 7-mm full width half maximum isotropic Gaussian kernel filter to improve S/N ratio. For each task we use parametrical analysis of first and second level. The model parameters were canonical hemodynamic response function (HRF) with time and derivatives, six multiple regressors for motion head to reduce intra- and intersubject variability, and high-pass filter of 128.

The second-level analysis consisted in a full factorial design; the first factor was the time of observation (pretreatment and post-treatment), the second factor was the group (IG and CG). We used an alpha of 0.05 without correction for all

analyses. The greater cluster with 10 voxels was included. The locations of the statistical findings are reported in a space coordinate (*x*, *y*, *z*) developed by the Consortium of Brain Mapping, Montreal Neurological Institute. Imaging data from resting fMRI were preprocessed using Statistical Parametric Mapping 8 (SPM5, http://www.fil.ion.uclac.uk/spm) and Data Processing Assistant for Resting-State fMRI (40, 41). In brief, the preprocessing included slice timing, head movement correction, spatial normalization, band-pass filtering (0.01–0.08 Hz), and global normalization. We decided to exclude the initial 10 volumes as part of the standardized process of the software (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) used for the task block analysis in order to allow magnetization to reach an equilibrium and reduce the noise before reaching the steady-state of imaging; the remaining volumes were then corrected and realigned to the first volume to correct displacement due to head motion (42).

Next, the individual T1-weighted images were co-registered to the mean realigned functional images using a linear transformation; the T1 was segmented into gray matter, white matter, and cerebrospinal fluid tissue maps followed by non-linear normalization into the Montreal Neurological Institute space. Temporal band-pass filtering (0.01–0.08 Hz) was performed on the residual time series of each voxel to reduce the effect of low-frequency drift and high-frequency noise (41). The final step in preprocessing was a spatial smoothing with an isotropic Gaussian kernel of 4 mm FWHM.

The functional connectivity was estimated with a procedure based on seeds or region of interest (ROI). The time sequence is extracted from each seed and that date is used as regressor for a linear correlative analysis. The correlation coefficient among all seeds was calculated, and subsequently, a symmetric and weighted matrix of connectivity for each subject was created. We used a whole brain approach, and the seeds were specified by the parcellation of automatic anatomical labeling or AAL atlas (43).

In order to identify changes in networks among pre- and post-test in the connectivity matrices of functional connectivity, a network-based statistic (NBS) was done. NBS allows to identify any potential connected structures formed by an appropriately chosen set of supra-threshold links, and the topological extent of any such structure is then used to determine its significance (44, 45). The parameters to analysis were 5,000 permutations and *p*-value of 0.05.

Imaging data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (http://rfmri.org/DPARSF). Functional connectivity was obtained with the seed method and the atlas AAL. The matrix of correlation of 116 regions of interest was analyzed by network-based statistic (44) (NBS, https://www.nitrc.org/projects/nbs/).

Biochemical Measurements

Biomarkers were measured with a MILLIPLEX® MAP human neurodegenerative disease panel (HNDG3MAG-36K, Millipore, USA). Antibody-coated, fluorescently labeled magnetic beads were incubated overnight with diluted plasma samples. After addition of a biotinylated detection antibody and extensive washing, streptavidin–phycoerythrin was added and the fluorescence of beads and phycoerythrin captured in a Luminex MAGPIX® (Millipore, USA) apparatus. Data were analyzed with the Xponent® (Austin, TX, USA) software. The lower limit of detection was 2 pg/ml for BDNF, PDGF-AA, and RANTES; 24 pg/ml for soluble intercellular adhesion molecule-1 (ICAM-1), MPO, cathepsin D, PDGFAB/BB, and NCAM; and 61 pg/ml for soluble vascular adhesion molecule-1 (sVCAM-1).

TABLE 1 | Baseline characteristics of study participants.

	Control group	Intervention group
Sex M/F	3:4	4:2
Age (years)	56.0	57.8
Time since diagnosis (range in years)	2–24	2–14
Body mass index (kg/m^2)	26.7	27.5
% body fat	22.8	19.6
% muscle mass	52.1	56.3
Waist circumference (cm)	91.5	94.0
VO_2max (ml O_2/kg/min)	18.7	19.4

Ethical Aspects

The study was approved by the Ethics Committee of Fundación Santa Fe de Bogotá, according to minute CCEI-2342 of November 25, 2014. All study patients provided written informed consent. Please also see below the declaration on *Ethics Approval and Consent to Participate*.

Statistical Analysis

Within-group changes in continuous variables (UPDRS, VO_2max, anthropometric measures, and biomarker levels) were performed using paired Student's *t*-tests. Between-group comparisons in the change in continuous variables were performed using analysis of covariance (ANCOVA), with baseline values as covariates and intervention group as fixed factor. Changes in continuous variables were correlated using Spearman's correlation coefficient.

RESULTS

The CG had three male and four female patients. The IG had four male and two female patients. None of the baseline variables differed significantly between groups (**Table 1**).

Clinical Severity

The CG experimented a deterioration in VO_2max during the study duration (from 18.7 to 17.1 ml/kg/min, intragroup $p = 0.092$), while VO_2max increased in the IG (from 19.4 to 25.1 ml/kg/min, intragroup $p = 0.008$; **Figure 1**). The between-group comparison in the change in VO_2max reached statistical significance ($p = 0.041$). Changes in weight, BMI, percent body fat, percent lean body mass, and waist circumference did not differ between groups (**Table 1**).

Baseline mean UPDRS was 57.7 in the CG and 54.8 in the IG. Patients in the CG experienced a mean 0.9-point increase

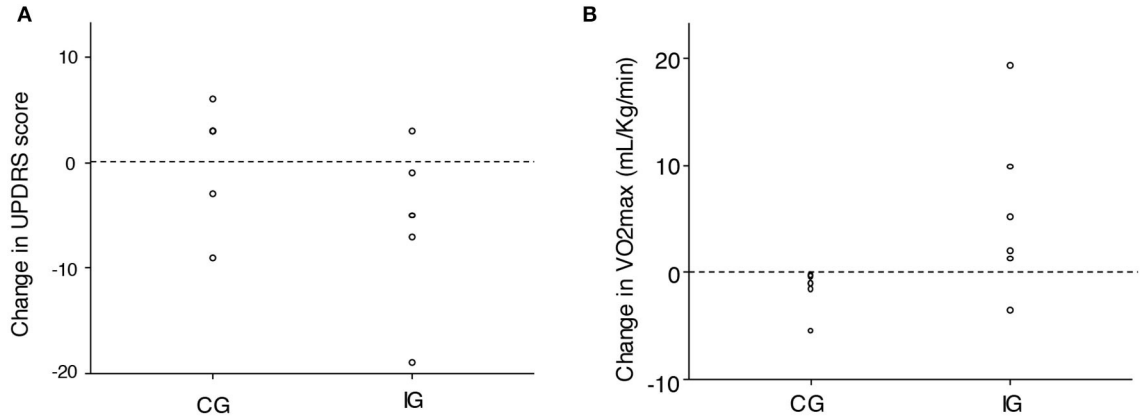

FIGURE 1 | Change in **(A)** total Unified Parkinson's Disease Rating Scale and **(B)** VO_2max in the study groups. IG, intervention group; CG, control group.

(intragroup $p = 0.67$), while those in the IG had a mean 5.7-point decrease (intragroup $p = 0.12$; **Figure 1**). The p-value for the between-group difference was $p = 0.11$.

Mean score in Part I of UPDRS [non-motor aspects of experiences of daily living (nM-EDL)] increased in both the CG (+2.7 points) and IG (+0.3 points) (between-group $p = 0.12$). Part II of UPDRS [motor aspects of experiences of daily living (M-EDL)] remained constant in both groups (+0.1 points in CG, +0.3 points in IG, $p = 0.96$). Part III of UPDRS (motor examination) was reduced by 6.7 points in the IG, while it went down by only 2.1 points in the CG. However, the difference did not reach statistical significance ($p = 0.32$). Mean score in Part IV of UPDRS (motor complications) also remained constant (+0.1 points in the CG, +0.5 points in the IG, $p = 0.61$).

fMRI

We found similar baseline activations in both groups in the motor right-hand task, including the left pre-central gyrus and cerebellum. The IG exhibited greater activation of the right fusiform gyrus and decreased activation of the left pre-central gyrus at study end, relative to the CG. In the verb generation task, pretreatment activations were similar in the IG and CG, involving portions of frontal cortex like the left pars triangularis. Final images revealed lower activation of this area in the IG compared to the CG. Network-based strategy (NBS) revealed post-exercise increases in functional connectivity between the right posterior cingulum and the middle frontal and superior orbital gyri, as well as between the vermis and the thalamus and posterior temporal gyrus (**Table 2** and **Figure 2**).

Changes in Biomarkers

In the IG, mean BDNF increased from 27.2 to 218.7 pg/ml (intragroup $p = 0.002$), PDGF-AA from 22.9 to 192 pg/ml (intragroup $p = 0.038$), and PDGF-AB/BB from 16.3 to 366 pg/ml (intragroup $p = 0.013$; **Table 3**). Contrastingly, no biomarker changed significantly in the CG. Finally, the between-group comparisons of change in BDNF (between-group $p = 0.005$) and RANTES (between-group $p = 0.030$) reached statistical significance.

Correlation Between Changes in Biomarkers and Changes in Clinical Variables

Larger increases in BDNF were associated with greater improvements in UPDRS (correlation between change in plasma BDNF and change in the total UPDRS $r = -0.58$, $p = 0.040$). Changes in BDNF were also positively correlated with improvements in VO_2max ($r = 0.58$, $p = 0.047$; **Figure 3**). Changes in NCAM were negatively correlated with changes in percent body fat ($r = -0.79$, $p = 0.001$).

Adverse Events

We did not encounter any physical or psychological adverse events during the course of the study.

DISCUSSION

To our knowledge, this pioneer study is the first to integrate clinical variables, fMRI, and biomarkers to assess the impact of a high-intensity tandem bicycle intervention in patients with PD. Despite some results not reaching statistical significance due to limited sample size, findings from this study suggest that high-intensity tandem bicycle induces improvements in clinical, biochemical, and functional neuroimaging variables in PD patients.

VO2 max improved in the IG, but remained constant in the CG, a difference that reached statistical significance. A similar trend was observed for UPDRS, even though in this case, the difference was not statistically significant. In fMRI, exercise promoted activation of the right fusiform gyrus during the motor task and functional connectivity between the cingulum and areas of the frontal cortex, and between the cerebellar vermis and the thalamus and posterior temporal gyrus. Plasma BDNF levels increased more than 10-fold in the IG and decreased in the CG, a significant difference. Larger increases in plasma BDNF

TABLE 2 | Functional magnetic resonance imaging main activations by task, group, and condition.

	Control group					Intervention group				
	Region	***t*-value**	***x***	***y***	***z***	**Region**	***t*-value**	***x***	***y***	***z***
RIGHT HAND TASK										
Baseline	Left pre-central gyrus	7.0	−36	−19	65	Left pre-central gyrus	6.7	−36	−19	65
	Left cerebellum (crus 1)	4.3	−30	−70	−31	Right fusiform gyrus	6.6	21	−85	−10
	Right cerebellum (VI)	4.1	24	−76	−22	Left cerebellum (crus 1)	5.2	−21	−85	−16
	Left inferior parietal lobule	3.7	−51	−46	53	Left posterior medial frontal gyrus	4.1	−9	−7	53
Post-treatment	Left pre-central gyrus	9.0	−36	−19	65	Right fusiform gyrus	7.2	24	−85	−10
	Left post-central gyrus	6.0	−51	−22	50	Left cerebellum (VI)	5.4	−21	−82	−16
	Left inferior parietal lobule	4.1	−51	−43	53	Left pre-central gyrus	5.2	−36	−19	65
	Left posterior medial frontal gyrus	4.7	−3	−1	59	Left mid-cingulate cortex	4.1	−12	−4	50
						Left cerebellum (VI)	4.0	−33	−67	−19
VERB GENERATION TASK										
Baseline	Left fusiform gyrus	4.1	−27	−82	−13	Left inferior frontal gyrus (pars triangularis)	5.3	−39	29	26
	Left inferior frontal gyrus (pars triangularis)	4.0	−39	14	14	Left superior medial gyrus	4.8	−9	17	47
						Left inferior frontal gyrus (pars orbitalis)	4.2	−48	20	−4
						Left middle frontal gyrus	4.5	−36	5	56
						Left posterior medial frontal gyrus	4.2	−6	2	62
Post-treatment	Left posterior medial frontal gyrus	5.9	−6	−1	65	Right fusiform gyrus	4.2	27	−82	−1
	Left inferior frontal gyrus (pars triangularis)	5.6	−36	26	29	Left insula lobe	3.7	−27	20	11
	Left pre-central gyrus	5.3	−39	−7	35	Left inferior frontal gyrus (pars triangularis)	3.5	−39	29	26
	Right fusiform gyrus	4.4	21	−85	−10	Left middle frontal gyrus	3.0	−15	−10	56

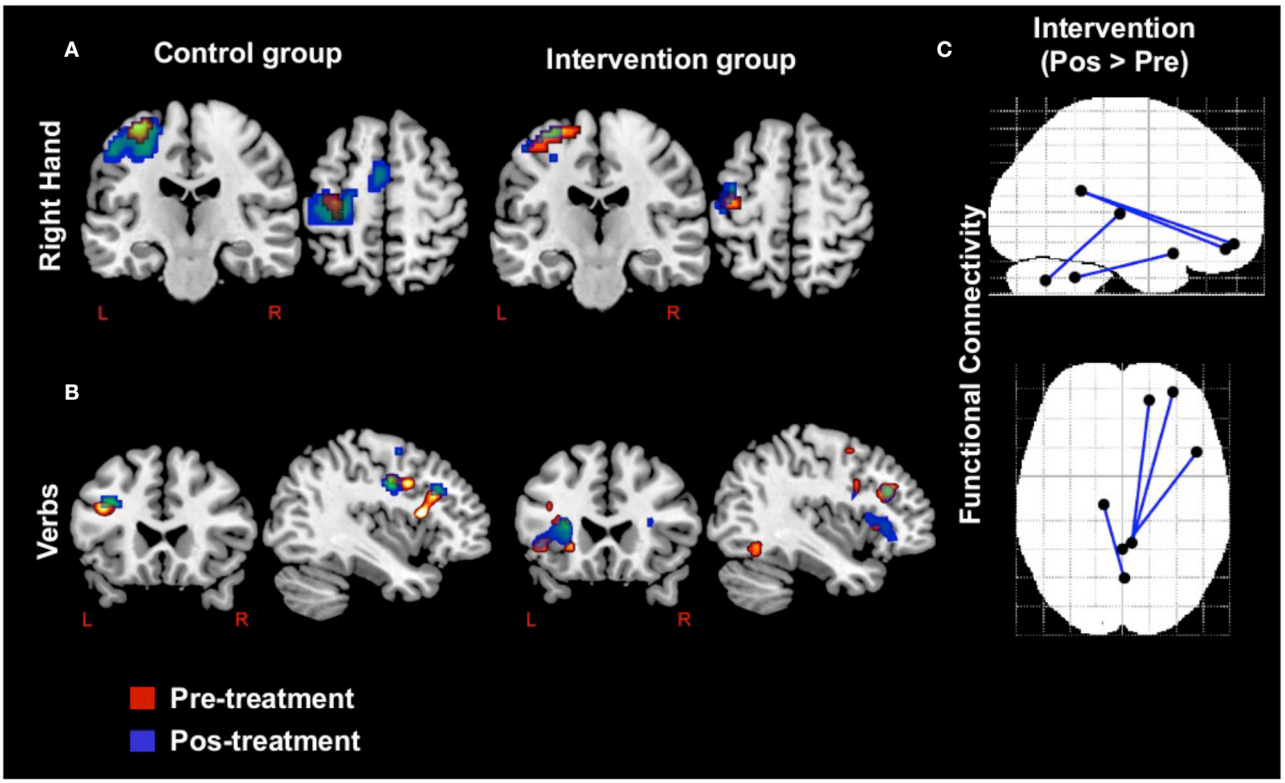

FIGURE 2 | Activations and connectivity in functional magnetic resonance imaging. **(a)** Activations in right hand motor task by group and condition. **(b)** Activations in verb generation task by group and condition. **(c)** Comparison between conditions with network-based strategy in resting functional magnetic resonance imaging.

TABLE 3 | Changes in plasma concentrations of biomarkers, by study group.

	Control group			Intervention group			Between-groups *p*-value
	Baseline	Final	Intragroup *p*-value	Baseline	Final	Intragroup *p*-value	
BDNF (pg/ml)	260.0	149.6	0.35	20.63	207.1	0.028	0.005
Cathepsin D (pg/ml)	4,824	3,559	0.92	3,637	3,716	0.50	0.63
sICAM-1 (pg/ml)	1,899	1,546	0.23	2,145	1,546	0.043	0.41
MPO (pg/ml)	28,150	3,559	0.14	46,992	3,733	0.080	0.78
PDGF-AA (pg/ml)	143.3	83.4	0.50	23.8	157.6	0.028	0.13
RANTES (pg/ml)	837.3	1,210	0.18	202	2,850	0.18	0.03
NCAM (pg/ml)	6,387	5,731	0.87	8,152	8,198	0.75	0.43
PDGF-AB/BB (pg/ml)	576.9	399.2	0.74	16.4	336.4	0.028	0.96
sVCAM-1 (pg/ml)	2,916	2,645	0.25	2,968	3,202	0.46	0.36

correlated with greater decreases in UPDRS. These findings are similar to those from previous studies showing that high-cadence tandem cycling improves motor function and mobility in patients with PD (6).

Several previous clinical studies have documented the positive impacts of exercise on PD (5–9, 19, 20). A systematic review of 104 studies concluded that there is good evidence supporting benefits of exercise on UPDRS (35), especially on the M-EDL subscale and motor examination, but this effect may vary according to exercise modality.

We found significant increases in plasma BDNF and PDGF-BB in the IG. A significant reduction in sICAM-1 was also achieved. Intracerebroventricular administration of PDGF-BB to a mouse model of PD restored striatal dopamine transporter binding sites and expression of nigral tyrosine hydroxylase (27). In addition, the impact of exercise on BDNF has been reported previously. Eight weeks of interval training in stationary bicycle incremented BDNF in PD patients (46, 47), and BDNF has shown potential to improve dopaminergic neuron survival (21, 22). Of note, plasma BDNF appropriately reflects concentrations in

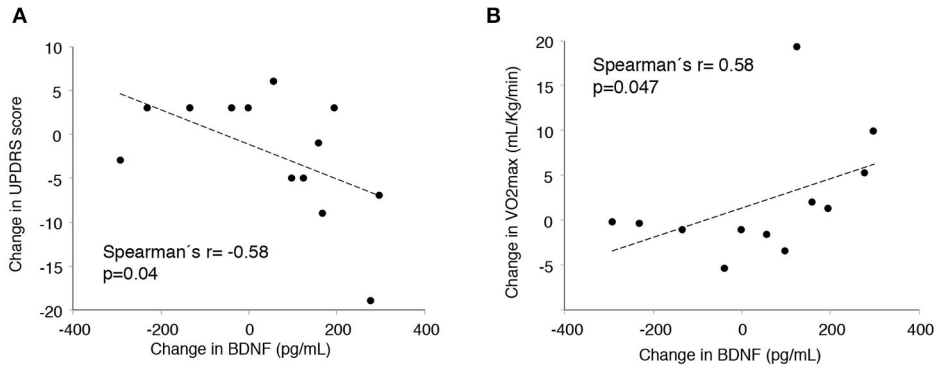

FIGURE 3 | Correlation between change in plasma brain-derived neurotrophic factor (BDNF) and change in clinical variables. **(A)** Unified Parkinson's Disease Rating Scale. **(B)** VO_2max.

central nervous system (48, 49). We found a marked correlation between increases in BDNF and improvements in UPDRS. The negative association between changes in this neurotrophin and changes in the clinical severity of PD is consistent with previous results (46, 47). Thus, BDNF biology, prior studies, and our own results support a potential involvement of BDNF on the impact of exercise on PD. Concerning sICAM-1, this molecule may constitute a marker of sustained brain inflammatory processes in both animals and humans (50). Higher plasma sICAM-1 was observed in stage 1 and 2 patients with PD when compared to healthy controls (51), suggesting a role of inflammatory agents in PD pathogenesis that could be mitigated by forced, high-intensity exercise.

Similar to earlier fMRI studies in PD (52, 53), we found baseline cerebellar hyperactivation in our PD patients. Concerning changes in fMRI induced by exercise, a prior tandem bicycle trial in PD found increased exercise-induced activity in the globus pallidus, thalamus, primary motor, and supplementary motor areas (54). None of these areas appeared to be differentially activated by the intervention in our study. Interestingly, what we did find was an exercise-induced activation of the fusiform gyrus that, to our knowledge, had not been documented previously. The fusiform gyrus is involved in the executive function that is frequently altered in PD patients as may occur in patients with rigidity and bradykinesia. If there is increased cortical activation with exercise, we consider that the executive function may deteriorate more slowly or may even improve in PD patients who exercise, reinforcing the importance of exercising in PD patients, as reductions in the gray matter volume of the fusiform gyrus (along with other temporal areas) seems to be associated with cognitive impairment and poorer executive function in PD patients (33, 55).

A previous study that evaluated an 8-week forced-rate pedaling exercise program reported stronger connectivity between the motor cortex and the ipsilateral thalamus (19). Similarly, we found increased connectivity between thalamus and posterior temporal gyrus in the IG. Hence, our exercise program induced cortical and connectivity changes associated with positive effects on PD.

High-intensity protocols based on tandem bicycle have shown to improve motor function, rigidity, and bradykinesia, as well as induce activity-dependent neuroplasticity (7, 12, 17, 18), probably by promoting high-frequency entry patterns to the sensorimotor cortex. Forcing a high pedaling rate seems to be a determinant of the effects of cycle training in PD (56), probably through induction of increases in afferent stimuli from osteotendinous structures (55). Other studies have proposed different hypothetic explanations regarding the mechanisms that improve motor function in PD patients after cycling.

Cycling may enhance both extrinsic and intrinsic sensory feedbacks from the periphery and the subsequent activation of basal ganglia circuits, which may enhance central motor processing (57); the pedals of a stationary bicycle inherently offer PD patients the mechanical constraint of a constant movement amplitude (57, 58).

Data from our study suggest that exercise may trigger several simultaneous mechanisms that integrated increased brain activation and improved activation of basal ganglia circuits and release of biochemical factors that act as potential neuroprotective and neurotrophic mediator agents (12–20). Our study provides comparative data against other high-intensity cycling interventions.

Additionally, these findings show that individuals with PD are able to participate in a high-intensity cycling intervention and benefit from it. While these findings do not directly answer the question regarding the optimal training variables (intensity/duration/frequency), they contribute to understand the mechanisms that improve motor function in PD patients after cycling.

Further examination of the correlation between changes in neuroimages, biomarkers, and clinical variables of PD induced by longer interventions are needed in order to develop individualized and more specific exercise-training programs.

Study Limitations

Despite the encouraging results, our study has several limitations. The integration of biomarkers and fMRI to

the clinical assessments makes this study not only unique and interesting but also highly expensive and logistically complex. Due to these considerations, we used a small convenience sample of 13 patients. In addition, the design was not randomized due to the requirement of a high degree of collaboration (continued attendance, adherence to exercise routines, multiple complex evaluations) by study participants.

Even so, the findings from our study provide a novel approach and original data to understand the mechanisms that improve motor function in PD patients after cycling.

CONCLUSION

Findings from this study suggest that high-intensity tandem bicycle improve motor function and biochemical and functional neuroimaging variables in PD patients. Further research is needed to better understand the mechanisms underlying the improvement of motor function, as well as the type, training variables (intensity/duration/frequency), and dose–response involved in each exercise training practice.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to institutional policies protecting patient privacy but are available in de-identified from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fundacion Santa Fe de Bogota. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS and ME participated in study conception, writing the protocol, writing the application for funding, coordinating the administrative task to buy study equipment, patient enrollment, consenting patients, patients evaluation, data collection, data analysis, and manuscript writing. JB participated in study conception, looking for funding, coordinating the administrative task to buy study equipment, patient enrollment, data collection, data analysis, and manuscript editing. CM participated in study conception, writing the protocol, writing the application for funding, coordinating the administrative task to buy study equipment, patient enrollment, consenting patients, data collection (laboratory analyses), data analysis, and manuscript writing. GS and NU participated in patient enrollment and evaluation, consenting patients, data collection (neuroimaging), data analysis (neuroimaging), and manuscript revision. OB-P participated in study conception, data collection (neurology data), data analysis, and manuscript writing revision. GM participated in study conception, search for funding, data analysis, and manuscript revision. LS, EH, MP-J, and AC-M participated in patient enrollment, data collection, and manuscript revision.

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Outcomes of STN-DBS in PD Patients With Different Rates of Disease Progression Over One Year of Follow-Up

Renli Qi†, Xin Geng†, Baihui Huang, Ye Chen, Honggao Jiang, Yanghong Zou, Wei Wang, Yubin Li, Yushan Li, Lei Yin, Anxiong Liu, Xuelan Yang, Jinghui Li and Hualin Yu**

Second Department of Neurosurgery, First Affiliated Hospital of Kunming Medical University, Kunming, China

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Edited by:
Mayela Rodríguez-Violante, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico

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***Correspondence:**
Jinghui Li
km_ljh@126.com
Hualin Yu
yhl308@163.com

†These authors have contributed equally to this work

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Parkinson's disease (PD) is a progressive neurodegenerative disorder, and the rate of progression is different across individuals. Subthalamic nucleus deep brain stimulation (STN-DBS) has been shown to produce long-term symptom improvement in PD. In this retrospective study, we wanted to explore the effects of bilateral STN-DBS in PD patients with different rates of disease progression. Forty patients with PD were included. An index of progression rate was calculated by the ratio of the Unified Parkinson Disease Rating Scale, part III (UPDRS-III), score in the off-medication condition at baseline and disease duration. The patients were divided into fast-, medium-, and slow-progression groups by this index. The outcome measurements at the 1st, 6th, and 12th months after surgery were the changes in UPDRS-III scores in the off-medication/on-stimulation condition compared with the baseline. We found the following. (1). Motor functions in the different PD progression groups were improved by bilateral STN-DBS treatment at 1 year of follow-up. (2). However, compared to the slow- and medium-progression groups, the fast-progression group had less improvement at the 6th- and 12th-month follow-up. The results indicated that bilateral STN-DBS can improve motor functions of Parkinson's patients over the 1-year follow-up. Moreover, the outcomes in the slow- and medium-progression patients were better than those with fast-progression rates.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, disease progression, outcome

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra accompanied by clinical symptoms of bradykinesia, tremor at rest, rigidity, postural instability, asymmetric onset, and levodopa responsiveness (1, 2). Levodopa and dopamine agonists are the primary treatment for PD patients, but motor and non-motor complications and drug-induced dyskinesia will often appear 5–10 years after pharmacologic treatment in advanced PD patients (3).

PD is a progressive neurodegenerative disorder, and studies indicate that motor deterioration might progress linearly in proportion to disease duration (4–6). However, in the clinic, the slope of the progression is different across individuals, which may be related to the differential pathological involvement of CNS structures (7).

Subthalamic nucleus deep brain stimulation (STN-DBS) has been shown to produce long-term symptom improvement on motor and non-motor symptom in PD. According to some reports, the motor improvement induced by STN-DBS is sustained for up to 5–8 years after surgery, but some of the initial improvements, mainly regarding axial signs, progressively deteriorated (8, 9). However, the reported improvements of motor function vary from 40 to 70% in off-medication/on-stimulation conditions at the 12th months after surgery (9–11). There are limited reports about the factors that correlated with the efficacy of STN-DBS, but recent work has reported that it seems inappropriate to combine substantially different populations of patients—newly diagnosed, early fluctuators, or advanced dyskinetic individuals—within the same group to evaluate the efficacy of STN-DBS (12). Therefore, it is necessary to explore the effects of STN-DBS on PD patients with different rates of progression. In this study, we divided PD patients who had received bilateral STN-DBS treatment in our center into slow-, medium-, and fast-progression groups by an index of the rates of progression. The index was calculated by the ratio of UPDRS-III scores evaluated in the off-medication condition and disease duration before operation. We wanted to explore the effects of STN-DBS on PD patients with different progression rates by comparing the outcomes at the 1st, 6th, and 12th months after surgery.

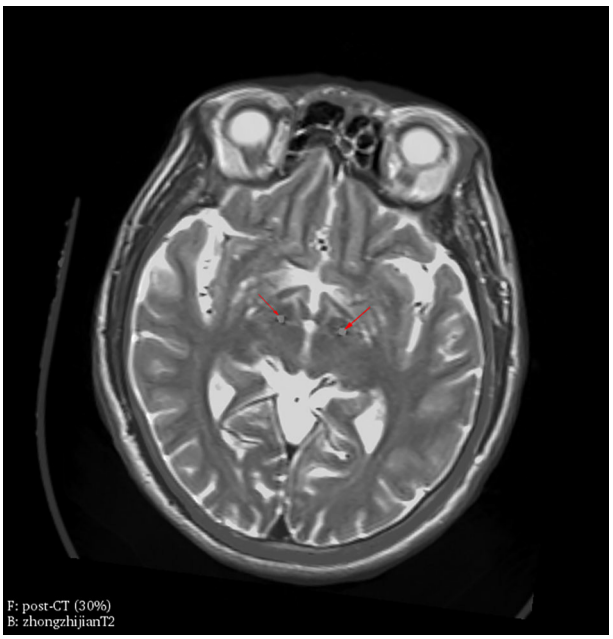

FIGURE 1 | Electrode location was verified by fusion images of postoperative CT and preoperative MRI. Electrodes were located in bilateral STN (red arrowheads) in one representative patient, which is confirmed by fusion images of postoperative CT (30% transparency) as foreground and preoperative MRI (T2, 0% transparency) as background.

METHODS

Patient Enrollment

Forty patients from a single DBS center in the First Affiliated Hospital of Kunming Medical University who underwent bilateral STN-DBS surgery and whose locations of electrodes were verified by CT/MRI from 2015 to 2017 were enrolled in this retrospective cohort study. The diagnosis of PD followed the standard diagnostic criteria of the International Parkinson and Movement Disorder Society in 2015 (13). The inclusion criteria included (1) good levodopa response on Unified Parkinson Disease Rating Scale part III (motor) (improvement >30%), (2) drug-related complications (e.g., dyskinesia, or "on-off phenomenon") even under optimal anti-parkinsonism medication adjustment, (3) absence of structural lesions in brain MRI, and (4) absence of dementia (mini-mental status exam >24) and active psychiatric diseases (depression). All patients provided written informed consent for STN-DBS surgery and for the study's evaluation procedure. This study was approved by the First Affiliated Hospital of Kunming Medical University Human Ethics Review Committee (No. 2016L46).

Surgical Procedures

The surgical procedure comprised two phases. First, bilateral stereotactic STN implantation was performed under local anesthesia using MRI/CT image fusion for anatomical targeting. Images for targeting were obtained from a 1.5-Tesla magnetic resonance imaging (MRI) unit (Siemens, MAGNETOM Avanto, Germany). The standard settings for preoperative targeting included T1-weighted axial images (TR: 26 ms, TE: 6.9 ms, matrix size: 256 × 192, thickness: 0.7 mm) and T2-weighted axial images (TR: 4,800 ms, TE: 95 ms, matrix size: 256 × 192, thickness: 2.0 mm). Each of these sequences was performed in contiguous axial slices. A Leksell frame was used for the stereotactic procedure on the day of the operation. CT images were obtained with the patients' head in the frame. The images were transferred to a neuro-navigation workstation (SurgiPlan, Elekta, Sweden). Anterior commissure and posterior commissure (AC-PC) lengths were identified, and the tentative surgical target was set at the dorsolateral part of the STN. Quadripolar leads (Electrode model L301; PINS, Beijing, China) were implanted following the selected trajectory. Intraoperative electrophysiological recording (NeuroNav, Alpha Omega, Israel) and acute microstimulation were performed to evaluate clinical effects of implanted electrodes. Second, the pulse generator (Model G102R; PINS, Beijing, China) was then implanted in the right subclavicular area and connected through extension cables to the leads under general anesthesia. Postoperative CT was performed to confirm electrode positioning and to identify surgical complications. The electrode positions of enrolled patients in this study are all located in STN confirmed by fusion images of postoperative CT and preoperative MRI (**Figure 1**).

Clinical Evaluation

Patients were evaluated at baseline and 1, 6, and 12 months after surgery. One month is the time when the stimulation generator was started to work after surgery. Baseline evaluations of motor symptoms (UPDRS-III) were performed in an

off-medication condition after overnight withdrawal of anti-parkinsonian medication and the acute levodopa challenge test (ALCT) were performed in an on-medication condition after the administration of 1.5 times the usual L-dopa morning dose before the operation. After surgery, the scores on the UPDRS-III were evaluated in on-stimulation/off-medication conditions at approximately the 1st, 6th, and 12th months, at which time the patients returned for parameter modulation in the outpatient department in off-medication conditions. Evaluated symptoms included bradykinesia (items 23–26 and 31), tremor at rest (items 20 and 21), and rigidity (item 22) in UPDRS-III. The axial score evaluation included speaking, rising from a chair, gait, and postural instability (items 18 and 27–30) (10, 11). The L-dopa-equivalent daily dose (LEDD) was calculated according to recognized standard conversions (14).

Statistical Analysis

The patients were divided into fast- (index $\geq$ 8), medium- (8 $>$ index $\geq$ 5), and slow- (index $<$ 5) progression groups based on the index. For studies that have indicated that motor deterioration might progress linearly in proportion to disease duration (4–6), the index in this study was calculated by the ratios of UPDRS-III scores in the off-medication condition and disease duration before operation. Disease duration was from the onset of PD symptom to the time of UPDRS-III evaluation, and the onset of PD symptom is the time patients found the onset of mild tremor or leg drag, bradykinesia, and so on. The improvement in the acute levodopa challenge test was calculated by the ratio of the difference value between UPDRS-III scores in the off-medication condition and the most comfortable medication condition after the administration of 1.5 times the usual L-dopa morning dose and the scores in the off-medication condition. The improvement in motor function after surgery was evaluated by the ratios of the difference values between baseline score (off-medication) and scores in the on-stimulation/off-medication condition and baseline scores in off-medication.

All data were processed with the SPSS software package (version 21; SPSS, Chicago, IL). Group comparisons of clinical characteristics, including age, gender, disease duration, LEDD, improvement after the acute levodopa challenge test, indexes of progression rate, and UPDRS-III scores, were analyzed using one-way ANOVA for continuous variables. Repeated-measures ANOVA was used to examine the outcomes of STN-DBS on UPDRS-III scores or subscores at the 1st, 6th, and 12th months after surgery in each of the three groups. A *post hoc* comparison with Bonferroni correction was adopted when we compared the differences during groups or times. All p-values were two-tailed, and $p < 0.05$ was considered significant.

RESULTS

Forty patients were divided into slow- (index $\geq$ 8, $N = 15$), medium- (8 $>$ index $\geq$ 5, $N = 14$), and fast- (index $<$ 5, $N = 11$) progression groups by the index of progression (IOP) rates. There were no differences in age, gender, LEDD, and improvement in the ALCT between the three groups. However, the fast-progression group had a shorter disease duration than the other two groups (both $p < 0.001$, one-way ANOVA). The UPDRS-III score of the fast-progression group evaluated in the off-medication condition was higher than that of the slow-progression group ($p < 0.001$, one-way ANOVA) but was not different from that of the medium-progression group (**Table 1**).

The Motor Abilities Evaluated by UPDRS-III Before the Operation

The patients were evaluated by UPDRS-III in the defined off-medication condition before the operation. The total score and subscores of tremor at rest (items 20 and 21), rigidity (item 22), bradykinesia (items 23–26 and 31), and axial signs (items 18 and 27–30) were compared in three different progression groups. Both the total scores and the subscores (tremor, rigidity, bradykinesia, and axial) of the slow-progression group were significantly lower than those of the medium and fast groups (p = 0.001, 0.001, 0.016, 0.001, and <0.001, respectively), however, there were no significant differences between the medium and

TABLE 1 | Baseline demographics and clinical data in the slow-, medium-, and fast-progression groups.

	SP group ($N = 15$)	MP group ($N = 14$)	FP group ($N = 11$)	t or $\chi 2$ (p-value), df
Age, mean (SD)	60.93 (2.31)	63.93 (1.82)	65.73 (8.60)	1.16 (0.32), 39
Male, *N* (%)	10 (66.7%)	7 (50%)	7 (63%)	9.37 (0.01), 2
Duration, mean (SD)	10.8 (0.68)	9.36 (0.75)	5.09 (0.59)*#	16.71 (<0.001), 39
LEDD, mean (SD)	618.77 (72.72)	629.04 (75.49)	679.59 (83.43)	0.164 (0.85), 39
IOP, mean (SD)	3.39 (0.21)	6.48 (0.23)*∧	13.7 (2.07)*#	26.06 (<0.001), 39
ALCT improvement, mean (SD)	78.25% (3.09)	73.78% (2.68)	71.34% (4.55)	1.4 (0.26), 39
UPDRS-III scores, mean (SE)	36.47 (3.31)	59.79 (4.0)*	61.91 (5.09)*	12.82 (<0.001), 39

There were significant differences in disease duration, UPDRS-III scores, and IOP-values between slow-, medium-, and fast-progression groups but not for the factors age, gender, LEDD, and improvement after the acute levodopa challenge test. Note: UPDRS-III, the Unified Parkinson Disease Rating Scale, part III; LEDD, the levodopa-equivalent daily dose; IOP, the index of progression rate. SP, MP, and FP groups, slow-, medium-, and fast-progression groups. "", $p < 0.05$ vs. the SP group; "#", $p < 0.05$ vs. the MP group; "∧", $p < 0.05$ vs. the FP group.*

TABLE 2 | The differences in motor ability in the slow-, medium-, and fast-progression groups.

UPDRS-III scores(Med-off)	SP group ($N = 15$)	MP group ($N = 14$)	FP group ($N = 11$)	t (p-value), df
Total scores, mean (SD)	36.47 (12.8)	59.79 (14.81)*	61.91 (16.89)*	12.82 (<0.001), 39
Tremor, mean (SD)	5.73 (1.118)	11.57 (1.32)*	11.91 (2.17)**	5.54 (0.001), 39
Rigidity, mean (SD)	9.47 (0.79)	12.71 (0.90)	14.91 (2.23)**	4.42 (<0.016), 39
Bradykinesia, mean (SD)	13.07 (1.72)	22.43 (2.19)*	27.91 (4.27)**	7.85 (0.001), 39
Axial, mean (SD)	5.67 (0.73)	10.43 (1.18)*	11.91 (0.93)**	8.85 (0.001), 39

The total scores and subscores of UPDRS-III evaluated in the off-medication condition at baseline in the slow, medium, and fast groups. The subscores of tremor at rest (items 20 and 21), rigidity (item 22), bradykinesia (items 23–26 and 31), and axial signs (items 18 and 27–30) were compared in three different progression groups. This indicates that both total scores and subscores in the medium and fast groups are higher than in the slow group. SP, MP, and FP groups, slow-, medium-, and fast-progression groups. One-way ANOVA with Bonferroni post hoc test. "", $p < 0.05$; "**", $p < 0.01$ vs. the SP group.*

TABLE 3 | The UPDRS-III scores evaluated at baseline in off-medication and the 1st, 6th, and 12th months in off-medication/on-stimulation condition in the slow-, medium-, and fast-progression groups.

	UPDRS-III scores, mean (SE)			
Group	Baseline	Post-op 1M	Post-op 6M	Post-op 12M
SP	36.47 (3.31)	7.33 (1.02)	10.47 (1.61)	11.20 (1.59)
MP	59.79 (4.0)	13.36 (1.73)	18.64 (2.46)	17.80 (2.42)
FP	61.91 (5.09)	12.81 (2.68)	28.91 (4.60)	33.55 (4.01)

fast groups (one-way ANOVA with Bonferroni *post hoc* test) (**Table 2**).

These results indicated that the motor ability of the slow group was significantly better than that of the medium and fast groups, but there was no difference between the medium and fast groups.

The Outcomes of Bilateral STN-DBS at the One-Year Follow-Up

The UPDRS-III scores evaluated at baseline and at the 1st, 6th, and 12th months are shown in **Table 3**. These results showed the UPDRS-III scores evaluated at the 1st, 6th, and 12th months after surgery were significant lower when compared to the baseline in all three groups (all $p < 0.001$, paired t-tests).

The outcomes of bilateral STN-DBS were measured by improvements in UPDRS-III motor scores in the off-medication/on-stimulation condition at the 1st, 6th, and 12th months after surgery, compared to the baseline (**Supplemental Table 1**). There are interaction effects between time (1st, 6th, and 12th months) and group (slow-, medium-, and fast-progression groups) on total UPDRS-III motor scores ($p = 0.04$, two-way repeated-measures ANOVA). For the group effect, there are no significant differences during three groups at three time points. For the time effect, there are significant differences in medium- ($p = 0.017$) and fast-progression groups ($p < 0.001$), but not in slow group. *Post hoc* tests with Bonferroni correction found that the improvements at the 6th and 12th months are significantly lower than that of the first month in the fast-progression group ($p = 0.023$ and 0.001) (**Figure 2A**).

The effects of bilateral STN-DBS on tremor, bradykinesia, and axial scores at the first, 6th, and 12th months in the slow-, medium-, and fast-progression groups were tested by two-way repeated ANOVA. There were main effects of time on the outcomes of tremor, bradykinesia, and axial scores ($p = 0.004$, 0.002, and 0.006, respectively), and there are no main effects of group or interactions between groups and times. A *post hoc* test with Bonferroni correction found that the improvement of tremor in the 12th month was lower than that in the first ($p = 0.011$) and 6th months ($p = 0.03$) (**Figure 2B**). The improvement of bradykinesia in the 12th month was lower than that in the first month ($p = 0.02$) and 6th month ($p = 0.006$) (**Figure 2D**). The axial outcomes in the 12th month were lower than in the first month ($p = 0.008$) (**Figure 2E**). There was an interaction between groups and times ($p = 0.001$, two-way repeated-measures ANOVA) on rigidity. For the group effect, there are significant differences at the 6th month ($p = 0.001$) and 12th month ($p = 0.012$); a *post hoc* test with Bonferroni correction found that the outcomes of STN-DBS on rigidity in the fast group are lower than the slow group both at the 6th ($p = 0.008$) and 12th months ($p = 0.027$) (**Figure 2C**).

These results indicated that the improvement in motor functions in the three groups was improved by bilateral STN-DBS treatment at the 1-year follow-up. However, the improvement in the fast progression group was not as good as in the slow and medium groups at the 6th and 12th months.

The Factors Affect the Movement Improvement at 12th Month After Deep Brain Stimulation

The effects of clinical data, such as, age, gender, IOP, ALCT improvement, and LEDD, on the movement improvement at the 12th month were tested by multiple linear regression model using the stepwise method. We found that the regression model only included the IOP variable that had statistical significance ($F = 12.575$, $p < 0.001$, adjusted $R^2 = 0.229$). The impact of IOP on the 12th-month improvement was significant ($p = 0.001$). The detailed results are shown in **Table 4**. The factors of age, gender, ALCT improvement, and LEDD have no significant effect on the improvement at the 12th month (all $p > 0.5$).

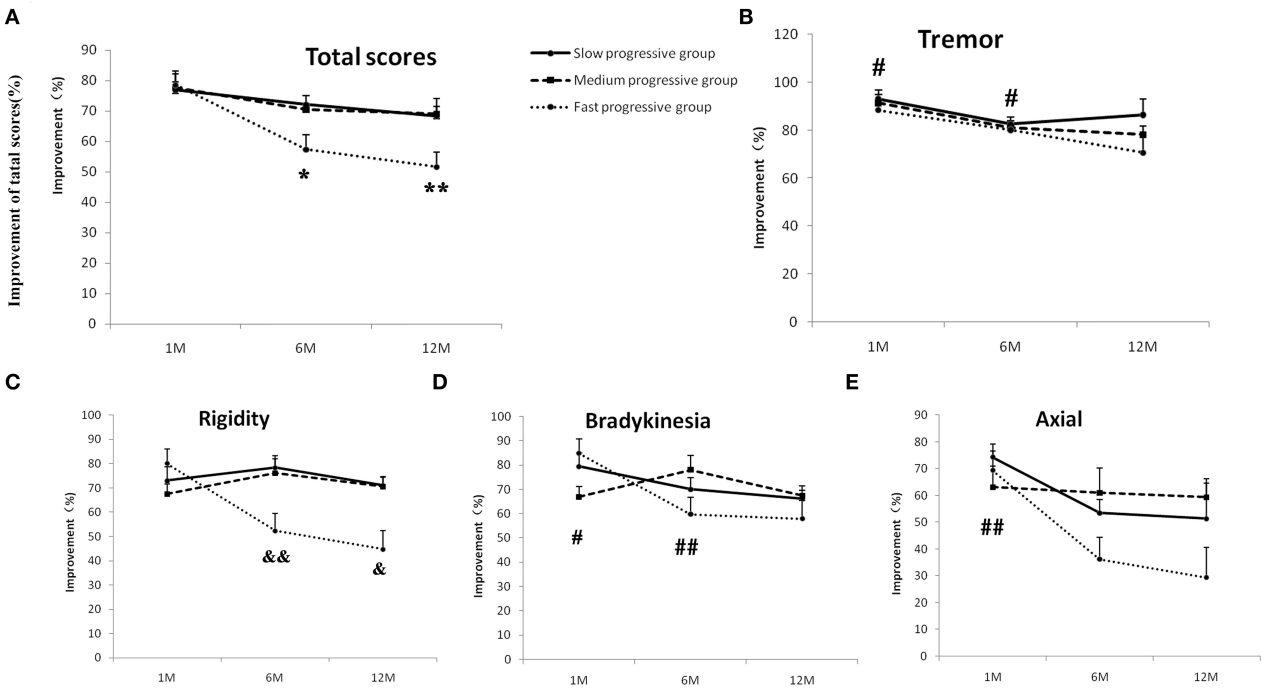

FIGURE 2 | The outcomes of bilateral STN-DBS at stimulation onset (1 month) and 6 and 12 months in the slow-, medium-, and fast-progression groups. The effect of bilateral STN-DBS on the total motor scores **(A)**, resting tremor scores **(B)**, rigidity scores **(C)**, bradykinesia scores **(D)**, and axial scores **(E)** assessed by UPDRS-III in the three different groups. There are interaction effects between times and groups for total scores and rigidity scores. The *post hoc* test with Bonferroni correction indicated that the improvements of total motor function at the 6th and 12th months are significantly lower than that of the first month in the fast-progression group **(A)**, and the improvements of rigidity in the fast group are lower than in the slow-progression groups at 6th and 12th months **(C)**. There were no interaction effects between time and group on the resting tremor, bradykinesia, and axial scores. The *post hoc* test with Bonferroni correction indicated that the improvements of tremor and bradykinesia scores in the 12th month are lower than in the 1st and 6th months **(B,D)**. The improvement in axial tremor in the 12th month was lower than in the first month **(E)**. "*"/"**" indicates a significant difference from the first month in the fast-progression group, $p < 0.05/0.01$, respectively, "#" indicates a significant difference between the improvement of the 1st/6th and 12th months, $p < 0.05/0.01$. "&" indicates a significant difference between the improvement in the fast- and slow-progression groups, $p < 0.05/0.01$.

TABLE 4 | The result of the multiple linear regression model.

Variable	Coefficient	Standard error	Standardized coefficient	Significant
Intercept	0.746	0.037		0.000
IOP	−0.015	0.004	−0.499	0.001

DISCUSSION

Previous work indicated that PD is a progressive disease, and the motor deterioration might progress linearly in proportion to disease duration (4–6); thus, the group information in this study was based on the index of progression rate, which was calculated by the ratios of the UPDRS-III scores in the off-medication condition and disease duration at baseline. Based on the group information, we found the following. (1). There were no differences in the LEDD and the improvement from the acute levodopa challenge test between the slow, medium, and fast groups at baseline. This finding may indicate that our patients in the fast group are not multiple-system atrophy with predominant parkinsonism (MSA-P), which would account for deterioration to greater severity and disability in a shorter time (15), accompanied by a poor response to levodopa (16). (2). The disease duration in the fast group was shorter than in the slow and medium groups, but the UPDRS-III score was higher than in the slow group, which means that the deterioration progressed very rapidly in the fast group. Previous studies have indicated that the progression rate in PD may be influenced by factors such as the onset age or complications associated with the disease. One study reported that an increase in the UPDRS-III score with similar disease duration was more pronounced in older patients than in younger patients (17). In another study, Burn and colleagues showed that the annual deterioration measured by the UPDRS-III score in PD patients with dementia was more severe than in PD patients without dementia (18). However, there were no significant differences in the onset ages among the three groups, and dementia was an exclusion criterion for our surgery.

In this study, we found marked improvement in motor function as evaluated by UPDRS-III scores in slow, medium, and fast groups at the 1st-, 6th-, and 12th-month follow-up. The improvements observed with bilateral STN-DBS in our study are in line with previous reports, which reported

that the efficiency of treatment is approximately 40–70% in the off-medication/on-stimulation conditions at the 12th month after surgery (9–11). Furthermore, we found that the improvements in motor function in the fast group at 6 and 12 months were not as good as in the slow and medium groups at the same period. Maybe there are many reasons for the decline in improvement with passage of time. The multiple linear regression model found only that the regression model that included the IOP variable had statistical significance on the improvement of total UPDRS-III scores at 12 months, but adjusted R^2 is low (0.229), which means the improvement at 12 months may have not linearly correlated with patients' IOP. We conduct Pearson correlation analysis between the improvement of total UPDRS-III scores at 12 months in three different groups and the clinical data before operation (IOP, gender, age, duration, UPDRS-III scores, ALCT improvement, and LEDD) (**Supplemental Figure 1**). The correlations are very poor between the improvement at 12 months and patients' gender (**Supplemental Figure 1B**), age (**Supplemental Figure 1C**), duration (**Supplemental Figure 1D**), UPDRS-III scores (**Supplemental Figure 1E**), ALCT improvement (**Supplemental Figure 1F**), and LEDD (**Supplemental Figure 1G**). The improvement lowly correlated with IOP of total groups ($R^2 = 0.25$) but more highly correlated with IOP of the fast group ($R^2 = 0.49$). Interestingly, the improvement has a good correlation to disease duration in the fast group ($R^2 = 0.61$), which may indicate the faster progression and poorer improvement in the fast group.

It is interesting that there were no motor function differences according to the UPDRS-III scores between the fast and medium groups in the off-medication condition before the operation, but the outcomes following bilateral STN-DBS were quite different. Moreover, the motor functions showed significant differences between the slow and medium groups before the operation, but the outcomes following bilateral STN-DBS were similar. This result indicates that the pathogenesis of disease in the fast-progression group may be different from those of the slow and medium groups, but the detailed mechanism is not clear.

The lower improvements in motor function in the fast group may be the result of severe deterioration in PD patients in this group. One recent study suggested that disease severity plays a central role in the efficacy of STN-DBS in PD patients (12). Moreover, the progression of deterioration is quite different during individual PD patients (19). Our study implies that the fast progression of deterioration may counteract the partial outcomes of STN-DBS, so the improvement in motor function in the fast group is lower than in the slow- and medium-progression groups.

Many studies have reported efficiency outcomes of bilateral STN-DBS at different durations after surgery, from 6 months to 11 years (9, 20–23), and across different ages of disease onset, i.e., young-onset and old-onset PD patients (11). However, this is the first report of the outcomes of STN-DBS in PD patients with different progression rates. Some studies have also reported the outcomes of histo-pathologically proven MSA patients who underwent STN-DBS surgery because they were considered having PD at the time of surgery, and these studies found that clinical improvements were short-lasting (∼6–12 months) and rapidly followed by the occurrence of disabling manifestations of MSA that counteracted the DBS benefits (24, 25). In our study, although the improvement in the fast-progression group was not as good as the slow and medium groups, the DBS benefit was significant when compared to baseline.

Some limitations of this study could be addressed in future research. First, the index of progression rate and the classification into slow, medium, and fast groups may not be very strict. Some researchers consider the progression of motor symptoms in medication-treated patients to be described in a linear model, but others think that the model is more complicated (5, 6, 19). Second, more comprehensive clinical data should be collected, such as UPDRS-I, II, and IV scores and outcomes in the on-medication/on-stimulation condition, to assess overall outcomes with STN-DBS.

In conclusion, our results supported the efficiency of STN-DBS for motor function in slow-, medium-, and fast-progression PD patients, but the outcomes for patients in the fast-progression group were not as good as those in the slow and medium groups. The different rates of outcomes could provide some guidance to neurosurgeons and neurologists when addressing the expectations of fast-progression patients before operations, as one study showed that addressing patients' expectations both preoperatively and postoperatively may play an important role in patient satisfaction and therefore in the overall success of STN-DBS surgery for Parkinson disease (26).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Kunming Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HY, JL, XG, and RQ designed and conducted the study, including patient recruitment, data collection, and data analysis. BH and YC prepared the manuscript draft with important intellectual input from HY and RQ. YZ, WW, HJ, YubL, YusL, LY, AL, and XY collected data and had complete access to the study data. YC and BH gave their editorial supports during the preparation of this manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00600/full#supplementary-material

Supplemental Figure 1 | The correlation between the improvements at 12th month and clinical data before operation. Pearson correlation analysis between the improvement of total UPDRS-III scores at 12 months and IOP **(A)**, gender **(B)**, age **(C)**, disease duration **(D)**, UPDRS-III scores **(E)**, ALCT improvement **(F)**, and LEDD **(G)**. Red dots represent the data of slow progression group; Green dots, medium group; purple dots, fast group. Black dashed lines are the correlation trend lines of total group, and the purple dashed lines are the trend lines of fast group.

Supplemental Table 1 | The improvements with bilateral STN-DBS at stimulation onset (1 month), and at the 6th and 12th month in the three different groups.

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SYSTEMATIC REVIEW
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Effectiveness of Acupuncture in the Treatment of Parkinson's Disease: An Overview of Systematic Reviews

Jinke Huang[1†], *Xiaohui Qin*[2†], *Xiaowen Cai*[3] *and Yong Huang*[3*]

[1] The Second Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou, China, [2] Department of Neurology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine; Guangdong Provincial Academy of Chinese Medical Sciences), Guangzhou, China, [3] School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China

Background: The effects of acupuncture on Parkinson's disease (PD) outcomes remain unclear. The aim of this overview was to comprehensively evaluate the methodological quality and applicability of the results of systematic reviews (SRs)/meta-analyses (MAs) that examined the use of acupuncture to treat PD.

Methods: Eight databases were searched to retrieve SRs/MAs on the use of acupuncture for the treatment of PD. Two reviewers independently screened and extracted the data using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) checklist to evaluate the methodological quality and using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria to assess the evidence quality of the included reviews.

Results: A total of 11 SRs/MAs were included. According to the AMSTAR-2 checklist results, all included SRs/MAs were rated as very-low-quality studies. The GRADE criteria revealed 20 studies with very-low-quality evidence, 9 with low-quality evidence, 3 with moderate-quality evidence, and 0 with high-quality evidence. Descriptive analysis showed that acupuncture appears to be a clinically effective and safe treatment for PD.

Conclusions: The use of acupuncture for the treatment of PD may be clinically effective and safe. This conclusion must be interpreted cautiously due to the generally low methodological quality and low quality of evidence of the included studies.

Keywords: Parkinson's disease, acupuncture, systematic review, GRADE, AMSTAR-2

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Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Dennis Qing Wang, Southern Medical University, China
Rachel Paes Guimarães, Campinas State University, Brazil

***Correspondence:**
Yong Huang
nanfanglihuang@163.com

†These authors have contributed equally to this work

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INTRODUCTION

Parkinson's disease (PD) is an extrapyramidal movement disorder characterized by static tremors, myotonia, bradykinesia, postural instability, and gait difficulty (1). As the second most prevalent neurodegenerative disorder worldwide, it has been reported that 1–2% of the global population >65 years of age is affected by PD (2). It is expected that the prevalence of PD will nearly double by 2030 (3), which will lead to substantial economic pressure for families and society. In addition to motor symptoms such as rigidity and resting tremor, PD patients also have non-motor symptoms such as sleep disorders, hallucinations, and constipation that seriously affect the mental health and quality of life of patients (4).

PD is a complex and slowly progressive neurodegenerative disease associated with multiple risk factors (5). Age and gender, environmental and behavioral factors, and other disease factors (i.e., sleep disturbances, hypertension, and traumatic brain injury) have been shown to be increased risk factors for the development of PD (5, 6). These risk factors are not only crucial to the early diagnosis of PD but also helpful in the development of effective neuroprotection and health care strategies for appropriate populations at risk for PD (5, 7).

In terms of pathology, PD is closely associated with the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta of the brain caused by familial and/or sporadic factors (8). Although the pathogenic mechanism of PD has not been clarified, regardless of the pathogenic mechanism, the pathological features and clinical symptoms of PD are inextricably linked to the reduction in the number of DA neurons. On the study of the mechanism of the occurrence and development of DA neurons' death, researchers have proposed a variety of hypotheses, and the possible mechanisms with high recognition so far are as follows: (a) misfolding and accumulation of α-synuclein. In 1997, researchers discovered that point mutations in α-synuclein can lead to familial PD and that the main component of Lewy bodies associated with the pathogenesis of sporadic PD was also composed of misfolded and aggregated α-synuclein, from which the relationship between genetic factors and PD was first established. α-synuclein can not only activate the immune response within the brain but also activate the proliferation and differentiation of peripheral T cells, achieving immune-inflammatory damage in concert with B cells and microglia and inducing apoptosis in surrounding normal neurons (9). Furthermore, misfolding and aggregation of α-synuclein can lead to a sustained and uncontrolled endoplasmic reticulum stress response, which in turn activates autophagy and apoptotic signaling in cells and causes apoptosis (10). (b) mitochondrial dysfunctions and oxidative stress. Mitochondrial dysfunctions and oxidative stress are important pathogenetic mechanisms leading to the death of DA neurons in PD patients, and reactive oxygen species generated during this process can cause damage to organelles and nucleic acids. Since neuronal cells have higher metabolic activity than other cells, they are very sensitive to insufficient energy production caused by mitochondrial dysfunctions, and their non-renewable attributes also determine the permanence of reactive oxygen species damage (11). Causes of reactive oxygen species generation in PD patients include dopamine metabolism, reduced glutathione levels, disturbed ion levels, and calcium overload (12). Studies have confirmed that there was a large amount of reactive oxygen species in DA neurons of PD patients, which further corroborated the important role of reactive oxygen species in the pathogenesis of PD (13). (c) Neuroinflammation was involved in the pathogenesis and disease progression of PD. Neuroinflammation in the central nervous system is characterized by the activation of astrogliosis and microglia, which produce a large number of inflammatory factors (e.g., IL-6, IL-8, TNF-α, etc.), chemokines, cytokines, and neuromodulins, which produce a destructive effect on the blood–brain barrier while causing damage and apoptosis of surrounding DA neurons (14). Furthermore, gut microbiota, neurotrophic factors (NTF) deficiency, and others have also been shown to be associated with apoptosis and altered morphology and function of DA neurons (15, 16). Moreover, various biomarkers accompanying the pathogenesis of PD (e.g., plasma superoxide dismutase, lipoprotein cholesterol, high-sensitivity C-reactive protein, plasma lipoprotein-associated phospholipase A2, superoxide dismutase, trefoil factor 3, cholinesterase, and homocysteine) are of great value in the diagnosis of PD and disease severity assessment (17–20).

Drug and non-drug treatments for PD have been reported. Clinically approved drug treatments for PD mainly include levodopa, DA receptor agonists, and monoamine oxidase-B inhibitors. The most commonly used drugs are levodopa preparations; however, there are many complications that accompany the use of levodopa (21). Typical adverse events include both DA effects (e.g., dyskinesia, dystonia, freezing of gait, on–off, and wearing-off phenomena) and non-DA effects (e.g., gastrointestinal symptoms, insomnia, and depression) (22). Therefore, based on the pathogenesis of Parkinson's disease, researchers have attempted to seek effective complementary therapies, and the possible treatment ideas are as follows: (a) Enhance protein degradation pathways. Timely removal of excessive α-synuclein in the matrix and extracellular matrix of nerve cells can protect cells from toxicity. For example, PRX002 is an antibody to the C-terminal sequence of α-synuclein, which reduces protein aggregation in the extracellular matrix by specifically binding α-synuclein. The effect of PRX00 against Parkinson's disease has been validated by phase I clinical trials (23). (b) Enhance mitochondrial function. For example, Vitamin B3 can alleviate neurodegenerative diseases by increasing the intracellular content of NAD+/NADH and enhancing the function of the mitochondrial respiratory chain complex (24). (c) Reduce oxidative stress. Glutathione is an important antioxidant in the organism, and increasing the content of glutathione by intravenous injection can play an effective role in treating PD (25). Superoxide radical dismutation was considered as a novel therapeutic strategy for PD (26). Furthermore, for the progressive death of DA neurons, the search for a therapy in which cells can replace or grow into DA neurons has attracted attention, but such a therapy was still in the preliminary research stage and was not promoted in clinical practice (27–29). Gene therapy was also one of the PD treatment strategies, which could use viral vectors to carry target genes into specific brain regions and alleviated PD behavioral disorders through the expression of target genes, but this therapy was still not widely applied (30). Deep brain stimulation in the subthalamic nucleus, subthalamic nucleus, globus pallidus internus, pedunculopontine nucleus,

Abbreviations: PD, Parkinson's disease; SR, systematic review; MA, meta-analysis; AMSTAR-2, Assessing the Methodological Quality of Systematic Reviews 2; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCTs, randomized clinical trials; CNKI, China National Knowledge Infrastructure; UPDRS, Unified Parkinson's Disease Rating Scale; PDSS, Parkinson's Disease Sleep Scale; HAMD, Hamilton Depression Rating Scale; NTFs, neurotrophic factors; DA, dopaminergic; AD, Alzheimer's disease; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1; Nrf2, nuclear factor-E2-related factor-2.

and thalamic complex by an experienced team of experts may be an effective method to treat both motor and non-motor symptoms in patients with PD; however, clinical trials have shown that it may have cognitive and psychiatric side effects (31).

The above therapies have limitations, such as a single target of action, immature technology, adverse effects, and difficult operation. Therefore, many PD patients seek complementary and alternative therapies. Acupuncture, an economical treatment without adverse effects used in China for more than 2000 years, is widely used worldwide for nervous system disorders including PD. Although the mechanisms underlying the effectiveness of acupuncture for PD remain elusive, studies have shown that acupuncture may help to inhibit the accumulation of toxic proteins in neurological diseases, modulate energy supply based on glucose metabolism, and depress neuronal apoptosis, thus exerting a wide range of neuroprotective effects (32). The advantage of acupuncture therapy lies in having either specific target mechanisms of action or multitargets mechanisms of action. A growing number of systematic reviews (SRs) and meta-analyses (MAs) have been published on the clinical effectiveness and safety of using acupuncture for the treatment of PD, but the results have been conflicting and should be studied further. Therefore, we conducted an overview of SRs/MAs to identify and summarize the existing evidence and to systematically determine the clinical effectiveness and safety of using acupuncture to treat PD.

METHODS

We carried out this study based on high-quality methodological overviews (33, 34) and the Cochrane Handbook (35).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) study types: SRs/MAs in which the participants were patients with PD and were diagnosed according to any internationally recognized clinical guidelines; (b) intervention: acupuncture therapy (e.g., manual acupuncture, electroacupuncture, or auricular acupuncture) vs. conventional medication (e.g., madopar or levodopa) or acupuncture therapy combined with conventional medication vs. conventional medication alone; (c) outcomes: reviews that assessed the motor and non-motor symptoms of PD as the main outcome measures were considered eligible. Measures of quality of life and activities of daily living were included if they were relevant to the assessment of PD symptoms. Studies were excluded if they used acupuncture alone or combined with other drugs in the control group.

Search Strategy

We searched the PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Sino-Med, Chongqing VIP, and Wanfang Data databases from inception to Feb 2020. The keywords used for the search were as follows: Parkinson disease, acupuncture, systematic review, and meta-analysis. The search strategy for the PubMed database is shown in **Table 1**, and it was adjusted for each database. We also searched conference abstracts and the reference lists of all retrieved articles to avoid missing relevant SRs/MAs.

TABLE 1 | Search strategy for the PubMed database.

Query	Search term
# 1	Parkinson Disease [Mesh]
# 2	Parkinson Disease [Title/Abstract] OR Parkinson's Disease [Title/Abstract] OR Parkinsonism [Title/Abstract] OR tremor syndrome [Title/Abstract] OR Paralysis Agitans [Title/Abstract]
# 3	#1 OR #2
# 4	Acupuncture [Mesh]
# 5	Acupuncture [Title/Abstract] OR pharmacoacupuncture [Title/Abstract] OR acupotomy [Title/Abstract] OR acupotomies [Title/Abstract] OR pharmacopuncture [Title/Abstract] OR needle[Title/Abstract] OR needling [Title/Abstract] OR body-acupuncture [Title/Abstract] OR electroacupuncture [Title/Abstract] OR electro-acupuncture [Title/Abstract] OR auricular acupuncture [Title/Abstract] OR warm needle [Title/Abstract]
# 6	#4 OR #5
# 7	Meta-Analysis as Topic [Mesh]
# 8	Systematic review [Title/Abstract] OR Meta-Analysis [Title/Abstract] OR meta-analyses [Title/Abstract]
# 9	#7 OR #8
# 10	#3 AND #6 AND #9

Data Extraction

All included SRs/MAs were screened independently by two reviewers (XH-Q and JK-H), and the data from the reviews were validated and extracted according to the predefined assessment criteria for this study. Any disagreements between the reviewers were resolved by discussion or by consulting a third reviewer for a final decision.

Quality Assessment

Two reviewers (XH-Q and JK-H) independently evaluated the quality of the included articles by using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) checklist (36). Any discrepancies in the ratings of the 16 items from the AMSTAR-2 checklist were resolved by discussion and adjudication by an experienced and authoritative third reviewer (Y-H). The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) framework (37) was used to categorize the quality of evidence into four levels: high, moderate, low, or very low. The initial grading could be decreased if there are study limitations, inconsistencies, imprecision, indirectness, or publication bias (38). Any disagreements were resolved by consensus or discussion with an experienced and authoritative third reviewer (Y-H).

RESULTS

Literature Search

Our search identified 146 articles. After screening the titles and abstracts, 127 duplicates and ineligible studies were excluded. The remaining 19 records were considered to be of interest. After full-text review, eight reviews were excluded due to not being

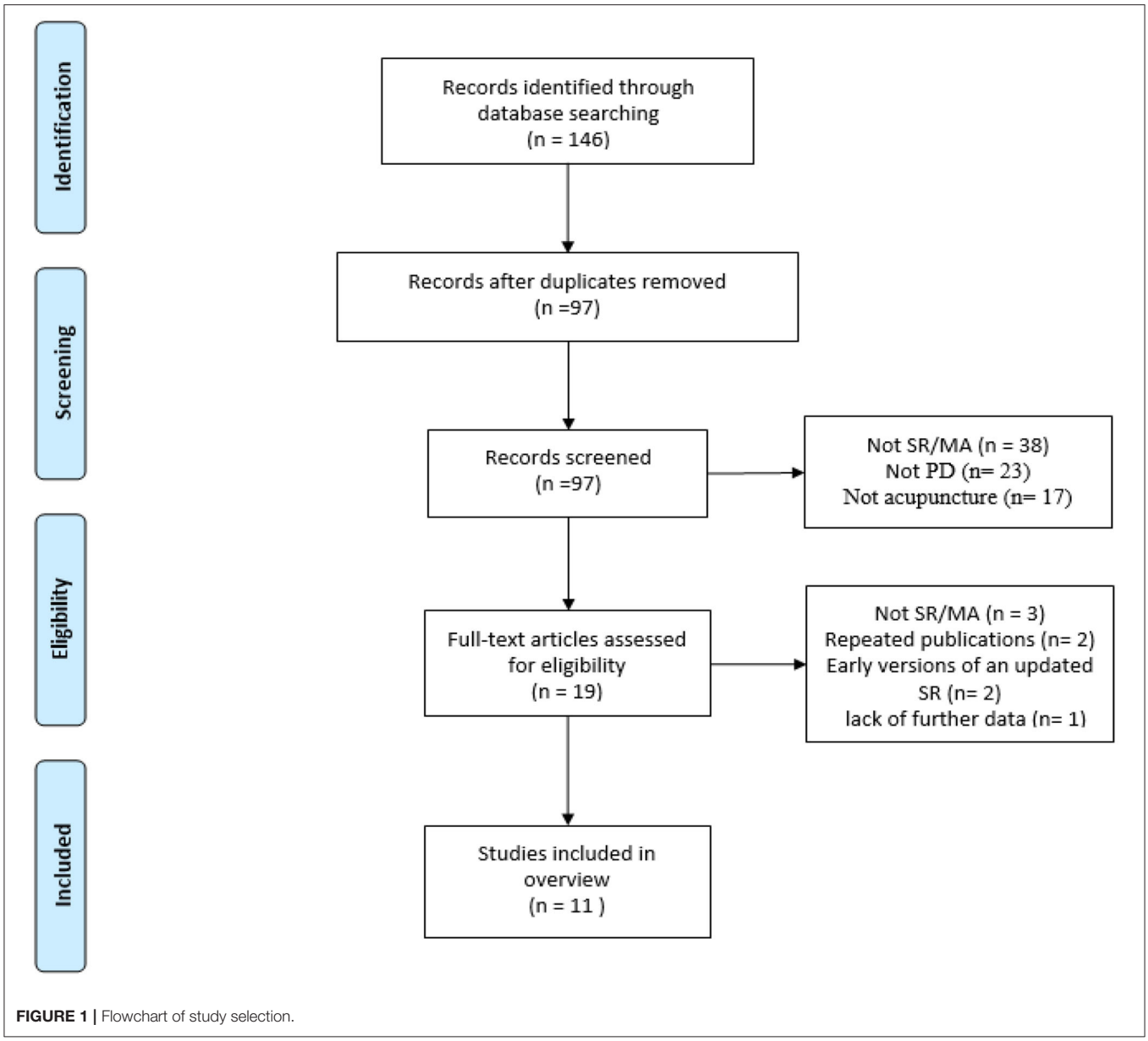

FIGURE 1 | Flowchart of study selection.

SRs/MAs ($n = 3$), being duplicate publications ($n = 2$), being early versions of an updated SR ($n = 2$), and lacking the necessary data ($n = 1$). Thus, 11 reviews (39–49) met the inclusion criteria and were included in the final analysis. **Figure 1** outlines the article selection process.

Characteristics of Included Reviews

The characteristics of the 11 SRs/MAs included in our final analysis are summarized in **Table 2**. They were published between 2010 and 2019, and 9 of them were published since 2015 (39–43, 45–48). The number of primary studies included in each review ranged from 8 to 42, and the sample sizes ranged from 474 to 2,625. The interventions in the therapy groups were mainly acupuncture or acupuncture plus medication, and the interventions in the control groups were mainly medication and sham placebo acupuncture. The conclusions from these reviews differed: 10 reviews reached the conclusion that acupuncture was effective in relieving PD symptoms, while the remaining 1 (47) reached the opposite conclusion.

Methodological Quality Results

The AMSTAR-2 assessment showed that all reviews had more than one critical item that was not met and were thus classified as very low quality (**Table 3**). The methodological limitations arose from three major items: item 2 (all included reviews were unregistered), item 4 (no gray literature search was performed in all included reviews), and item 7 (seven reviews did not assess the possible effect of publication bias). Other details can be found in **Table 3**.

TABLE 2 | Characteristics of the included reviews.

Reviews	Country	Trials (sample size)	Treatment intervention	Control intervention	Quality assessment tool	Conclusion summary
Liu et al. (39)	China	12 (864)	Scalp AT, Scalp AT + medication	Medication	Cochrane criteria	Scalp AT (or combined with medication) treatment was superior to medication alone in improving motor symptoms and activities of daily living in PD patients.
Liu et al. (40)	China	12 (892)	AT, EA, AT + madopar	Madopar	Jadad	Acupuncture had a certain clinical effect on PD—it can relieve the clinical symptoms of PD to some extent and postpone the progression of PD, which improves the quality of life of PD patients.
Ou and Xu (41)	China	21 (1,487)	AT, EA, AT + madopar	Madopar	Jadad	Acupuncture was effective in the treatment of PD and had few adverse reactions, and thus, it may be an effective and safe treatment for PD.
Gui et al. (42)	China	8 (590)	AT + madopar	Madopar	Cochrane criteria	Acupuncture combined with drug treatment of PD was slightly better than drug treatment alone.
Yin et al. (43)	China	9 (655)	AT, AT + medication	Medication	Cochrane criteria	The total effective rate of acupuncture for PD was significantly superior to those of the control group.
Sun and Zhang (44)	China	18 (1,325)	AT, AT+madopar	Madopar	Cochrane criteria	Acupuncture treatment had a certain effect on some non-motor symptoms of PD.
Qiang et al. (45)	China	9 (474)	SEA + medication	Medication	Cochrane criteria	The combination of SEA and medication may be a promising intervention for patients with PD, especially regarding the improvement of motor function.
Liu et al. (46)	China	11 (831)	AT + madopar	Madopar	Cochrane criteria	Acupuncture combined with Madopar appeared, to some extent, to improve clinical effectiveness and safety in the treatment of PD, compared with Madopar alone. This conclusion must be considered cautiously, given that the quality of most of the studies included was low.
Noh et al. (47)	Korean	42 (2,625)	AT, EA, AT + medication	Medication, placebo acupuncture	Cochrane criteria	A combination of electroacupuncture and medication was not significantly more effective than medication alone based on the UPDRS III, the Webster Scale, and the Tension Assessment Scale. The results also failed to show that acupuncture was significantly more effective than placebo acupuncture in total UPDRS.
Lee and Lim (48)	Korean	25 (982)	AT, AT + madopar	Madopar, no treatment	PEDro score	Acupuncture was effective in relieving PD symptoms compared with no treatment and conventional treatment alone, and acupuncture plus conventional treatment had a more significant effect than conventional treatment alone.
Yang et al. (49)	China	13 (832)	AT	Madopar	Jadad	Acupuncture was safe and effective in the treatment of PD. Acupuncture plus Western drugs may be superior to Western drugs alone.

AT, acupuncture therapy; EA, electroacupuncture; SEA, scalp electroacupuncture.

GRADE Results

The 11 SRs/MAs included 32 outcomes related to the effectiveness of acupuncture for treating PD. The GRADE assessment revealed that no outcomes had high-quality evidence, and only three outcomes provided moderate-quality evidence (**Table 4**). The evidence was downgraded because of the following limitations: (1) All the original RCTs were of low quality. The bias of randomization, blinding, and allocation concealment decreased the validity of the GRADE approach. (2) For 27 (27/32, 84.4%) outcomes, we downgraded the quality of evidence based on publication bias owing to the incomprehensive literature search as well as the number of RCTs. (3) For 18 (18/32, 56.3%) outcomes, we downgraded the quality of evidence based on imprecision owing to the wide confidence intervals or small

TABLE 3 | Result of the AMSTAR-2 assessments.

Reviews	AMSTAR-2																Quality
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	
Liu et al. (39)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	VL
Liu et al. (40)	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Ou and Xu (41)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	VL
Gui et al. (42)	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Yin et al. (43)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	VL
Sun and Zhang (44)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	VL
Qiang et al. (45)	Y	PY	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	VL
Liu et al. (46)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	VL
Noh et al. (47)	Y	PY	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	VL
Lee and Lim (48)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	VL
Yang et al. (49)	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	VL

Y, Yes; PY, partial Yes; N, No; VL, Very low; L, Low; H, High.

number of participants (<300). (4) For 10 (10/32, 31.3%) outcomes, we downgraded the quality of evidence based on inconsistency owing to the high heterogeneity. Other details can be found in **Table 4**.

OUTCOMES

Effective Rate

A total of seven reviews (40, 42, 43, 45, 46, 48, 49) analyzed the effective rate of acupuncture for PD. In six reviews (40, 42, 43, 45, 46, 48) that used effective rate to compare the effects of acupuncture plus madopar treatment vs. madopar treatment alone, the combined treatment had a significantly greater effect on PD symptoms. Two reviews (48, 49) used effective rate to compare the effects of acupuncture vs. madopar treatment alone. The results of Lee (48) showed that acupuncture treatment had a significant effect on PD symptoms [RR = 1.71, 95% CI (0.99,2.96), $P = 0.06$], while the results of Yang (49) showed that there was no significant difference between treatments [RR = 1.17, 95% CI (0.89, 1.54), $P = 0.1$]. One study (48) used effective rate to compare the effects of acupuncture vs. no treatment and found that acupuncture had a significantly greater effect on PD symptoms [MD = 7.36, 95% CI (5.58, 9.14), $P < 0.00001$].

UPDRS Score

Eight reviews (39–41, 44–48) compared the effects of acupuncture plus madopar treatment vs. madopar treatment alone using the UPDRS score, and the results showed that the combined treatment had a greater effect than madopar treatment alone. However, one review compared the effects of acupuncture vs. madopar alone and found no significant difference in the UPDRS score between treatments [WMD = −2.55, 95% CI (−11.15, 6.05), $P = 0.56$]. In addition, Noh et al. (47) compared the effects of acupuncture vs. placebo acupuncture and observed no significant effect of acupuncture on PD symptoms [MD = −2.46, 95% CI (−11.36, −6.45), $P = 0.59$].

The Webster Scale

Six reviews (39–41, 44, 45, 48) used the Webster Scale to compare the effects of acupuncture plus madopar vs. madopar alone and found that the combined treatment had a greater effect than madopar alone. In two reviews (41, 48) that used the Webster Scale to compare the effects of acupuncture vs. madopar, a significant effect of acupuncture on PD symptoms was observed [WMD = −2.50. 95% CI (−2.77, −2.23), $P < 0.00001$; WMD = 3.08, 95% CI (2.81, −3.35), $P < 0.001$]. Lee et al. (48) compared the effects of acupuncture vs. no treatment and observed that acupuncture had a significant effect on PD symptoms [WMD = 7.36, 95% CI (5.58, 9.14), $P < 0.001$].

Other Outcomes

One study (39) compared the effects of acupuncture plus madopar vs. madopar alone on the HAMD score, and the results showed that combined treatment had a greater effect than madopar alone [SMD = −4.42, 95% CI (−6.44, −2.39), $P < 0.0001$]. Sun et al. (44) compared the effects of acupuncture plus madopar vs. madopar alone on the PDSS score, and the results showed that the combined treatment had a significant effect on PD symptoms [SMD = 2.67, 95% CI (−0.27, 5.60), $P = 0.08$].

Adverse Events

One review (46) showed that acupuncture combined with madopar in the treatment of PD may not significantly improve dyskinesia but may significantly relieve gastrointestinal reactions, on–off phenomena, and mental disorders.

DISCUSSION

Neurological diseases can manifest a series of symptoms due to abnormalities in nerve structure, biochemistry, or electrophysiology in the brain, spinal cord, or other nerve (6). Most of them are characterized by progressive neurodegeneration and injury closely related to aging, including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis, et cetera. Although the pathogenesis of neurodegenerative diseases

TABLE 4 | GRADE evaluation results.

Reviews	Interventions	Outcomes	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
Liu et al. (39)	Scalp AT + madopar vs. Madopar	Webster scale score	−1①	0	0	0	−1④	L
		UPDRS score	−1①	−1②	0	−1③	−1④	VL
		PDSS score	−1①	0	0	−1③	−1④	VL
Liu et al. (40)	AT + madopar vs. Madopar	Effectiveness	−1①	0	0	0	−1④	VL
		Webster scale score	−1①	−1②	0	0	−1④	VL
		UPDRS score	−1①	0	0	−1③	−1④	VL
Ou and Xu (41)	AT + madopar vs. Madopar	UPDRS score	−1①	−1②	0	−1③	−1④	VL
		Webster scale score	−1①	0	0	−1③	−1④	VL
	AT vs. Madopar	UPDRS score	−1①	−1②	0	−1③	−1④	VL
		Webster scale score	−1①	0	0	−1③	−1④	VL
Gui et al. (42)	AT + madopar vs. Madopar	Effectiveness	−1①	0	0	0	−1⑤	L
Yin et al. (43)	AT + madopar vs. Madopar	Effectiveness	−1①	0	0	0	−1⑤	L
Sun and Zhang (44)	AT + madopar vs. Madopar	HAMD score	−1①	0	0	0	−1④	L
		UPDRS I score	−1①	−1②	0	0	−1④	VL
		UPDRS II score	−1①	0	0	0	−1④	L
		Webster scale score	−1①	0	0	0	−1④	L
Qiang et al. (45)	SEA + medication vs. Medication	UPDRS score	−1①	−1②	0	−1③	−1④	VL
		Webster scale score	−1①	0	0	−1③	−1④	VL
		Effectiveness	−1①	0	0	0	0	M
Liu et al. (46)	AT + madopar vs. Madopar	Effectiveness	−1①	0	0	0	0	M
		UPDRS score	−1①	−1②	0	0	−1④	VL
		Adverse events	−1①	0	0	−1③	−1④	VL
Noh et al. (47)	AT + medication vs. Medication	UPDRS score	−1①	0	0	−1③	0	M
	EA + medication vs. Medication	UPDRS score	−1①	0	0	−1③	0	L
	AT vs. placebo AT	UPDRS score	−1①	0	0	−1③	0	L
Lee and Lim (48)	AT + madopar vs. Madopar	UPDRS score	−1①	0	0	0	−1④	L
		Webster scale score	−1①	−1②	0	−1③	−1④	VL
		Effectiveness	−1①	−1②	0	−1③	−1④	VL
	AT + madopar vs. Madopar	Webster scale score	−1①	0	0	−1③	−1④	VL
		Effectiveness	−1①	0	0	−1③	−1④	VL
	AT vs. no treatment	Webster scale score	−1①	0	0	−1③	−1④	VL
		Effectiveness	−1①	0	0	−1③	−1④	VL
Yang et al. (49)	AT vs. Madopar	Effectiveness	−1①	−1②	0	−1③	−1④	VL

VL, Very low; L, Low; M, Moderate; H, High. AT, acupuncture therapy; EA, electroacupuncture; SEA, scalp electroacupuncture; UPDRS, Unified Parkinson's Disease Rating Scale; PDSS, Parkinson's Disease Sleep Scale; HAMD, Hamilton Depression Rating Scale; ①: The experimental design had a large bias in random, distributive findings or was blind. ②: The confidence intervals overlapped less, the P-value for the heterogeneity test was very small, and the I^2 was larger. ③: The confidence interval was not narrow enough. ④: Fewer studies were included, and there may have been greater publication bias. ⑤: Funnel graph asymmetry.

varies, they still share many common pathogenic features and mechanisms, such as misfolded protein aggregation, neuronal apoptosis, synaptic loss, neurotransmitter abnormalities, et cetera (50, 51).

Acupuncture, an effective and safe treatment method used in China for more than 2000 years, has been widely used worldwide for various neurological diseases. In various models of neurological diseases, peripheral nerve stimulation using acupuncture may have protective effects on neural tissues by increasing expression of NTFs, such as brain-derived NTF and glial-derived NTF, in the central nervous system, especially the brain (52). Furthermore, acupuncture may contribute to recovery from functional impairments following brain damage by encouraging neural stem cell proliferation, which is active at the initial stage of injury, and by further facilitating differentiation (52). Therefore, acupuncture may act as a stimulator to activate peripheral nerves at specific acupoints and induce the expression of various NTFs. Subsequently, NTFs induced by this treatment trigger autocrine or paracrine signaling, which stimulates adult neurogenesis and thus exerts therapeutic effects on functional impairment in neurological disorders (28, 52).

Acupuncture has been shown to be neuroprotective in neurodegenerative disorder such as PD and AD (14, 53). Acupuncture exerts its therapeutic effects by activating and increasing the expression of brain NTFs, including brain-derived NTF and glial-derived NTF. Moreover, acupuncture

can stimulate the proliferation and differentiation of NTFs, which in turn activate and promote adult neurogenesis (8). NTF levels are regulated by the therapeutic effects of acupuncture and are associated with enhanced survival, proliferation, and differentiation of NTFs. Acupuncture enhances the expression of NTFs, which may stimulate neurogenesis and thus exert a therapeutic effect on the functional recovery in neurological diseases (50). Therefore, one possible neurophysiological mechanism for the therapeutic effects of acupuncture is to regulate the plasticity of the brain (52). There may also be a synergistic effect when acupuncture was combined with medication, again promoting neurogenesis (52).

With the widespread use of acupuncture as a complementary and alternative therapy for PD, the mechanism of action of acupuncture in the treatment of PD has been extensively studied, and the possible mechanisms of its therapeutic effect for PD are as follows: (a) Neuronal survival. Further mechanism studies have confirmed the neuroprotective effects of acupuncture via the activation of survival pathways of Akt and brain-derived NTF in the substantia nigra region. It was confirmed that acupuncture increased the DA neuronal survival via the nigrostriatal pathway, the expression of DJ-1, and the activities of superoxide dismutase and catalase in the striatum (8). Furthermore, researchers reported that acupuncture can activate the hypothalamic melanin-concentrating hormone biosynthesis and attenuate the reduction of tyrosine hydroxylase in the substantia nigra region (50). (b) Neurotransmitters. Researchers reported that acupuncture was able to improve striatal dopamine levels and enhance dopamine availability, which in turn improved motor function (54). The experiment demonstrated that acupuncture could enhance memory and neuronal density in CA3 and dentate gyrus of PD mouse model, while increasing glutathione peroxidase, and decreasing acetylcholinesterase, monoamine oxidase B, and malondialdehyde in the hippocampus (50). Additionally, proteomic analysis demonstrated that acupuncture reversed a variety of proteins in the lesioned motor cortex of the PD model that may be involved in maintaining the balance of neurotransmitters (55). (c) α-synuclein. Researchers reported that acupuncture stimulation promoted the autophagic clearance of α-synuclein and mammalian target of rapamycin-independent autophagic clearance of aggregation-prone proteins in a PD mouse model (56). (d) Neuroinflammation. Further studies showed that acupuncture suppressed tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in the striatum and midbrain, while it improved nuclear factor-E2-related factor-2 (Nrf2) and Nrf2-regulated antioxidant enzymes in the PD model. In addition, acupuncture could also play a protective role in cranial nerves by regulating blood pressure and improving cerebral circulation (57, 58). Some of the above mechanisms have also been confirmed by imaging-based research in PD patients (50, 59). Overall, acupuncture, like other neuroprotective agents, is anti-inflammatory, antioxidative, antiapoptotic, and neurotrophic, and the advantage of acupuncture therapy lies in having either specific target mechanisms of action or multitarget mechanisms of action (46).

In this overview, the findings regarding the effectiveness of acupuncture for treating PD were as follows. (a) Eleven SRs/MAs examining the use acupuncture for treating PD were included in this overview, and nine (9/11, 81.82%) of them had been published since 2015, indicating that the scientific interest in using acupuncture for PD patients is increasing. The country with the highest number of included SRs was China (9/11, 81.82%), which is the birthplace of acupuncture. (b) Of the included reviews, 90.9% reached positive conclusions. The effect of acupuncture on relieving PD symptoms seems to be better than that of the effects of control treatments, and acupuncture may significantly relieve side effects (e.g., gastrointestinal reaction and mental disorders). However, most SRs/MAs did not draw firm conclusions due to small sample sizes or their low methodological quality. Further research is needed to provide higher-quality SRs/MAs and RCT-based evidence for the use of acupuncture to treat PD. (c) There is considerable room for addressing the methodological quality of the included SRs/MAs. All included SRs/MAs had multiple critical criteria that were unmet (e.g., being unregistered, lacking a gray literature search). Future studies could avoid these obvious deficiencies to improve methodological quality. (d) There is also considerable room for addressing the methodological quality of RCTs. The GRADE results showed that the evidence quality of all outcomes was downgraded because of the risk of bias. Most of these RCTs did not mention the generation of random sequences in detail; most of them did not specifically describe allocation concealment, and the process of allocation concealment was unclear. Because of the nature of acupuncture, only a small part of the included RCTs mentioned blinding. Well-designed and implemented RCTs are considered gold standards for avoiding the risk of bias (60).

A total of 11 SRs/MAs were included in this overview, and the methodological quality evaluation was very low. By comparing and analyzing the clinical efficacy of acupuncture or acupuncture combined with conventional drugs in the treatment of Parkinson's disease, the clinical effective rate, UPDRS score, Webster Scale score, HAMD score, PDSS score, and the main motor symptoms of Parkinson's disease were analyzed. The results showed that the effective rate, UPDRS score, Webster Scale score, HAMD score, and PDSS score in the treatment group were significantly more improved than those in the control group. These results indicate that acupuncture treatment can improve some motor and non-motor symptoms in patients with Parkinson's disease, which may act by regulating neurotransmitter balance, regulating immunity, reducing oxidative stress, and improving brain electrical function. An analysis of the improvement of specific symptoms of Parkinson's disease revealed that acupuncture significantly improved bradykinesia, myotonia, and postural gait, but there was no significant difference in resting tremor between acupuncture and madopar treatment. This may be related to the fact that acupuncture treatment can only produce corresponding pathophysiological changes in the body through indirect acupoint stimulation and microregulate the internal environment of the lesion circuit but cannot directly supplement reduced dopamine to improve transmitter imbalance. These results are helpful for guiding the selective use of acupuncture as an adjuvant therapy according to different clinical manifestations (61).

Strengths and Limitations

To our knowledge, our study is the first overview of SRs/MAs on the use of acupuncture for treating PD, and the findings of this overview were based on relatively recent evidence, as 81.82% of the included SRs/MAs were conducted in the past 5 years. However, there are some limitations that need to be considered. First, the methodological quality and evidence quality of the included SRs/MAs were generally low; thus, results based on primary studies should be interpreted with caution. Furthermore, we only searched Chinese and English databases, so SRs/MAs published in other languages that met the inclusion criteria may have been missed.

CONCLUSION

Acupuncture may be a promising treatment for patients with PD, and it may be especially effective at improving motor function. This conclusion must be interpreted cautiously, given the generally low methodological quality and low quality of evidence of the included SRs/MAs. Additional studies with rigorous experimental designs and larger sample sizes are needed to verify these results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JH and XQ designed this study. JH, XQ, and YH performed the data extraction and statistical analysis. JH, XQ, XC, and YH revised and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Prodromal Markers of Parkinson's Disease in Patients With Essential Tremor

Xi-Xi Wang[1,2†], Ya Feng[1†], Xuan Li[1], Xiao-Ying Zhu[1], Daniel Truong[3,4], William G. Ondo[5] and Yun-Cheng Wu[1]*

[1] Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Shanghai General Hospital of Nanjing Medical University, Nanjing, China, [3] Orange Coast Memorial Medical Center, The Truong Neurosciences Institute, Fountain Valley, CA, United States, [4] Department of Neurosciences and Psychiatry, University of California, Riverside, Riverside, CA, United States, [5] Weill Cornell Medical School, Methodist Neurological Institute, Houston, TX, United States

Background: Essential tremor (ET) is manifested as an isolated syndrome of bilateral upper limb action tremor. Parkinson's disease (PD) is the second most common neurodegenerative disease, with typical motor symptoms of bradykinesia, rigidity, and resting tremor. ET-PD describes the new-onset of PD in ET patients. Recently, numerous studies on epidemiology, genetics, pathology, clinical features, and neuroimaging studies are challenging the idea that ET is an isolated disease, suggesting that patients with ET have the tendency to develop PD.

Methods: In this review article, we collected recent findings that reveal prodromal markers of PD in patients with ET.

Results: Substantia nigra hyperechogenicity serves as a prodromal marker for predicting the development of PD in patients with ET and provides a reference for therapeutic strategies. Additional potential markers include other neuroimaging, clinical features, heart rate, and genetics, whereas others lack sufficient evidence.

Conclusion: In consideration of the limited research of PD in patients with ET, we are still far from revealing the prodromal markers. However, from the existing follow-up studies on ET patients, Substantia nigra hyperechogenicity may enable further exploration of the relationship between ET and PD and the search for pathogenesis-based therapies.

Keywords: essential tremor, Parkinson's disease, ET-PD, prodromal markers, substantia nigra hyperechogenicity

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***Correspondence:**
Yun-Cheng Wu
yunchw@medmail.com.cn

[†] *These authors have contributed equally to this work*

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INTRODUCTION

Essential tremor (ET) is defined as an isolated postural and/or kinetic tremor syndrome of the bilateral upper limbs, with or without tremor in other locations (e.g., head, voice, or lower limbs). The traditional idea proposes that no other neurological signs such as dystonia, ataxia, or parkinsonism are present (1–3), although ET is sometimes considered a diagnostic of exclusion (4). With accumulated studies on ET, researchers today recognize the concept of ET plus (3), which refers to tremor with the characteristics of ET and additional neurological signs such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs. However, these additional neurological signs are of unknown significance and are insufficient to

make an additional syndrome classification or diagnosis. Dividing ET into two categories (ET and ET plus) is helpful in determining pathophysiological characteristics and therapeutic strategies.

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by the degeneration of dopaminergic neurons in the substantia nigra (SN) and reduced dopamine levels in the midbrain (5–8). The pathological hallmark of PD is the presence of Lewy bodies, and the classical motor symptoms of PD are bradykinesia, rigidity and resting tremor, and numerous non-motor symptoms including constipation, hyposmia/anosmia, rapid eye movement sleep behavior disorder (RBD), and so on (9).

ET-PD referred to in this article means new onset of PD in patients previously diagnosed with ET. Essential tremor has been traditionally viewed as a "benign" disease; however, accumulated data from the studies of clinical characteristics, epidemiology, neuroimaging, genetics, and pathology support a poorer prognosis than originally believed (10–12). Evidence indicates that patients with ET are four times more likely to develop PD than those without baseline ET (13). Additionally, nigrostriatal degeneration developed before the onset of motor symptoms of parkinsonism (14, 15). Sensitive and effective prodromal markers predicting which ET patients will subsequently develop PD are needed to further understand the biological nature of ET, which will provide a pathology-based categorization, diagnosis, prognosis, and eventual treatment of ET.

NEUROIMAGING

Transcranial Sonography

Transcranial sonography (TCS) can show the structure of the brain parenchyma and reveal the lesions of the SN. It is anecdotally viewed as a non-invasive tool that can be utilized to detect the intensity of the SN and measure the ratio of the hyperechoic area to midbrain area (S/M ratio). The SN hyperechogenicity refers to the high intensity and large area (>0.8–0.2 cm^2) of the echo in the SN shown by transcranial ultrasound.

As early as 1995 (16), scientists first described the mysterious relationship between SN hyperechogenicity and PD, which provided a new perspective and direction for research. It was verified that SN hyperechogenicity as reflected by TCS, seemed to be a prodromal marker for PD (17–20). In 2007, research including 164 healthy Taiwanese, 40 early-onset PD patients, and 40 late-onset PD patients focused on the area of SN hyperechogenicity and the S/M ratio (21). The results indicated that the S/M ratio is a more sensitive marker than SN hyperechogenicity in diagnosing PD. Based on the investigation that tremor-dominant PD (TDPD) patients had significantly higher nigral R2* relaxation rate values in magnetic resonance imaging (MRI) (34.1 ± 5.7) than those with tremor in dystonia (30.0 ± 3.9), ET (30.6 ± 4.8), and controls (30.0 ± 2.8). This and other research confirm that increased iron content in the SN is significantly associated with PD. Afterward, combining iron metabolism and the features of TCS (22, 23), researchers presumed that the change of the echogenicity in the SN may be attributed to oxidative stress and the injury of neurons caused by the fluctuation of iron content. In a prospective multicenter study, researchers also demonstrated that the elderly with SN hyperechogenicity had a higher risk of developing PD (24).

Transcranial sonography measurement of the midbrain is a sensitive and specific preliminary screening method to identify certain population with higher risk of developing PD. A small trial also supported its use at predicting ET patients who will develop PD, but this needs to be replicated in larger trials (25). After performing TCS of the SN and clinical examination in 80 PD patients, 30 ET patients, and 80 age- and gender-matched controls, researchers realized that SN hyperechogenicity may be associated with an increased risk developing PD later in life or might be due to the damage of areas near the nucleus ruber in ET patients (26). Subsequently, Sprenger et al. (27) conducted a prospective cohort study in 70 ET patients, which evaluated demographics, TCS, Bain tremor scale, and Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale. After an average of 6.16 years' follow-up, they identified nine ET-PD patients, seven of whom had SN hyperechogenicity greater than baseline. Statistical analysis showed that the relative risk of developing PD in patients with ET who had hyperechogenicity at baseline vs. those without hyperechogenicity was 7.00 (27). Moreover, a recent longitudinal study demonstrated that after 3 years' follow-up, 9 of 59 ET patients developed clinical features meeting diagnostic criteria for probable PD (ET-PD), and this group had a significantly greater SN hyperechogenicity at baseline from healthy controls (28).

Several studies have consistently demonstrated that SN hyperechogenicity on TCS is a prodromal marker for development of PD in ET patients (29, 30). It serves as a visualization tool for the diagnosis and prognosis of ET patients. Different characteristics of the echo are associated with not only the diagnosis of PD but also the therapeutic response (31). Hence, in addition to differential diagnosis between PD and other movement disorders (32), SN hyperechogenicity can also serve as a prodromal marker for predicting the development of PD in patients with ET and provide a guidance for therapeutic strategy (**Table 1**).

Other Neuroimaging

Brain structural and functional neuroimaging methods might show abnormalities in ET patients. Voxel-based morphometry (VBM) is commonly used to learn about gray matter and white matter size. Benito-Leon et al. (33) found significant white matter changes in right cerebellum, left medulla, right parietal lobe, and right limbic lobe, as well as gray matter alteration in bilateral cerebellum, bilateral parietal lobe, right frontal lobe, and right insula in ET patients compared with 20 age- and gender-matched healthy controls. Lin et al. (34) compared VBM in 10 ET patients with 10 PD patients and revealed that PD and ET caused specific patterns of brain volume alterations in the examined brains. The brain volume of the ET group was significantly smaller in the

Abbreviations: ET, essential tremor; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder; SN, substantia nigra; TCS, Transcranial sonography; TSI, Tremor Stability Index; RBDSQ, RBD screening questionnaire; pRBD, probable RBD; SS-16, 16-item Sniffin' Sticks test; HRV, Heart rate variability; TDPD, tremor-dominant PD.

TABLE 1 | Studies on SN hyperechogenicity indicate a role in prediction of the risk of PD.

Time & Country & Reference	Subjects	Results
1995. Germany (16)	30 patients with PD and 30 age- and sex-matched non-Parkinsonian controls	The degree of hyperechogenicity of the SN closely correlated with the severity and duration of PD.
2001. Germany (19)	93 subjects older than 60 years without history of extrapyramidal disorder	With increasing age, subjects with SN hyperechogenicity develop a more substantial slowing of movements than subjects without this echo pattern, stressing the functional relevance of this sonographic finding.
2004. Germany (18)	7 symptomatic and 7 asymptomatic PMC from large kindred with adult-onset parkinsonism	SN hyperechogenicity is an early marker to detect preclinical Parkinsonism.
2007. Taiwan (21)	164 healthy Taiwanese, 40 EOPD patients, and 40 LOPD patients	S/M ratio is a more sensitive measure than SN hyperechogenicity in diagnosing PD.
2011. Germany (20)	1,847 participants who are 50 years or older without evidence of PD or any other neurodegenerative disease	A highly increased risk for PD in elderly individuals with SN hyperechogenicity.
2013. Germany (24)	1,271 of the initial 1,847 at baseline PD-free participants 50 years or older,	SN hyperechogenicity is an important risk marker for PD.
2007. Austria (25)	44 ET patients with 100 controls and 100 PD patients	An increased risk of ET patients to develop PD.
2016. Austria & Germany (27)	70 patients suffering from ET	SN hyperechogenicity is also associated with an increased risk for PD in patients with ET.
2019. Italy (28)	79 with PD, 59 with ET and 50 matched controls	SN hyperechogenicity in ET seems to represent a risk marker for developing early parkinsonian symptoms or signs in the 3 years following TCS assessment.

SN, substantia nigra; PD, Parkinson's disease; PMC, parkin mutation carriers; EOPD, early-onset PD; LOPD, late-onset PD; S/M ratio, the ratio of hyperechoic area to midbrain area; ET, essential tremor.

thalamus and the middle temporal gyrus and larger of the gray matter in the middle frontal gyrus, the middle temporal gyrus, and the cerebellum posterior lobe than that of the PD group (34). These studies suggested comprehensive changes in the gray and white matter of brain in ET patients.

Diffusion tensor imaging (DTI) derived mean diffusivity (MD) and fractional anisotropy. It exhibits great fidelity in showing brain microstructure and connections. A DTI-based study performed in 67 ET patients (29 ET with and 38 without resting tremor) and 39 age-matched healthy controls indicated that MD was significantly higher in the cerebellar gray matter in the ET group. It demonstrates that ET patients have cerebellum microstructural changes, and some other networks alterations may exist in the development of ET (35).

After enrolling 15 ET patients with resting tremor and 15 TDPD patients, Cherubini et al. (36) did a combination of VBM and DTI to distinguish these two groups with a ground truth of Dopamine transporter 123I-FP-CIT-single-photon emission tomography (DAT-SPECT), and they found the combination shows 100% accuracy in differentiating these two groups.

Proton MR spectroscopy (^{1}H-MRS) is a non-invasive, quantitative technique that reflects the neurometabolic alterations *in vivo*. There are many biochemical markers including NAA/Cr (a neural density marker), Glx/Cr (an intracellular neurotransmitter marker), and Cho/Cr (a membrane marker). In 2002, researchers measured 16 ET patients and 11 controls with MRS and found that cortical NAA/Cr in the cerebellar was reduced in ET cases, and the value was inversely proportional to arm tremor severity (37). With the application of a 3-T scanner, Barbagallo et al. (38) found a statistically significant increase in Glx and Glx/Cr values in 16 ET patients in both thalami compared to 14 healthy controls, and the tremor severity was directly proportional to these two values. These results suggested that increased thalamic glutamatergic transmission and cerebellum play a role in the pathogenesis in ET. In addition to these imaging techniques (**Table 2**), MRI imaging focused on brain iron deposition, and functional MRI and other neuroimaging methods also indicated the details of the involved brain networks in ET and provided some help to differentiate mixed tremor, ET, and PD (39–41). Even though some of the research did not explore prodromal markers of PD in ET patients from a longitudinal-study perspective, it still reflects the relationship between the two disorders, provides methods in differential diagnosis, and promotes the knowledge of behind pathophysiologic mechanisms.

CLINICAL CHARACTERISTICS

Identifying clinical characteristics that increase the risk of developing PD in ET patients may help in the development of potential disease-modifying therapies. Essential tremor classically presents as a bilateral but asymmetric kinetic and postural tremor of the upper limbs, head, voice, or a combination. Parkinson disease is generally manifested as asymmetric symptoms of bradykinesia, rigidity, resting tremor, and later postural instability. Many studies have summarized the similarities and differences of the two diseases based on clinical characteristics (i.e., motor and non-motor symptoms) (30, 42, 43), but there are still few prodromal markers with respect

TABLE 2 | Studies on other neuroimaging about prodromal markers of new-onset PD in ET patients.

	Neuroimaging techniques	Subjects	Results	References
Structural neuroimaging	VBM	ET vs. healthy controls	White and gray matter of many brain regions changed in ET patients	(33)
		ET vs. PD	PD and ET caused specific patterns of brain volume alterations	(34)
	DTI	ET vs. healthy controls	MD was significantly higher in the cerebellar gray matter of ET group, indicating cerebellum microstructural changes and some other networks involved	(35)
	VBM+DTI	ET vs. PD	Combination of two methods helps in differentiating two kinds of patients	(36)
Metabolic neuroimaging	1H-MRS	ET vs. healthy controls	Cortical NAA/Cr in the cerebellar was reduced in ET cases and the value was inversely proportional to arm tremor severity	(37)
		ET vs. healthy controls	Glx and Glx/Cr values increased in both thalami of ET patients and the value was proportional to tremor severity, indicating thalamic glutamatergic transmission and cerebellum invloved	(38)
	Iron deposition	ET vs. healthy controls	Iron accumulation increased in ET patients, suggesting a possible involvement of motor systems outside of the cerebellar pathway	(39)
Functional neuroimaging	DAT-SPECT+MIBG	Mixed tremor vs. PD vs. ET vs. controls	Combined use of these two techniques can help distinguish ET patients from PD patients and parkinsonism	(40)
	fMRI	ET VS healthy controls	Cerebellar neurodegeneration underlying essential tremor is reflected in abnormal communications between key working memory regions and that adaptive mechanisms involved in to influence cognition	(41)

VBM, voxel-based morphometry; PD, Parkinson's disease; ET, essential tremor; DTI, Diffusion tensor imaging; MD, Mean diffusivity; 1H-MRS, Proton MR Spectroscopy; NAA, N-acetyl-aspartate + N-acetyl-aspartyl-glutamate; Cr, creatine + phosphocreatine; Glx, glutamate + glutamine; DAT-SPECT, Dopamine transporter 123I-FP-CIT-single-photon emission tomography; MIBG, myocardial scintigraphy with 123metaiodobenzylguanidine.

TABLE 3 | Clinical characteristics which can predict the risk of ET patients developing into PD.

Clinical characteristics	Prodromal markers	References
Tremor	Circumscribed resting tremor	(44)
	Late onset asymmetrical postural tremor	(45)
	Jaw tremor in ET	(46, 47)
	A kinematic data: TSI	(48)
Non-motor symptoms	Olfactory decline (hyposmia/anosmia)	(49–51)
	Cognitive decline	(52–54)
	Sleep disorder, especially RBD	(55–59)
	RBD & autonomic symptoms	(60)

ET, essential tremor; PD, Parkinson's diseases; TSI, the tremor stability index; RBD, REM sleep behavior disorder.

to the clinical characteristics of ET-PD patients, and many of them are still in the conjecture stage (**Table 3**).

Tremor

An epidemiological survey showed that tremor of the upper limbs was presented in more than 95% of the ET patients, followed by the head (>30%), voice (>20%), tongue (20%), face and/or jaw (10%), lower limbs (10%) and trunk (5%) (61, 62). Essential tremor and PD tremor are mainly identified based on aspects of location, frequency, and form. However, few studies have identified risk markers based on tremor characteristics in ET patients who have the potential to develop PD.

The location of tremor in the two groups was most common in upper limbs, whereas the prevalence of resting tremor in ET-PD patients was higher than that in patients with isolated ET, and the tremor distribution was more limited in ET-PD ($p < 0.05$) (30). Another study involving 53 ET-PD patients and 150 ET patients noted a biased distribution toward male (67.9% male) of ET-PD, which is identical to that of PD (67.9% male) (44). The latency from the onset of ET to develop into PD ranged from short duration (<5 years, in 38.5%) to long duration (>20 years), with a mean duration of 14 ± 15 years. In ET-PD patients, the side of dominant initial ET severity usually coincides with that of dominant PD severity ($p < 0.05$). The initial cardinal sign was resting tremor in the vast majority of PD patients, which indicated that resting tremor may be an omen of PD (44). This evidence implied that circumscribed resting tremor may be a prodromal marker for ET patients to develop PD. However, some studies also pointed out that resting tremor (in the arms but not the legs) can occur as a late feature in ET patients (63), so it is worth considering the role of circumscribed resting tremor in the course of predicting PD in ET patients. Additionally, data from a retrospective observation of 13 patients initially diagnosed as ET based on tremor characteristics, alcohol responsiveness, and family history who met the PD criteria after a variable long latent period suggest that late-onset asymmetrical postural tremor may

be a signal for developing PD in the long term even if there is no resting tremor (45).

In addition to upper limbs, tremors of the head, voice, and jaw also exist in ET with long disease duration (46). The incidence of jaw tremor ranges from 7.5 to 18% (47, 64, 65) in ET patients. Essential tremor patients with jaw tremor have more severe clinical symptoms and more widely distributed tremor than patients without it. Essential tremor patients with head tremor may be also regarded as a more severe clinical subtype (66). This manifestation combined with the hypothesis that the evolution from ET to PD is caused by the spread of Lewy bodies in the cerebellothalamocortical circuit leads us to speculate that there may be some relationship between jaw tremor and subsequent PD. Additional longitudinal studies are needed to assess whether jaw tremor in ET is a prodromal marker for subsequent PD.

In addition to the research on prodromal markers based on the position, range, and form of the tremor (67–70), a recent study investigated the motor feature: the Tremor Stability Index (TSI) (48). The TSI can be obtained by kinematics measurement of tremor activity and applied to the analysis of tremor characteristics. After testing a cohort comprising 16 rest tremor recordings in TDPD and 20 postural tremor recordings in ET, researchers found a difference in TSI between these two groups [mean 0.7 $\pm$ 0.175 (SEM) in TDPD, 1.9 $\pm$ 0.134 in ET, $t_{(34)} = -5.481$, $p < 0.001$]. This suggests electrophysiological methods may be helpful to evaluate the nature of the tremor and to explore the underlying central oscillator circuits from peripheral tremor. We can also examine additional parameters to evaluate the prognosis of ET patients.

Non-motor Symptoms

Non-motor symptoms are increasingly recognized as an important part of ET. Essential tremor patients show a variety of non-motor symptoms, such as cognitive decline, mood disorder, and hearing loss (71–78). However, studies on non-motor symptoms as possible prodromal factors for developing PD in ET patients are mostly lacking.

There has been increasing interest in olfactory dysfunction because it was identified as a prodromal feature of PD. Just as in PD patients, olfactory decline (hyposmia or anosmia) becomes more evident as the disease progresses in ET patients (49, 79); however, there are also studies that show no olfactory loss in ET. In 2008, Louis et al. (50) found that higher blood harmane concentration was correlated with olfactory decline in 83 ET cases (62.5%, $p < 0.001$). As a cerebellar toxin, harmane reflects the relationship between olfactory decline and a part of pathophysiology in the cerebellum. In 2016, a large European multicenter study using the 16-item Sniffin' Sticks test (SS-16) found that olfactory performance was lower in PD patients compared with atypical parkinsonism and non-PD patients in all cohorts (each $p < 0.001$), and a set of eight smell reduction olfactory tests can be used as a rapid detection tool for PD (51). This calls for olfactory testing of ET patients and longitudinal studies to explore whether hyposmia can be used as a prodromal marker for the development of PD in ET patients.

It is still controversial whether cognition declines in ET. As early as 2001, Gasparini et al. (52) carried out a preliminary study focusing on performance on frontal lobe tasks of 27 ET patients, 15 PD patients, and 15 healthy controls, and they found significant impairments both in attention and conceptual thinking tasks in ET patients, but with no statistical difference between ET patients and PD patients. Consistent with this research, many subsequent studies identified cognitive impairments in ET patients (80, 81). In 2019, researchers enrolled 23 ET patients and 23 healthy controls to evaluate topological properties of brain function network with the aid of resting-state functional MRI, which revealed that changes took place in many regions including hippocampus in ET patients (82). By employing a structured neuropsychological battery to access cognition in 40 ET patients and 40 healthy controls, Prasad et al. (83) revealed that ET patients with cognitive impairment have significant volumetric abnormalities of specific brain regions including several hippocampal subfields.

Recently, by evaluating the hippocampal subregions of PD with cognitive decline and PD without cognitive decline, Xu et al. (84) found that the hippocampal CA2/3, CA4, and DG subfields appeared sensitive in groups of PD with cognitive decline longitudinally, and the volume loss of CA2/3 and CA4-DG correlated with the degree of cognitive impairment. With the assistance of quantitative susceptibility mapping, Thomas et al. (85) tracked cognitive changes in PD and identified lower Montreal Cognitive Assessment (MoCA) scores in the hippocampus and thalamus. Compared with PD patients, ET-PD patients have poorer cognitive performance. After enrolling 30 ET-PD patients and 53 age-matched PD patients, researchers found that both the cursory total score of Mini-Mental State Examination ($p = 0.001$) and the Telephone Interview for Cognitive Status ($p < 0.001$) were lower in ET-PD than in PD, as well as the subscores related to orientation ($p < 0.001$), language ($p < 0.001$), and working memory ($p = 0.001$) (53). It has also been demonstrated that hippocampal microstructural damage is related to subclinical memory impairment in ET patients (57). Considering that cognitive disorders with involvement of the hippocampus occurred both in ET and PD patients, and ET-PD patients have poorer cognitive performance than PD patients, the role of cognitive impairment in predicting the development of PD in ET patients is worth exploring in future research.

Numerous studies have indicated that sleep disturbance, especially RBD, may be an early prodromal marker for developing PD in ET patients (58–60, 86). One study using the RBD Screening Questionnaire (RBDSQ) revealed that ∼0.5% in the general population suffered from RBD (43.5%) (87). Another study in which 92 ET patients were assessed on the Scales for Outcomes in Parkinson's Disease–Autonomic questionnaire to evaluate autonomic symptoms and the RBDSQ to assess the RBD symptoms with ≥5 as a cut-off value for probable RBD (pRBD), 26.4% of the ET patients had pRBD and 98.1% of them reported at least one autonomic

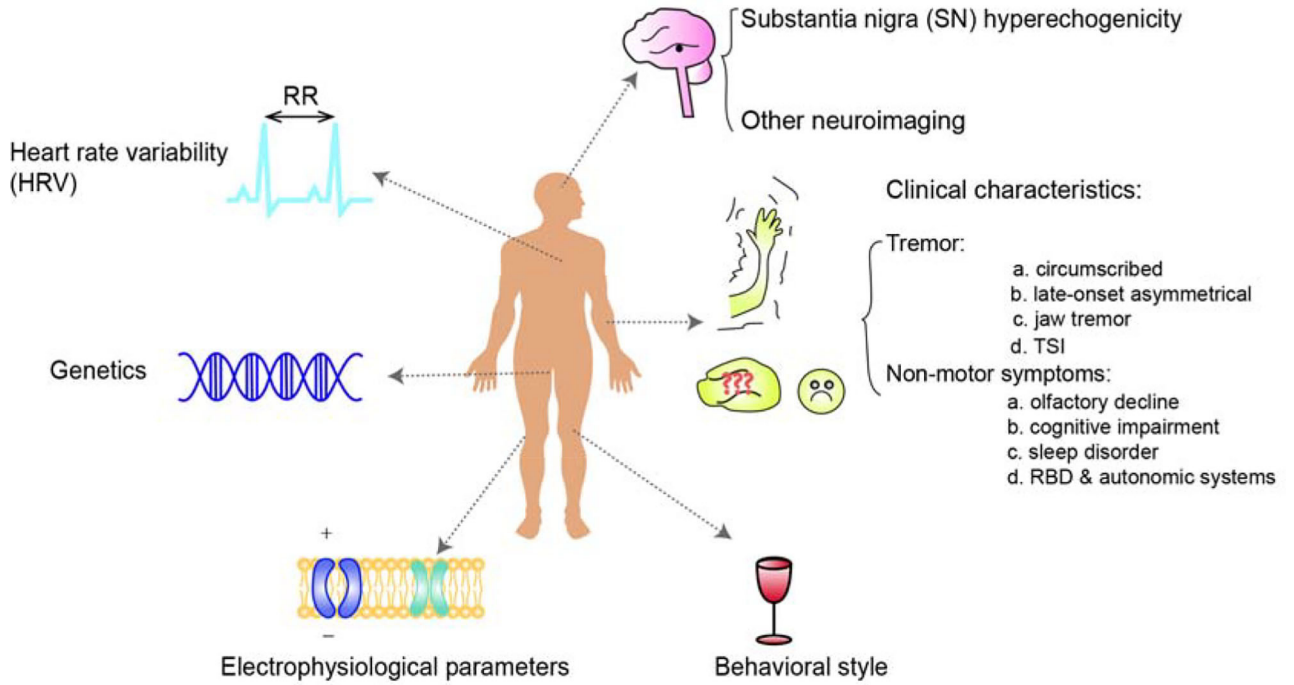

FIGURE 1 | An overview of the risk markers of Parkinson's disease in patients with essential tremor. Essential tremor patients have an increased risk of the development of PD, especially those with SN hyperechogenicity in TCS. Similarly, ET patients with specific tremor or non-motor symptoms, additional HRV, genetic risk, or the other risk markers such as Tremor Stability Index are undergoing a higher risk of the development of PD afterward.

symptom (88). This association suggested that a subgroup of ET patients with pRBD may be at higher risk of PD progression. Salsone et al. (89) proposed that the presence of RBD in ET could identify a specific clinical phenotype and demonstrated significantly reduced scores on memory of ET patients with RBD compared to those without RBD, indicating RBD in ET patients is associated with cognitive impairment. Because RBD is a risk marker of PD in healthy people, its role in prediction of PD in ET patients deserves further longitudinal study.

HEART RATE VARIABILITY

Recent autonomic symptom questionnaire-based analyses and sympathetic skin response–based studies have shown a variety of autonomic dysfunctions associated with ET, especially in the fields of cardiovascular and urogenital diseases (90–92).

Heart rate variability (HRV) evaluates cardiac autonomic nervous regulation function based on the measurements of beat-to-beat RR variability, including time domains and frequency domains analysis. By measuring the components of HRV analysis in the frequency domain during a 12-h daytime and verifying by DAT-SPECT and cardiac MIBG uptake of 10 ET patients, 10 PD patients, and 10 age-sex-matched controls, investigators found that low-frequency components of HRV analysis helped differentiate between ET and PD (93). In another case-control study enrolling 23 ET patients, 27 TDPD patients, and 23 healthy controls, researchers found that HRV was significantly lower in the TDPD group, and the low-frequency component was the best diagnostic marker (AUC = 0.87) for differentiating ET and PD (94). Another study based on sympathoneural imaging in four family members indicated that overexpression of normal α-synuclein and cardiac sympathetic denervation had an impact on parkinsonism (95).

Heart rate variability analysis as a non-invasive tool and a reflection of autonomic nervous function plays an important role in differentiating ET and TDPD at the early stage of disease (94). However, the results of HRV can be affected by many factors, including age, gender, cardiovascular risk factors, and medications. Even deep brain stimulation can produce certain effect on cardiac electrophysiological activity (96, 97). The analysis of HRV can reflect autonomic nerve regulation of the heart and provide information about sympathetic nerve function status.

A recent clinical study with PD showed that failure to increase total peripheral resistance with cardiac denervation under orthostatic stress was associated with systolic blood pressure reduction leading to orthostatic hypotension (98). Another study that enrolled 75 elderly patients with ET and 25 age-matched controls found no difference between the two groups in orthostatic vital signs, ambulatory 24-h blood pressure

TABLE 4 | Brief summary of study design with regard to different prodromal markers.

	Prodromal markers	References	Place	Study design	Number of subjects	Main results
Follow-up ET patients (direct evidence)	SN hyperechogenicity	Sprenger et al. (27)	Austria	Prospective follow-up cohort study Follow-up: mean 6.16 ± 2.05 years	70 ET patients	The relative risk for developing PD in patients with ET who had hyperechogenicity at baseline versus those without this hyperechogenicity was 7.00 (95 CI, 1.62–30.34; sensitivity, 77.8%; specificity, 75.6%)
		Cardaioli et al. (28)	Italy	Longitudinal study Follow-up: 3-year	79 with PD, 59 with ET and 50 matched controls	The maximum size of the SN hyperechogenicity was as follows: 5.62 ± 5.40 mm^2 in the control group, 19.02 ± 14.27 mm^2 in patients with PD, 9.15 ± 11.26 mm^2 in patients with ET-, 20.05 ± 13.78 mm^2 in patients with ET+ and 20.13 ± 13.51 mm^2 in patients with ET-PD. ET-PD maximum values were significantly different from controls. Maximum values in patients with ET+ were different from both controls and patients with ET
Explore the characteristics of ET, PD, or ET-PD patients	SN hyperechogenicity	Budisic et al. (26)	Croatia	Case-control study	80 PD patients, 30 ET patients, and 80 matched controls	Bilateral SN hyperechogenicity over the margin of 0.20 cm (2) was found in 91% of PD patients, 10% of healthy subjects, and in 13% patients with ET
Patients or make differential diagnosis (partial lateral evidence)	Circumscribed resting tremor	Minen and Louis (44)	USA	Retrospective study	53 ET-PD, 53 PD and 150 ET patients	The initial cardinal sign of PD was rest tremor in 100% of patients. In ET-PD, the side of greatest initial ET severity usually matched that of greatest PD severity ($P < 0.05$)
	Late onset asymmetrical postural tremor	Chaudhuri et al. (45)	UK	Longitudinal study	13 ET-PD patients	After a variable and long latent period all patients developed additional signs suggesting a clinical diagnosis of PD although picking up an initial label of ET
	TSI	di Biase et al. (48)	Italy	Cohort study	16 TDPD and 20 ET patients	TSI with a cut-off of 1.05 gave good classification performance for PD tremor and ET, in both test and validation datasets
	Olfactory decline	Louis et al. (50)	USA	Case-control study	83 ET patients and 69 controls	In 83 ET cases, higher log blood harmane concentration was correlated with lower UPSIT score (rho = −0.46, $p < 0.001$)
	Cognitive decline	Louis et al. (53)	USA	Clinical-epidemiological study	30 ET-PD and 53 age-matched PD patients	The MMSE score was lower in ET-PD than PD [26.5 ± 3.1 (median 28.0) vs. 28.4 ± 2.2 (median 29.0), $p = 0.001$]. The TICS score was lower in ET-PD than PD [31.7 ± 3.9 (32.0) vs. 35.0 ± 2.0 (35.0), $p < 0.001$]
	Sleep disorder, especially RBD	Lacerte et al. (87)	Canada	Cross-sectional study	50 ET patients	Using a screening questionnaire for RBD, 43.5% of ET patients are possibly suffering from RBD, whereas in the general population prevalence is estimated to be 0.5%
	HRV	Yoon et al. (94)	South Korea	Case-control study	23 with ET, 27 with TDPD and 23 healthy controls	In the TDPD group, SDNN, LF, HF, and TP were significantly lower than those in the ET group. In a receiver operating characteristic AUC analysis, LF was the best potential diagnostic marker (AUC = 0.87)

(Continued)

TABLE 4 | Continued

	Prodromal markers	References	Place	Study design	Number of subjects	Main results
	Others	Yavuz et al. (129)	Turkey	Case-control study	15 ET, 7 ET with resting tremor, 25 ET-PD, 10 PD and 12 healthy subjects	Probability of ASR was significantly lower in ET-PD group whereas it was similar to healthy subjects in ET and PD ($P < 0.001$). LLR II was more common in ET, PD and ET-PD groups. LLR III was far more common in the PD group ($n = 3$, 13.6% in ET; $n = 4$, 16.0% in ET-PD and $n = 7$, 46.7% in PD; $p = 0.037$)

ET, essential tremor; SN, Substantia nigra; PD, Parkinson's disease; ET-PD, new-onset of PD in patients previously diagnosed with ET; ET+, ET developed new-onset parkinsonian features, without fulfilling criteria for PD diagnosis; ET-, ET patients did not develop parkinsonian features; TSI, Tremor stability index; TDPD, tremor-dominant PD; UPSIT, the University of Pennsylvania Smell Identification Test; MMSE, Mini-Mental State Examination, TICS, Telephone Interview for Cognitive Status; RBD, REM sleep behavior disorder; HRV, Heart rate variability; SDMN, standard deviation of the normal-to-normal RR interval; LF, low-frequency; HF, high-frequency; TP, total spectral power; AUC, area under the curve; ASR, auditory startle reaction; LLR, long latency reflex.

monitoring and 24-h Holter monitoring values (99). Therefore, more studies are needed to explore the role of HRV in the development of ET-PD.

GENETICS

Elucidating the genetic background of ET and PD is crucial for understanding the pathogenesis and improving diagnostic and therapeutic strategies. Research has shown that the risk of ET is significantly increased in PD relatives (100, 101); similarly, studies have found that the risk of PD is increased in first-degree relatives of ET patients (102), which indicate that although the two diseases are mostly distinct in their etiology and symptoms, there may be potential genetic pleiotropy between them.

By comparing and analyzing the clinical characteristics of 25 patients with ET-PD and a control group, Ryu et al. (69) found that ET-PD patients had an obvious family history of tremor of first-degree relatives. Abundant genetic studies have revealed that the family history of tremor may be a prodromal marker for PD in ET patients (103).

While a number of studies have failed to identify the causative genes (104–111), several risk genes appear to have an overlapping role in ET and PD (112). For instance, association studies have found that leucine-rich repeat and immunoglobulin containing 1 gene is involved in the pathogenesis of ET and PD (113–118) and serves as a potential therapeutic target in these two disorders. HTRA2, which encodes a serine protease, plays a role in the pathogenesis of genetic type ET (119, 120), and its homozygous allele is involved in the pathogenesis of PD (121), providing genetic evidence of a link between the two disorders, although an Asian study did not find a role for this gene in ET-PD (122, 123). Moreover, using polymerase chain reaction, research has shown that the intermediate copy number of C9ORF72 repeats increases the risk of PD and ET-PD (124). However, a recent study focusing on the genotype excluded 56 samples from analysis as they had genotyping call rates <0.90. There were no variants significantly deviated from Hardy–Weinberg equilibrium (all had $p > 0.01$) (125). Generally, the role of genetic risk factors in neurodegenerative diseases needs to be further explored in larger studies, including genes that can serve as prodromal markers for the development of PD in ET.

OTHER PRODROMAL MARKERS

Electrophysiological parameters of tremors have the potential to become prodromal markers as technology becomes more clinic-friendly. A study found that the concordance rate between clinical and electrophysiological methods in diagnosing of ET was 94.4% (51 of 54) (126), indicating that electrophysiological methods may be of value in quantifying preclinical patients. One study utilizing an electrophysiological approach to access children and adolescents found an interesting phenomenon: the mean tremor frequency with arms extended was different between children (5.3 Hz) and adolescents (9.0 Hz) (127). This finding suggests that the pathogenesis may be different between children and adolescents. Previous studies have shown an

increased R2 recovery of the blink reflex in PD and increased R2 recovery component of the blink reflex (R2-BRrc) in ET associated with resting tremor while normal in ET patients (128). A 2015 study revealed that the probability of the auditory startle reaction was significantly lower in ET-PD patients, whereas it was similar in both healthy subjects and ET or PD patients ($P < 0.001$) (129). Another study that enrolled 19 ET-PD patients and 85 controls (i.e., 48 ET patients and 37 PD patients) found that electrophysiological parameters (i.e., a synchronous resting tremor pattern and the abnormal blink-recovery cycle) were the most accurate biomarkers in distinguishing ET-PD patients from ET or PD patients (130), which calls for longitudinal studies to evaluate whether it can be used as a prodromal marker for the development of PD in ET. Additionally, Crowell et al. (131) utilized an electrocorticography study to address movement disorders such as PD, primary dystonia, and ET with abnormalities in synchronized oscillatory activity. With the development of artificial intelligence and big data, smart phones and sports bracelets can sense and record the characteristics of various parameters of tremor and then enter them into big data analyses (132, 133). Electrophysiological approaches may be new and effective prodromal markers for predicting the development of PD in ET patients.

Studies of behavioral factors in ET and PD are indispensable. For instance, alcohol consumption and dairy intake may be risk factors for PD (134). A study using a population-based, case-control design analyzed ever smokers and never smokers and revealed that ever smokers had less than half the risk of ET (odds ratio = 0.58, 95% confidence interval = 0.40–0.84, $p = 0.004$). The amount of smoking played a subtle role in the development (135). Another study that examined body mass index and waist circumference of PD patients found a possible interaction between anthropometry, sex, and smoking and PD risk (136). Similarly, new prodromal markers are expected to be found when large-scale statistical analyses of patient lifestyle factors are completed.

CONCLUSION

Identification of prodromal markers for the development of PD from ET represents one of the most urgent unmet needs in neurology. This relationship is garnering an increasing amount of interest among researchers. Evidence based on clinical characteristics, epidemiology, neuroimaging, genetics, pathology, and many other aspects has demonstrated numerous associations between these two conditions. Essential tremor patients have an increased risk of developing PD, especially those with SN hyperechogenicity in TCS which is directly demonstrated by a longitudinal study or a prospective cohort study among ET patients. Similarly, ET patients with specific tremor characteristics or non-motor symptoms, HRV, and certain genetic variations are likely to have a higher risk of developing of PD afterward (**Figure 1**) with the evidence derived from retrospective study, cross-sectional study or prospective study focusing on the characteristics of ET, PD, ET-PD or the differential diagnosis (**Table 4**). However, given the lack of research directly evaluating PD prodromal markers in ET, we are far from understanding the relationship, and large longitudinal studies of clinical characteristics, genetics, and pathology are needed.

AUTHOR CONTRIBUTIONS

Y-CW provided fund support, revised the manuscript, and designed the project ideas. X-XW, YF, and XL searched for literature and wrote the manuscript. X-YZ, DT, and WO revised the paper. All authors contributed to the article and approved the submitted version.

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The Impact of Sex and Gender on the Multidisciplinary Management of Care for Persons With Parkinson's Disease

Irene Göttgens[1], Angelika D. van Halteren[2], Nienke M. de Vries[2], Marjan J. Meinders[3], Yoav Ben-Shlomo[4], Bastiaan R. Bloem[2], Sirwan K. L. Darweesh[2] and Sabine Oertelt-Prigione[1]**

[1] Department of Primary and Community Care, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, Netherlands, [2] Department of Neurology, Center of Expertise for Parkinson & Movement Disorders, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, Netherlands, [3] Scientific Center for Quality of Healthcare (IQ Healthcare), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, Netherlands, [4] Department of Population Health Sciences, University of Bristol, Bristol, United Kingdom

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***Correspondence:**
Sirwan K. L. Darweesh
Sirwan.Darweesh@radboudumc.nl
Sabine Oertelt-Prigione
Sabine.Oertelt-Prigione@radboudumc.nl

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The impact of sex and gender on disease incidence, progression, and provision of care has gained increasing attention in many areas of medicine. Biological factors–sex–and sociocultural and behavioral factors–gender–greatly impact on health and disease. While sex can modulate disease progression and response to therapy, gender can influence patient-provider communication, non-pharmacological disease management, and need for assistance. Sex and gender issues are especially relevant in chronic progressive diseases, such as Parkinson's disease (PD), because affected patients require multidisciplinary care for prolonged periods of time. In this perspective paper, we draw from evidence in the field of PD and various other areas of medicine to address how sex and gender could impact PD care provision. We highlight examples for which differences have been reported and formulate research topics and considerations on how to optimize the multidisciplinary care of persons with PD.

Keywords: Parkinson's disease, multidisciplinary care, sex factors, gender, disease progression, male, female, caregivers

INTRODUCTION

Sex and gender impact disease incidence, progression, and provision of care in different medical disciplines (1). "Sex" differences are based on biological variations due to differences in genetics, hormones, and physiology. "Gender" differences are rooted in different expressions of identity, adherence to norms, and socially defined behaviors (2). Sex can impact the biological bases of disease progression, response to diagnostics, and therapies, while gender can influence access to healthcare, coping with disease, compliance with therapies, and patient-provider communication. Taken together, these aspects warrant consideration in the provision of care to people living with a disease.

The influences of sex and gender on care delivery are especially relevant for chronic diseases that are characterized by a heterogeneous and progressive spectrum of clinical features. A prime example of such a disease is Parkinson's disease (PD), which is the second most common neurodegenerative disease worldwide and which demonstrates a rapidly rising prevalence (3). PD

is partially characterized by motor features, but affected persons typically also experience a highly variable combination of non-motor features. Given the multifaceted and heterogenous nature of the disease, care delivery to people with PD typically involves healthcare professionals from a wide range of different professional disciplines to accommodate the specific clinical features, needs and coping styles of a person with PD (4–7). Ideally, any person with PD should be treated by a diverse, multidisciplinary team, consisting of a general practitioner, neurologist, PD nurse specialist, physiotherapist, occupational therapist, speech- and language therapist, neuropsychologist, dietician, or other healthcare professionals, depending on the needs of the patient (7).

At the time of clinical diagnosis, differences in the prevalence of motor and non-motor features might exist between men and women with PD. For instance, men might experience more rigidity and women more tremor (8). As the disease progresses, sex, and gender differences can emerge in the incidence of clinical features, such as postural instability or depressive symptoms (8, 9). In addition to these differences in clinical phenotype, coping styles may also vary between men and women with PD (10). Given this broad spectrum of potential differences, the consideration of sex- and gender-specific problems and needs of people with PD appears to be essential to provide personalized care. However, to date, empirical insight on the influence of sex and gender on disease progression and care for people with PD remains scarce.

This perspective paper addresses how sex and gender may impact care for people with PD, drawing from both the PD literature as well as from other fields of medicine. We will specifically focus on the following domains: (1) motor features, (2) non-motor features, (3) lifestyle, and (4) coping and informal care. To illustrate the potential impact of sex or gender, we highlight examples for which differences have been reported in PD, although the level of evidence varies substantially. For each section, the reviewed data on sex and gender differences in PD are summarized, and considerations for multidisciplinary and sex- and gender-sensitive care for people with PD are highlighted.

SEX AND GENDER ASPECTS IN PD

Sex and Gender Aspects in Motor Features

PD is primarily known as a clinical syndrome described as "Parkinsonism," which entails bradykinesia in combination with at least one of the following: resting tremor, rigidity, or postural instability (11, 12). As the disease progresses, people with PD are prone to develop fluctuations in motor impairments related to dopaminergic therapy, as well as to freezing of gait (13). Several differences in motor features between men and women with PD have been reported and have been summarized elsewhere (8, 14, 15). However, the relevance of these differences for care provision to people with PD remains largely unknown.

The potential impact of sex or gender differences on multidisciplinary care for mobility impairments comes from other fields of medicine, such as recent recommendations for osteoporosis screening guidelines based on underlying sex differences (16). Osteoporosis predominantly affects postmenopausal females (17) but also impacts many elderly males (18, 19). Given the higher mortality of men with bone fractures, several osteoporosis, and endocrinology societies now recommend screening in all men above 65 or 70 years (19, 20), but this recommendation is not routinely implemented in clinical practice (16).

Similarly, it is possible that sex or gender differences in the prevalence of common motor features in PD may influence clinical recommendations in the future. At the moment, however, several gaps in empirical evidence hamper development of such sex- and gender-sensitive guidelines. In **Table 1**, we highlight key questions that, once addressed, could guide the implementation of sex- and gender-sensitive approaches to care for people with PD.

An illustration of the current gaps in knowledge is the recent observation that postural instability appears to be more common among women with PD than among men (8, 21). This observation is based on a few relatively small studies, rendering uncertainty on whether this reflects a true sex difference in the prevalence of this feature. If larger studies replicated this finding, it would encourage preferential referral of women with PD to a physiotherapist for preventive and symptomatic interventions, such as technology-assisted balance training. But for this selective referral to be effective, we also need insight on whether the effectiveness of symptomatic interventions differs between men and women with PD. Future studies should be adequately powered to examine clinically meaningful effect modification by gender, which requires larger sample sizes.

Furthermore, knowledge about the impact of gender-specific differences in activities of daily living (ADL) among people with PD is relatively scarce. The available literature, however, suggests that causal influences on ADL may differ substantially by gender. For instance, women report greater difficulty shopping and cleaning compared to men with PD, highlighting not only the practical consequences of mobility impairment, but also its gendered dimension (22). If these differences are replicated in other studies, this would encourage the development of gender-sensitive targeted occupational therapy interventions for ADL impairment (23). Taken together, empirical evidence for targeted care interventions which consider sex and gender differences in mobility impairment could eventually influence clinical guidelines for people with PD.

An additional area of potential sex- or gender-related influences on care revolves around interactions between patients and healthcare professionals. In the field of surgery, two gender-related factors affect the indication for total joint arthroplasty (24): less referral of women by their primary care physician, i.e., reflecting a potential bias on the side of the physician; and less requests by women to undergo surgery, i.e., bias on the side of the patient. A recent study suggests that women with PD are less likely to undergo Deep Brain Stimulation (DBS) surgery than men with PD (25, 26). This is of particular note given that the current literature suggests that women may experience a greater improvement in quality of life after DBS than men (9, 27). This imbalance needs to be further investigated to remove potential referral or request bias through targeted interventions on the provider or patient side (26, 28).

TABLE 1 | Considerations for sex- and gender sensitive multidisciplinary PD care.

Domain	Feature(s)	Reported to be more common in	Possible sex- and gender sensitive care intervention(s) for this feature	Key questions that could guide sex- and gender-sensitive approaches
Motor features	Poor balance	Women	• Referral to (technology-assisted) balance training interventions	• Are differences between men and women taken into account when assessing the effectiveness of balance training intervention? • Do men and women prefer different features in technology-assisted balance training interventions?
	Dyskinesia	Women	• Deep brain stimulation	• What are the underlying reasons for delayed access to deep brain stimulation surgery, on average, in women compared to men? • Do underlying gender-biases influence the shared decision-making process concerning deep brain stimulation surgery?
Non-motor features	Impulse control disorders	Men	• Reduction or discontinuation of dopaminergic therapies • Cognitive behavior therapy	• Are gender differences in ICBs due to different disease entities or socially-accepted gender behaviors? • How are patients addressed and informed about sex differences in response to dopamine replacement therapies? • Do sex or gender predict outcome in psychotherapy interventions such as cognitive behavior therapy?
	Episodes of depression and anxiety	Women	• Referral for coping skills training e.g: mindfulness-based interventions • Social support interventions	• Do screening measures for depression and anxiety take differences in gender roles into account? • Do gender traits predict or affect the responsiveness to depression and anxiety care interventions?
Lifestyle	Weight loss related impairment	Men	• Regular weight self-monitoring • Development and regular review of diet plan	• Are differences in food choices and practices between men and women taken into account in weight monitoring? • Do sex and gender aspects contribute to differences in food intake and processing?
	Limited physical activity	Women	• Exercise enhanced by motivational app elements • Physical exercise interventions	• Do exercise apps take different drivers and motivations for exercise between men and women into account? • Do exercise apps take gender-specific triggers and rewards into account in their design?
Care support	Less informal care resources	Women	• Proactive identification of social network and care capacities of the patient • Referral to social support interventions/ cognitive behavioral therapy	• Are social support interventions taking gender-specific drivers and motivators into account? • Are there gender differences in social support needs and social support perspection and how are these taking into account?
	Higher caregiver strain	Women	• Regular screening of caregiver burden • Care giver education about disease progress, symptoms and experiences	• Do screening measures of caregiver burden take gender differences in caregiver experiences into account? • Are there gender differences in information and education needs about disease progression and (advanced) care planning?

Sex and Gender Aspects in Non-motor Features

Although PD is widely (and inadvertently) perceived as being primarily characterized by motor symptoms, non-motor symptoms are actually at least as common, and importantly, these can have a considerable impact on quality of life in persons with PD. In this section, we discuss two examples that highlight the potential impact of sex and gender differences on multidisciplinary care for people with PD: impulse control disorders and depressive symptoms.

Impulse control behaviors (ICBs) are associated with dopamine replacement therapy in PD. Overall, ICBs are generally more common in men compared to women with PD (29). However, the direction of these differences might differ by the specific type ICB: hypersexuality and gambling are more common in men, while compulsive buying is more common in women (30). Analogous differences have been reported for compulsive disorders in people without PD, with women presenting more contamination/cleaning symptoms or eating disorders whereas men more commonly present with sexual and

aggressive symptoms (31, 32). It remains to be investigated if these differences are due to different disease entities or simply to socially-acceptable gendered behaviors (**Table 1**).

Depressive symptoms and anxiety are among the most common non-motor symptoms in people with PD (33, 34). Depressive symptoms and anxiety in PD are likely to be multifactorial, related to the influence of PD pathology and the indirect impact of impaired mobility and social isolation (35, 36). Sex differences in depression have been linked to differences in expression of susceptibility genes and hormonal influences as well as gender-related differences in reporting (37, 38). Although females and males with PD experience similar physical symptoms, the associated psychological burden appears to differ. Men primarily report difficulties in self-presentation, whereas women report greater psychological burden and larger impact on their intimate relationships (39, 40). This associates with a significant reduction in quality of life in women with PD (41). Also, higher anxiety levels have been reported in women with PD, especially in the early clinical phase of the disease (42–44).

However, to date, the impact of sex and gender differences in anxiety and depressive symptoms on care provision for people with PD has remained limited. Again, the field of PD is not unique in this regard. In 2008, the masculine depression scale (MDS) was developed to facilitate diagnosis of masculine depressive symptoms (45). A recent study found that men and women who endorse a masculine gender role are relatively more likely to display externalizing symptoms (e.g., anger, somatic symptoms, using substance, or sex to feel better) in response to negative life events, and less likely to report typical, internalizing depressive symptoms, as measured by, e.g., the widely used Beck Depression Inventory (e.g., depressed mood or crying) (46). Therefore, clinicians should be aware that individuals who strongly adhere to masculine gender roles, whether they be men or women, might display different signs and symptoms and may respond differently to behavioral interventions for depression and anxiety than individuals who adhere more strongly to a feminine gender role (**Table 1**).

Gender Aspects in Lifestyle

Few differences in lifestyle between men and women with PD have been reported. In this section, we discuss two examples that highlight the potential impact of such differences on multidisciplinary care for people with PD: weight loss and physical activity.

Progressive weight loss is common among people with PD, likely due to a combination of physical inactivity (causing muscle loss), lower intake of solid foods due to oropharyngeal dysphagia and a catabolic state (15, 47). A decreased intake of solid foods may result in less consumption of fresh foods and vegetables, which leads to a risk of malnutrition (47). Researchers in other fields consistently reported healthier food choices among women compared to men, including increased consumption of fresh fruit and vegetables and reduced consumption of processed food and alcohol (48, 49). Encouragement by nutritionists of the consumption of healthy, solid, foods should consider these gender norms, as well as direct assessment of the abililty to prepare and consume foods due to disease-related physical limitations. Again, this is an area in which a gender-sensitive care intervention for people with PD could be informed by data from other fields. However, to our knowledge, no studies have examined the effectiveness of gender-sensitive approaches to nutrition among people with PD to date.

Once validated, gender-sensitive approaches may also help to better understand differences in body weight related impairments between men and women with PD. A useful example here comes from the field of cardiometabolic diseases, in which the observation of body fat distribution differences between women and men led to the identification of the hip-to-waist ratio as a better predictor of risk than BMI, especially for women (50). Among people with PD, weight loss generally associates with higher mortality and worse quality of life (51). While unexplained weight change is reported more commonly in women with PD (52, 53), clinically significant weight loss is reported to be associated with lower 1-year survival rates in men, compared to women with PD (54). Future studies should examine the sex-specific prognostic utility of weight loss among people with PD.

Gender considerations are also relevant in the context of physical activity. Women worldwide appear to engage less frequently in physical activity compared to men (55). Different drivers can modulate the uptake of physical activity in women and men with PD. Women appear to rely on enjoyment as the primary motivator while men describe self-efficacy as the primary driver for physical activity (56). In different regions, gender-related factors might also be at play. For example, in a qualitative study in Jordan, women with PD reported family commitment and support as important elements to initiate and maintain an exercise program. However, gender norms acted as barriers as unequal division of household tasks and childcare limited the time available for exercise (57). Different motivation strategies might be needed for women and men with PD and gender norms should be made explicit to reduce barriers to exercise (**Table 1**). Examples could be drawn from gender-sensitive programs to increase physical activity and promote healthy weight such as WISEWOMAN in the United States and Football Fans in Training (FFIT) in the UK (58, 59).

Gender Aspects in Coping and Informal Care

Several differences in care management between men and women with PD have been reported. In this section, we discuss two examples that highlight the potential impact of such differences on multidisciplinary care for people with PD: coping strategies and informal care.

Gender can influence individual coping strategies and should be taken into account in systematically measuring differences in distress and coping (43). General studies on gender differences coping strategies are conflicting. Some authors report that women use more emotion-focused coping strategies while men prefer focusing on avoidant coping (60, 61). However, a study targeting coping strategies among people with PD reported the opposite, with women reporting more problem-focused coping strategies compared to males (10). Interestingly, less polarized gender roles might associate with better quality of life in women.

Specifically, androgynous women with PD, expressing masculine and feminine personality traits equally, scored significantly better on quality of life than androgynous men with PD (62). Similar to the impact of gender roles on the reponse to negative life events in the context of depression, clinicians should be aware of the potential impact of gender roles on (in)effective coping strategies. Additionally, researchers should continue to explore the impact of different gender dimensions on coping strategies and health-related quality of life in people with PD.

In the context of informal care, women with PD report less social support and less informal caregiving resources compared to men (8). Women worldwide are still more frequently active caregivers than men, although this is changing in younger generations (63). Previous studies describe fewer negative outcomes and less impaired quality of life in male caregivers (64, 65). Women caregivers reported exhaustion, social constraints, and time limitations more frequently than men and women report more adverse consequences from the progression of the disease of their partners, such as feelings of manipulation, excessive demands, and lack of freedom (38). One study noted that women caregivers appeared to experience a higher incidence of depression and dysfunctional fear of progression compared to men caregivers (66), but another failed to find any gender differences in psychological, social, and health outcomes (67). Progression of disease and the potentially associated cognitive decline, which is higher in men with PD compared to women, also places a higher burden on caregivers with potential impact on their health (14, 68–71).

Proactive identification of social network and care capacities of the patient, for example by a PD nurse specialist, is needed to prevent gender disparaties in care support (**Table 1**). Furthermore, caregiver strain might affect female and male caregivers differently. This aspect should be actively explored, as caregivers might refrain from addressing it directly. Targeted options such as logistic support through social workers and social support through caregiver associations, should be discussed with caregivers. Psychological and educational support might be needed and should be proactively addressed with the caregiver (**Table 1**).

DISCUSSION

In this perspective paper, we highlight the potential impact of sex and gender on care for people with PD, and identify key knowledge gaps that hamper immediate implementation of sex- or gender-sensitive approaches. The intersection between biological differences and social norms and behaviors highlights the complexity of individualized care. Although knowledge in the area of sex and gender differences is increasing, the current state of evidence does not yet allow for specific recommendations for sex- and gender sensitive approaches for individual patients. In the case of PD, few studies have focused on the role of gender and the ones that did, lacked a clear definition of the concept of gender itself. Gender consists of several dimensions, such as identity, roles, and relations, and these should be clearly defined and operationalized when embarking into its investigation (72). As the previously described studies on quality of life demonstrated, gender rather then sex was predictive (62). This is in line with findings in the field of cardiology and highlights the continuous nature of the concept opposed to the simple man/woman dichotomy (73). More methodological precision in the analysis of sex and gender differences in PD will aid the transferability of the acquired knowledge into practical steps toward individualized care.

Furthermore, while the prevalence of PD has typically been higher in men than in women in clinical studies, population-based studies which include door-to-door screening and validation have demonstrated a markedly smaller gender difference in the prevalence of PD (3, 74). This discrepancy suggests that women with PD are not being referred to clinical settings as readily as men. In fact, a previous study showed that there is a considerable delay in referral of women with PD to movement disorder specialists (75). Furthermore, women are also underrepresented in clinical trials on PD and efforts to bridge this gender gap in future RCTs should be undertaken (76).

The present perspective has highlighted various areas in need of additional research. Gender-specific preferences and priorities in health care provision need to be further investigated. Which symptoms are more burdening for women and men with PD and which potential barriers exist toward optimal care provision? Are there gender-specific dimensions that contribute to long-term maintenance of quality of life? How do gender roles impact the patient's choices and can addressing them affect coping strategies? Answers to these important questions could support further refinement of multidisciplinary care programs tailored specifically to the needs of people with PD and remove potential unconscious gender-specific barriers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SO-P and SD contributed to conception and design of the study. SO-P and IG performed the literature review and wrote the first draft of the manuscript. SO-P, IG, SD, and AH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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MINI REVIEW
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Non-pharmacological Treatment Challenges in Early Parkinson's Disease for Axial and Cognitive Symptoms: A Mini Review

Gabriella Sharpe[1], *Antonella Macerollo*[2,3], *Margherita Fabbri*[4]* *and Elina Tripoliti*[5]

[1] School of Allied Health, Faculty of Health Sciences, Australian Catholic University, Brisbane, QLD, Australia, [2] Department of Neurology, The Walton Center for Neurology and Neurosurgery, Liverpool, United Kingdom, [3] Department of Neurosciences, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom, [4] Clinical Investigation Center CIC 1436, Parkinson Toulouse Expert Center, NS-Park/FCRIN Network, NeuroToul COEN Center, Toulouse University Hospital, INSERM, University of Toulouse 3, Toulouse, France, [5] Department of Clinical and Movement Neurosciences, Institute of Neurology, University College London, London, United Kingdom

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Daniel Martinez-Ramirez, Tecnológico de Monterrey, Mexico

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***Correspondence:**
Margherita Fabbri
margheritafabbrimd@gmail.com

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Background: Parkinson's disease (PD) is now known to be a multisystemic heterogeneous neurodegenerative disease, including a wide spectrum of both motor and non-motor symptoms. PD patients' management must encompass a multidisciplinary approach to effectively address its complex nature. There are still challenges in terms of treating axial (gait, balance, posture, speech, and swallowing) and cognitive symptoms that typically arise with disease progression becoming poorly responsive to dopaminergic or surgical treatments.

Objective: The objectives of the study are to further establish the presentation of axial and cognitive symptoms in early PD [Hoehn and Yahr (H&Y) scale $\leq$ 2] and to discuss the evidence for non-pharmacological approaches in early PD.

Results: Mild and subtle changes in the investigated domains can be present even in early PD. Over the last 15 years, a few randomized clinical trials have been focused on these areas. Due to the low number of studies and the heterogeneity of the results, no definitive recommendations are possible. However, positive results have been obtained, with effective treatments being high-intensity treadmill and cueing for gait disturbances, high-intensity voice treatment, video-assisted swallowing therapy for dysphagia, and warm-up exercises and Wii Fit™ training for cognition.

Conclusions: Considering the association of motor, speech, and cognitive function, future trials should focus on multidisciplinary approaches to combined non-pharmacological management. We highlight the need for a more unified approach in managing these "orphan" symptoms, from the very beginning of the disease. The concept "the sooner the better" should be applied to multidisciplinary non-pharmacological management in PD.

Keywords: early Parkinson's disease, speech, swallowing, axial symptoms, cognition, multidisciplinary care

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by a spectrum of both motor and non-motor symptoms. Effective management of patients with PD (PwPD) must encompass a multidisciplinary individualized approach (1–3). Medical management of PD has improved parkinsonian symptoms and quality of life (QoL) either through pharmacological or neurosurgical interventions (4). Nevertheless, there are still challenges in terms of treating the axial (gait, posture, balance, speech, and swallowing) and cognitive symptoms that typically arise with disease progression becoming poorly responsive to both dopaminergic and surgical treatments (5, 6). Particular attention should be paid to axial and cognitive disabilities, which are predictions of dependency development and mortality (7, 8). Identifying the extent to which these symptoms are present in early PD and treating these symptoms early could help reduce their burden in later disease stages. Indeed, the ideal time frame to apply a certain treatment is actually a topic of discussion, especially for trials on disease-modifying treatment (9). What seems to be clear is that if we apply a neuroprotective treatment in early/intermediate PD, it is too late, as the neurodegenerative process is too advanced (9). The same concept could be applied for non-pharmacological treatment for those troublesome symptoms that characterize the advanced PD stage; we need to elaborate and identify strategies that could prevent disabilities and act before their manifested appearance (10).

In this mini review, the presentation of axial and cognitive symptoms in early PD [i.e., Hoehn and Yahr scale (H&Y) ≤ 2] is reviewed, and the evidence for non-pharmacological treatments for these symptoms in early PD is discussed. Randomized clinical trials (RCTs) on non-pharmacological treatments and written in English from 2005 to 2020 were identified in MEDLINE. Non-invasive brain stimulation was not included in our search. The following search terms (and derivatives) that were used included Parkinson, early, treatment, falls, balance, posture, gait, speech, communication, voice, dysphagia, swallowing, cognition, dementia, and executive function. Relevant treatment studies were selected according to the flow diagram shown in **Figure 1**. Overall, 11 RCTs (7 studies for gait, one of which had balance as secondary outcome and 0 for posture, 1 for speech, 2 for swallowing, and 1 for cognition) were selected and reviewed (**Table 1**).

Gait, balance, posture, speech, and swallowing problems represent the typical axial clinical features of PwPD. Axial impairment is very common among PwPD, inexorably worsening with disease progression, with a severe impact on autonomy and QoL (22, 23). Axial signs are often resistant to pharmacological and surgical treatments. Therefore, non-pharmacological approaches may offer a valuable add-on treatment rescue.

Gait Symptoms

Gait is controlled by cortical and subcortical neuronal networks, which are both altered in PwPD due to basal ganglia loop disruption and the frontal lobe dysfunction, the latter usually appearing with disease progression (24, 25). However, gait disorders are not only present in advanced PD. It has been shown that in the first 5 years from diagnosis, several gait parameters differ between PwPD and controls, such as lower step width, stride duration, and swing velocity that contribute to reduced gait velocity and a stooped posture (26, 27). Freezing of gait (FoG) can be present in 15–25% of early PD (28, 29). It is associated with the akineto-rigid PD subtype, older age, higher daily levodopa (L-dopa) dose, postural instability, and declining executive function (30), as well as with a higher risk of falls and fear of falling (31). It is often resistant to pharmacological treatment and rarely even worsened by L-dopa (32).

Gait Intervention

Overall, seven RCTs have specifically looked at gait interventions for early PD, such as treadmill programs, global postural reeducation, high-intensity exercise, or multidisciplinary intensive rehabilitation (11–17). The main findings ranged from no to mild-moderate improvements when compared to traditional care/physiotherapy (**Table 1**). Studies involving participants at different stages of the disease have also shown similar findings for gait intervention. For example, a Cochrane meta-analysis of 39 RCTs (H&Y 1–4) reported that physical activity and exercise improved gait speed, FoG, and functional mobility over a short term (<3 months) with no clear differences among physiotherapy techniques (33). Further, a recent phase II trial (H&Y 1–3) reported that a high-intensity treadmill program is safe and feasible (34). Finally, cueing has also been shown to be a useful rescue strategy for patients with drug-resistant FoG (35). Recently, performance-based cueing devices tailored to specific patients' gait performance have been developed, thanks to the use of wearable technology (36). The only small cross-over trial study on patients with disabling FoG based in the laboratory setting suggested positive results (37).

Balance Symptoms

Static balance depends on the interactions between the characteristics of the person, the task, and the environment. Balance disturbances are related to different subsystem dysfunctions, including muscle weakness, proprioceptive sensory loss, increase in sensory thresholds, alteration of motor coordination, and cognitive decline. Interestingly, subtle balance impairments have been observed in patients with idiopathic REM behavior disorder, when compared to healthy controls (38) as well as altered postural sway during cognitive multitasking in early PD (39). For clinical assessment, the most reliable predictive factor of balance impairment is a 12-month history of falls, followed by FoG episodes in the previous month, and comfortable gait speed of <1.1 m/s (40).

Balance Intervention

Overall, there are no RCTs available on rehabilitation effect specifically for early PD patients. This is partly due to the fact that postural instability is usually clinically relevant in H&Y ≥ 3 patients. Only one single-blind RCT evaluated the effect of Nintendo Wii^{TM}-based motor cognitive training vs. balance exercise therapy without feedback or cognitive stimulation on

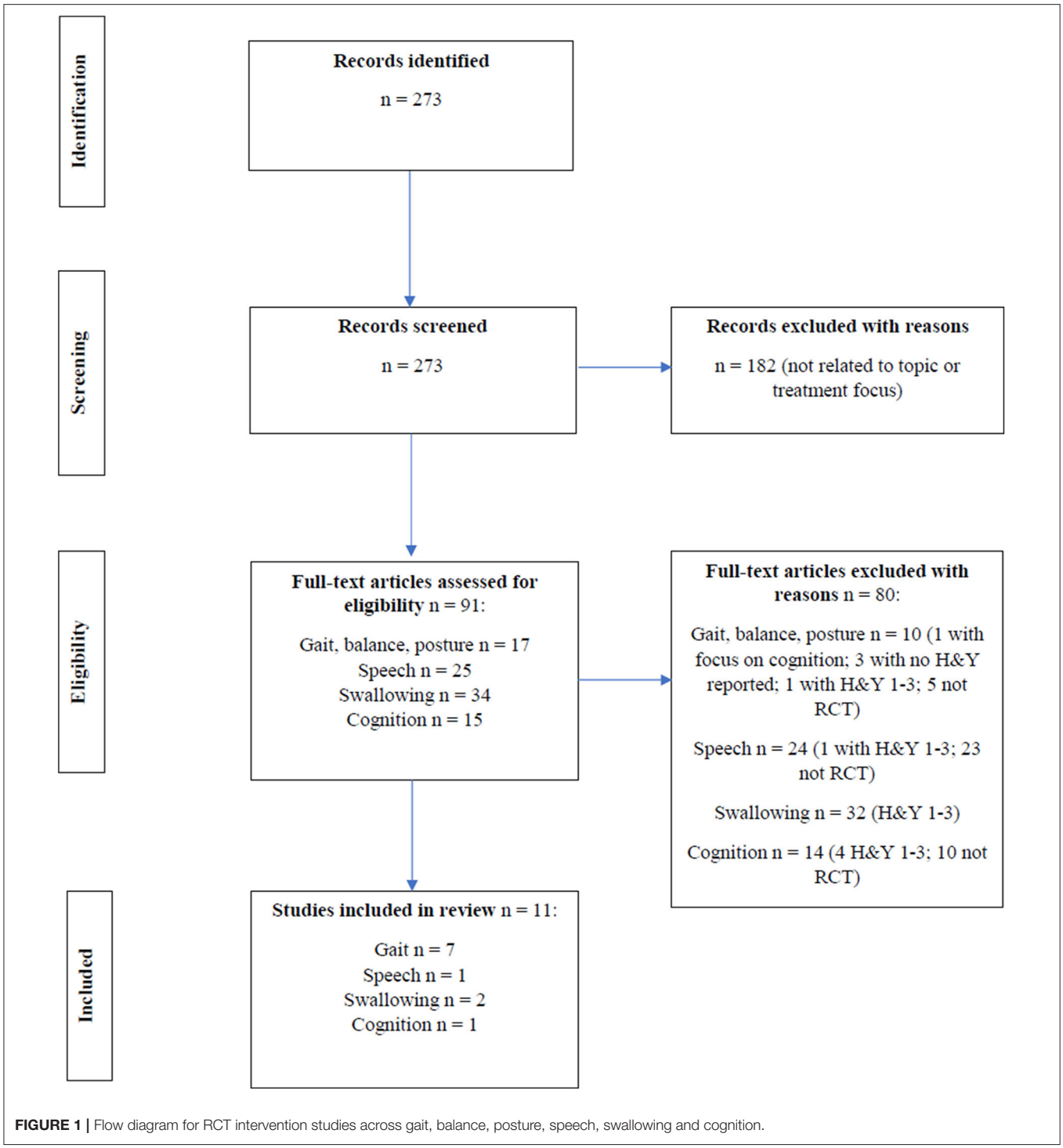

FIGURE 1 | Flow diagram for RCT intervention studies across gait, balance, posture, speech, swallowing and cognition.

activities of daily living (UPDRS-II). This study also explored the balance Berg scale as a secondary outcome among H&Y 1–2 patients finding an improvement in both groups (14) (**Table 1**). The most consistent treatment results are seen with motor training and traditional Chinese medical exercise (i.e., Tai Chi and Qigong) as shown by several meta-analyses of randomized RCTs and participants with H&Y 1–4 (41, 42). Of note, reduction in falls has been reported only by Tai Chi trials. It has been recently suggested that aquatic exercise may have equal or greater benefit on balance and fear of falling than land-based exercise (43).

Posture Symptoms

PD postural abnormalities include: (a) camptocormia, defined as forward trunk bending $\geq 30^{\circ}$ at the lumbar fulcrum (lower) or $\geq 45^{\circ}$ at the thoracic fulcrum (upper); (b) Pisa syndrome,

TABLE 1 | RCT studies across gait, speech, swallowing and cognition intervention.

References	Participant number; H&Y; disease duration (range or mean)	Intervention and follow-up	Main outcomes	Main results	Study limitations
Gait intervention					
Canning et al. (11)	20 (10 per group); H&Y 1–2; duration: 6.1 years	Semisupervised home-based treadmill training vs. usual physical activities 6 weeks, 30–40 min, 4x per week 6 weeks follow-up	6-min timed walk	No significant difference between the two groups (36 m vs. 41.5 m)	Small sample size
Nadeau et al. (12)	93; H&Y 1.5–2; duration not specified	Speed treadmill training (TT, 29 pts) vs. mixed TT (30 pts) vs. controls (light exercise only, 34 pts) 24 weeks, 72 1-h sessions	MDS-UPDRS; PDQ-39; spatiotemporal parameters of gait; 6-min timed walk	No differences between groups on MDS-UPDRS and PDQ-39 (95% CI not stated) Both training groups improved on speed, cadence, and stride length during self-selected walking conditions post-treatment Both training groups improved in distance traveled	Only 34 out of 93 subjects were available for analysis
Agosti et al. (13)	20 (10 per group); H&Y 1.7 ± 0.6; duration: 6 years	Global postural reeducation (GPR) program individual sessions vs. control physiotherapy treatment 12 weeks, 40 min, 3x per week	Kinematic gait parameters of thigh, knee, and ankle	Improvement in kinematic gait pattern with increased flexion amplitudes of knee and thigh post-treatment Significant interaction between time and groups was observed for UPDRS-III score with GPR program	Small sample size; no clear clinically relevant outcome
Pompeu et al. (14)	32; H&Y 1–2; duration not specified	Wii Fit™ games balance training vs. balance exercise therapy (stretching, strengthening, balance exercises) 7 weeks, 1 h, 2x per week	UPDRS-II; Berg balance scale; Static balance using a unipedal stance test	Both groups showed improvement in the UPDRS-II and Berg balance scale No significant difference between groups	No control group without intervention
Fisher et al. (15)	30; H&Y 1–2; duration: <3 years	High-intensity exercise using body weight-supported treadmill training vs. low-intensity exercise vs. zero-intensity education group 8 weeks; 24 sessions; 5 education classes	UPDRS, biomechanic analysis of self-selected, fast walking, and sit-to-stand tasks; corticomotor excitability	All groups showed small improvements in total and motor UPDRS Improvements for high-intensity group only on gait speed, step and stride length, hip and ankle joint excursion during self-selected and fast gait; and weight distribution during sit-to-stand	Small sample size; large variability at baseline
Park et al. (16)	31; H&Y 1–2; duration: <3 years	Early-start group (ESG) or a delayed-start group (DST) exercise program; ESG underwent a 48-week rigorous formal group exercise program for 1 h 3x a week vs. 24–48 weeks of identical program for DSG	UPDRS; get-up-and-go walking test; Tinetti mobility test; PDQ-39, BDI	No significant difference for motor scores between groups, but the ESG group scored significantly better on the BDI	Small sample size; single blinding
Frazzitta et al. (17)	40 (20 per group); H&Y 1–2; *de novo*	Multidisciplinary intensive rehabilitation treatments (MIRT) group vs. control group (only pharmacological treatment) 28-day treatment delivered twice, at 1-year intervals	UPDRS II and III; 6-min timed walk; timed up-and-go test (TUG); PD Disability Scale (PDDS)	Significant improvements over 2 years for MIRT group only on UPDRS II and III, TUG, and PDDS	
Speech intervention					
Levy et al. (18)	57 (19 per group); H&Y 2; duration: 4.9–5.0 years	Intensive voice treatment [Lee Silverman Voice Treatment (LSVT LOUD)] vs. intensive articulation treatment (LSVT ARTIC) vs. no treatment controls	Intelligibility measured by transcription accuracy of unfamiliar listeners	Only LSVT LOUD group made significant improvements in transcription accuracy post-treatment	Small sample size

(Continued)

TABLE 1 | Continued

References	Participant number; H&Y; disease duration (range or mean)	Intervention and follow-up	Main outcomes	Main results	Study limitations
Swallowing intervention					
Manor et al. (19)	42 (21 per group); H&Y 2; duration: 7 years	Video-assisted swallowing therapy (VAST) vs. conventional therapy (mainly repeated forceful swallows) 6 sessions each group 1-month follow-up	Degree of reduction of food residue in the larynx using fiberoptic endoscopic evaluation of swallowing (FEES); quality of life—pleasure from eating scale	VAST (education on the swallowing process using visual feedback from patient's own swallowing) was most effective for amount of pharyngeal residue	Small sample size; no long-term follow-up
Baijens et al. (20)	109; H&Y 2; duration: 5 years	Conventional treatment only vs. conventional treatment and surface electrical stimulation (SES)-motor vs. conventional treatment and SES-sensory 15 daily sessions for 30 min; 85 different therapists	FEES and videofluoroscopy (VFS)	Improved swallowing with all treatments No significant differences between treatments	Too many variables, measurements, and therapists; too many muscles in the submental region so high chance for no significance SES tool alone may not be able to trigger changes in the central or peripheral nerve system in Parkinson's disease (PD)
Cognition intervention					
dos Santos Mendes et al. (21)	16; H&Y 1–2; duration: 4.7 ± 5.4 years 11 healthy controls	Warm-up exercises and Wii Fit™ training 14 individual sessions 2x week A 60-day follow up	Learning and retention assessed on the scores of 10 Wii Fit games Transfer of learning assessed by the functional reach test	PD participants showed: no deficit in learning or retention on 7 of 10 games; poorer performance on 5 games compared to controls; marked learning deficits on 3 other games associated with cognitive demands Ability to transfer trained motor ability from trained on the games to a similar untrained task	Small participant numbers in each group

H&Y, Hoehn and Yahr scale; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire (PDQ)-39; BDI, Beck Depression Inventory.

defined as $\geq 10^{\circ}$ of lateral trunk bending that resolve almost completely when lying supine; and (c) anterocollis, $\geq 45^{\circ}$ of forward neck bending. While in advanced stage postural abnormalities may be present in 30% of PwPD, few data is available to characterize postural abnormalities in early PD, which seems to occur in ∼5% of H&Y 1–2 patients, and it appears usually isolated (44). Indeed, early and severe postural abnormalities, especially anterocollis, is a red flag for multiple system atrophy diagnosis (45). Multifactorial pathophysiology underlines postural abnormalities, which can be related to a higher disability due to increased risk of falls, back pain, and reduced mobility (46). Postural abnormalities and associated pain treatment remain an unmet clinical need. Camptocormia might improve with dopaminergic treatment, if associated with off periods, or with DBS if it is not yet fixed, while a few positive results have been obtained with botulinum toxin injections for fixed posture.

Posture Intervention

There are no RCTs available on rehabilitation effect specifically for early PD patients. However, high-intensity programs including stretching, strengthening, gait and balance training, or patient-tailored proprioceptive and tactile stimulation have shown promise in a small group of patients (H&Y 2–4) with moderate postural abnormalities. The positive effect was reported up to 6 months post-intervention (47, 48). However, postural deformities are potentially reversible with early recognition and management. Therefore, patients with mild postural abnormalities might be the best target for rehabilitation.

Speech Symptoms

Studies have confirmed that speech difficulties are present in early PD, most commonly mild and including features from one or more of the speech subsystems of respiration (e.g., reduced phonation time), phonation (e.g., breathy or rough vocal quality, increased jitter and shimmer), articulation (e.g., imprecise articulation and slow alternating movements), and prosody (e.g., monopitch and monoloudness) (49–56). Variation was noted across studies in relation to the speech subsystem that was most impaired including articulation, phonation, or prosody (52, 55).

Several associations were also found between speech difficulties and/or motor or cognitive abnormalities in early PD. Speech difficulties have been associated with limb bradykinesia and rigidity, more for participants with akineto-rigid motor phenotype (70%) compared to tremor-dominant phenotype (19%) (49). Moreover, monoloudness was found to be correlated to bradykinesia (50), possibly linked to bradykinesia and rigidity at the laryngeal level (53). Furthermore, speech difficulties were found to be a predictor of cognitive decline in PD (53).

Speech Intervention

Only one RCT is available on the rehabilitation effect specifically for early PD patients. Levy and colleagues (18) found that only the high-intensity voice treatment, Lee Silverman Voice Treatment (LSVT) LOUD®, resulted in significant improvements in intelligibility for patients with mean H&Y 2.1. This was compared to patients receiving a high-intensity articulation treatment or no treatment. The findings are also consistent with the earlier reports from the RCT by Ramig et al. (57) where participants with H&Y 1–3 showed significant improvements in loudness level and functional communication only in the LSVT LOUD® group. Improvements were noted at 1 and 7 months post-treatment.

Swallowing Symptoms

The most common cause of death in PD patients is aspiration pneumonia, resulting from preexisting dysphagia (58, 59), and therefore, its management should be prioritized. Dysphagia is not just a symptom of late stage PD. In a recent study, Pflug et al. (60) used fiberoptic endoscopic evaluation of swallowing (FEES) on 119 consecutive PwPD and found that 20% of the patients with a disease duration of <2 years had aspiration and that 12% (7 out of 57 patients) with H&Y 2 suffered from severe aspiration. Thus, there is a need to manage dysphagia and avoid complications as early as possible.

A number of existing clinical tools have been shown to be unreliable in detecting PD-related dysphagia. For example, swallowing questionnaires were found to detect swallowing problems in 12–27% of the PwPD, with <10% of the PwPD reporting spontaneously about dysphagia (61–63). Clinical bedside predictors of aspiration used for stroke, like the "normal" water swallow test (64), have been shown to be unreliable in PD (65). The Dutch guidelines estimating the maximum swallowing volume or the maximum swallowing speed (66) were not a suitable screening instrument to predict aspiration in PD patients (60). Increased drooling (sialorrhea) was also deemed a sign of penetration or aspiration (67) until Nienstedt et al. (62, 68) found that drooling cannot be considered an early sign of dysphagia. Therefore, instrumental methods [FEES and Videofluoroscopic Swallow Study (VFSS)] are the most valid and reliable methods of detecting risk of aspiration and penetration in PwPD (67, 68), particularly if they present with the following four symptoms: delayed mastication, reduced lingual motility prior to transfer, aspiration, and total swallow time (69). This information is crucial when evaluating studies on swallowing therapy and the validity of outcome measures.

Swallowing Intervention

Three RCTs were identified (70), comparing specific rehabilitative techniques to conventional dysphagia therapy, defined as dietary and postural changes. Logemann et al. (71) studied the validity of compensatory strategies and found that the thickness of the bolus is more effective than postural adjustments ("chin down" maneuver) in preventing the incidence of aspiration in the largest sample to date of PwPD ($N = 711$).

Two RCTs have looked specifically at swallowing intervention in early PD. The use of electrical stimulation therapy (SES) by the Baijens et al. (20, 72) was based on the hypothesis that sensory electrical stimulation (delivered through the VitaStim therapy device for 80 Hz, 700 ms, 0–25 mA) on the submental muscles would have a positive effect on FEES and VFS dysphagia ratings. They compared patients (H&Y ≤1–4) undergoing conventional dysphagia therapy with those undergoing sensory- or motor-level stimulation in the submental muscles, 30 min daily for 15 days. There was no significant difference between the groups. This could be due to the lack of physiological rationale over the choice of electrical stimulation in the submental region and the lack of specificity of the muscles stimulated.

Manor et al. (19) compared specific swallowing exercise therapy to conventional therapy and published the results of video-assisted swallowing therapy (VAST) in a group of 21 patients. This therapy was based on the hypothesis that six sessions of visual information and biofeedback from the swallowing process can be more effective than traditional therapy alone. There was a significant improvement in swallowing function from both interventions, with just the pharyngeal residue parameter being significantly better in the experimental group.

The third RCT examined another form of exercise, the strengthening of the expiratory muscles in order to increase the hyolaryngeal movement that protects the airway from liquid or food penetration or aspiration. The expiratory muscle strength training (EMST) device—a calibrated, spring-loaded valve to mechanically overload the expiratory and submental muscles—can improve submental muscle contraction that helps to elevate the hyolaryngeal complex during swallowing and to strengthen the protective cough. In a study of PD participants with mean H&Y of 2.5, Troche et al. (73) compared the EMST with a sham device. The primary outcome measure, the penetration–aspiration score, significantly improved in the EMST group.

Cognition Symptoms

Mild cognitive impairment with specific involvement of memory, visuospatial, and executive function has been described in early PwPD (74, 75). The executive dysfunction is characterized by deficits in internal control of attention, set shifting, planning, inhibitory control, dual task performance, and on a range of decision making and social cognition tasks (76). Moreover, mild cognitive impairment represents a significant risk factor for early dementia (77). Frontal dysfunction has also been noted using the executive and social cognition battery (78).

Kluger et al. found that fatigue, assessed by the Fatigue Severity Scale, was correlated to reduced visuospatial abilities (79). Cognitive decline in early PD has been associated with

worse motor and non-motor symptoms, suggesting that this reflects a faster progressive phenotype (80). Postural control strategies are strictly correlated to cognitive performance, and Fernandes et al. (81) found that cognitive tasks might improve the postural control strategies during gait initiation.

Cognition Intervention

One RCT has focused on improvements in cognition in early PD based on physical activity. Warm-up exercises and Nintendo Wii Fit™ motor and cognitive skills improved performance in both types of skills in PwPD. However, the ability to learn, retain, and transfer performance improvements after extensive training on Wii Fit games depended largely on the demands, particularly cognitive, of the specific games involved. Thus, those in which patients exhibited no learning deficit have the greatest indication for therapeutic use (21).

Two additional studies with participants at H&Y 1–3 stages have also suggested benefits of physical activity on cognition. Tanaka et al. (82) observed significant improvements in components of executive function on completion of an exercise program. Of note, abstract thinking and the ability to make appropriate decisions under certain circumstances were the primary subsets targeted and improved with the above exercise program. Moreover, the physical activity program resulted in positive trends in verbal fluency and organization of words as well as fewer errors in spatial working memory.

Further, cognitive function showed an improvement after a training period when they were monitored through the Parkinson's Disease Questionnaire (PDQ-39) by Dibble and colleagues (83). Indeed, when PDQ-39 results were compared between PwPD who exercised and those who did not, an improvement in cognitive function was found in the first group.

DISCUSSION

The findings from this mini review have highlighted that subtle changes in the fundamental areas of axial symptoms and cognition can be present even in early PD (**Table 2**). Further database searches should be conducted to substantiate the findings from this mini review, which does not aim to present a systematic review of the topic.

In relation to non-pharmacological interventions over the last 15 years, only a limited number of RCTs have been conducted across areas of axial and cognition with the specific focus on early PD as defined by H&Y $\leq$ 2. However, in spite of this, positive results have been obtained in the studies, with improvements shown across a range of parameters, allowing to suggest several non-pharmacological approaches for gait, speech, swallowing, and cognitive symptoms in early PD (**Table 2**). Overall high-intensity treadmill and cueing strategies have obtained some positive results on gait and FoG, Tai Chi and Qigong, and aquatic exercise for balance, LSVT LOUD for speech, VAST and EMST for swallowing and warm-up exercises, and Nintendo Wii Fit™ skills for cognitive symptoms (**Table 2**). As these symptoms are particularly troublesome and resistant to dopaminergic and surgical treatment in more advanced stages of PD, attention should be given to the development of multidisciplinary non-pharmacological interventions as early as possible before these symptoms become troublesome, as already suggested for palliative care intervention (84). An early treatment approach could help to delay or reduce the high burden and/or medical complications that are often associated with the appearance of these disability milestones in later PD, in spite of the absence of any strong evidences of a clear disease-modifying effect. Although beyond the scope of this mini review, further consideration should also be given to the timing of treatment

TABLE 2 | Gait, balance, posture, speech, swallowing, and cognitive symptoms in early PD and current non-pharmacological treatment strategies.

Symptoms	Early features	Non-pharmacological approaches/strategies
Gait	Lower step width, lower stride duration, and slower swing velocity that contribute to lower reduced gait velocity if compared to healthy subjects	High-intensity treadmill, flexibility/balance/function exercise, supervised aerobic exercise
Freezing of gait (FoG)	No specific FoG features in early PD though more responsive to dopaminergic treatment as more related to off periods	Cueing strategies
Posture	Mild stooped posture, generally isolated postural abnormalities (not combined): either isolated PS, isolated camptocomia, or isolated anterocollis	No specific data only for early PD, for H&Y 1–4 PD-positive data for stretching, strengthening, gait and balance training, or patient-tailored proprioceptive and tactile stimulation
Balance	Subtle postural sway	No specific data for early PD; in H&Y 1–4 PD suggested motor exercise (treadmill, walk with auditory/verbal cueing, partnered dance, step training, aerobic exercise, physiotherapy), Tai Chi and Qigong, and aquatic exercise
Speech	Mild difficulties occurring in 1 or more of respiration, phonation, articulation, and prosody Associations between speech and motor or cognition	High-intensity voice treatment (LSVT LOUD) improved intelligibility in H&Y 1–2 and vocal loudness and functional communication for H&Y 1–3
Swallowing	Aspiration detected in 20% of patients within the first 2 years of the disease	Video-assisted swallow therapy (evidence for H&Y2) and expiratory muscle strength training (EMST) (evidence for H&Y 1–3)
Cognition	MCI with involvement in memory, visuospatial, and executive function; MCI as significant risk factor for early dementia Associations between cognitive decline and motor and non-motor symptoms	Improvements in cognition based on physical activity including Wii Fit games and exercise programs

in early PD and whether the greatest benefit would be for pre-symptomatic or symptomatic patients with PD. In addition, we should clarify if those symptoms need to be targeted directly or rather their risk factors represent the most effective approach. Indeed, we have observed that axial and cognitive symptoms may be subtle in early stage of the disease and eventually difficult to treat or to define a "minimally clinically relevant improvement" for patients. At the same time, recognized risk factors for their occurrence are an older age at disease onset, the need for high L-dopa dose, and the presence of other axial symptoms, such as freezing of gait, falls, or patients who have a postural instability and gait disorder phenotype (30, 85, 86). However, once the abovementioned risk factors are present, it may be too late to achieve optimal gains due to the increased symptoms across axial and cognition domains. This could suggest the need to define if we should apply from the very beginning of the disease specific non-pharmacological strategies to a subgroup of patients with a postural instability and gait disorder phenotype or if we should focus on the pre-symptomatic population, who only present a clinical defined biomarker of possible parkinsonism and dementia development, such as patients with a REM behavior disorder (87).

Early and individualized rehabilitation across the presented axial and cognitive domains would help individuals with PD to maintain a positive impact on QoL and maintain employment and family/social life, while dysphagia and fall management could help to further reduce or delay hospitalization and consequent complications in later stages. A recent longitudinal observational study on the physical activity and early PD has already shown that higher self-reported physical activity is associated with slower disease progression (88). This lends further support to intensive rehabilitation and physical activity in early PD. Despite the few RCTs on early PD, the available evidences suggest that "the sooner the better" is a concept that could be suitable for non-pharmacological multidisciplinary interventions for these four "orphan" symptoms, from the very beginning of the disease.

Further large-scale RCTs are needed to specifically look at interventions for early PD across the areas axial and cognitive domains in a longitudinal manner. To further increase clinical relevance, studies should evaluate treatments that are based on the neurophysiology of PD such as increasing amplitude of movement, sensory–motor calibration, and visual cueing and feedback, using functional outcomes (19, 57, 73). Further, as associations were noted between motor, speech, and cognitive functions, future research should focus on multidisciplinary approaches to combined non-pharmacological management. Advances in this area will continue to empower patients early on in the disease process. The final aim should be to pull together the trends toward a more unified approach in managing these "orphan symptoms" in early PD using a multidisciplinary and individualized care approach that could reduce the disease burden in later PD.

AUTHOR CONTRIBUTIONS

ET and GS were responsible for drafting and revising the manuscript, study concept and design, acquisition, analysis and interpretation of data, and study execution. AM and MF were responsible for drafting/revising the manuscript, study concept and design, interpretation of data, and study execution. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Prevalence of Extrapyramidal Symptoms in In-Patients With Severe Mental Illnesses: Focus on Parkinsonism

Beatrice Roiter, Giorgio Pigato and Angelo Antonini*

Department of Neuroscience, University of Padova, Padova, Italy

Patients with severe mental illnesses may present extrapyramidal symptoms as part of a concomitant neurological disorder or secondary to medications. Extrapyramidal symptoms are frequently unrecognized, have negative consequences for adherence to treatment, negatively affect quality of life and can induce stigma. We estimated and correlated with demographic and clinical variables prevalence of extrapyramidal symptoms in in-patients with severe mental illnesses. Additionally we evaluated ^{123}I-FP-CIT SPECT binding to striatal dopamine transporter in subjects with clinical manifestations suggestive of Parkinson's Disease and recorded therapeutic management and clinical evolution for 6-months. Extrapyramidal symptoms were present in 144 out of 285 patients (50.5%), mainly tremor (94 patients, 33%). There were 38 patients (13.3%) with parkinsonism and they had older age, more medical comorbidities and medical treatments. In 15/38 patients striatal dopamine transporter binding was abnormal resulting in dose reduction or change of psychotropic drugs as well as combination with antiparkinson therapy. Our study confirmed the clinical and epidemiological relevance of extrapyramidal symptoms among inpatients with severe mental illnesses. A small percentage of patients with extrapyramidal symptoms had features compatible with possible diagnosis of Parkinson's Disease. ^{123}I-FP-CIT SPECT was useful to identify dopaminergic dysfunction and initiate dopamine replacement therapy.

Keywords: psychiatric inpatient, Parkinson's disease, dopamine replacement therapy, extrapyramidal symptoms, DaTscan SPECT

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****Correspondence:***
Beatrice Roiter
beatrice.roiter@gmail.com

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INTRODUCTION

Patients with Severe Mental Illnesses (SMI) can present Extrapyramidal Symptoms (EPS) as part of primary neurological disorders or following psychotropic treatment. EPS are linked to lower treatment adherence, poorer psychiatric prognosis and increased mortality (1, 2) and are more severe and frequent in patients with SMI than in other psychiatric disorders, with higher prevalence (68–74%) among hospitalized patients (3, 4). Patients with bipolar disorder are particularly likely to develop Parkinson's Disease (PD) (5).

First Generation (FGAs) more than Second Generation Antipsychotics (SGAs) are drugs with the highest risk to trigger drug-induced parkinsonism (DIP) (6–8), but also Selective Serotonin Reuptake Inhibitors (SSRI), lithium salts and valproate can occasionally induce EPS (9–11).

Among EPS, parkinsonism is particularly challenging because it may unmask a neurodegenerative disease. Recent studies in patients chronically exposed to antipsychotics (APS) have shown, in some individuals, loss of dopamine nerve terminals with ^{123}I-FP-CIT SPECT and benefit from levodopa replacement therapy (12–14). However, these studies regarded almost exclusively patients with schizophrenia.

We aimed at assessing prevalence of EPS in psychiatric inpatients and at evaluating prospectively clinical outcome of patients with parkinsonism, particularly in relation to possible PD.

MATERIALS AND METHODS

We performed two monocentric observational studies: the first was cross-sectional and regarded all psychiatric inpatients compared for presence/absence of EPS; the second was prospective and focused on patients with Parkinsonism. Both studies were approved by our Local Ethics Committee (CESC Padova, AOP0300-DDMEDP-3323/AO/14), informed consent was obtained after all procedures had been fully explained and all data have been stored in our Department.

Our objectives were: to evaluate prevalence rates of whole as well as of single EPS in subjects consecutively admitted to our Inpatient Psychiatric Unit during a period of 18 months; to test for significant association between EPS and demographic (age, gender) and clinical variables (psychiatric and neurological family history, medical comorbidities, psychiatric diagnosis and duration of psychiatric disorder); to evaluate clinical outcome of patients with SMI and features suggestive of PD during a 6-month follow up. Patients discharged after short hospital stay ($\leq$4 days) were excluded from the study.

Psychiatric diagnosis was made according to Diagnostic and Statistical Manual of Mental Disorders (DSM 5) criteria through a semi-structured clinical interview (MINI International Neuropsychiatric Interview DSM 5). Current medications were recorded.

A complete neurological examination was carried out and standardized through a predefined form enriched by items of the Unified Parkinson Disease Rating Scale part III and of DSM 5 to establish the presence of EPS including dystonia, akathisia, dyskinesia, tremor and parkinsonism. Particularly we included items of UPDRS about tremor, rigidity, finger tapping, leg agility, gait and posture. Diagnosis of dystonia, akathisia, dyskinesia and tremor were based on DSM 5 definitions and in line with the indications from the Movement Disorders Society. We listed separately the presence of motor abnormalities, such as postural instability, mild alterations of gait, isolated bradykinesia and isolated extrapyramidal rigidity which we named "non-specific extrapyramidal alterations."

Patients with parkinsonism and clinical features which may have suggested PD (asymmetry, predominant tremor over rigidity and bradykinesia, no other drug-induced movement disorders) (15, 16) underwent ^{123}I-FP-CIT SPECT. ^{123}I-FP-CIT SPECT was evaluated by a specialist in nuclear medicine blind to the clinical condition of the patient and defined as abnormal or normal.

These patients were first managed with targeted interventions based on clinical judgement: watchful monitoring, reduction of APS or switching to a different APS with less propensity to induce EPS. Patients with scan abnormalities in case of low or absent

TABLE 1 | Demographic and clinical variables.

Total sample (N)	325	
Final sample	285	
	Mean (SD)	Median [25°,75° percentile] min:max
Age (years)	46 (17)	45 [33, 56] 14:92
	N	%
Gender (male)	143	50
Familiarity for psychiatric disorder	147	51.6
Familiarity for EPS	47	16.5
Medical comorbidity (any)	171	60
Neurologic	40	14
Endocrine	57	20
Cardiovascular	74	26
Other	105	37
Medical treatment (any)	143	50.2
Dopaminergic/anticolinergic	11	3.9
Drugs inducing EPS	0	0
Psychiatric disorder		
Schizophrenia and other non-affective disorders	76	26.7
Bipolar disorder	79	27.7
Depressive disorder	74	26
Personality disorder	51	17.8
Substance abuse	41	14.4
Intellectual disability	9	3.2
Others	35	12.3
	Mean (SD)	
Duration of psychiatric disorder (years)	33 (18)	
Current psychiatric treatment	N	%
APS	216	75.8
FGAs	16	5.6
SGAs	202	71
Mood stabilizers	119	41.8
Lithium salts	26	9.1
Valproate	64	22.5
Others	29	10.2
Antidepressants	131	46
Tricyclics	4	1.4
Selective Serotonine Reuptake Inibitors	69	24.2
Others	57	20
Benzodiazepines	189	66.3

reduction of parkinsonian symptoms at 1st month were treated with levodopa.

A clinical evaluation at baseline and at 1, 3, and 6 months follow up was performed for all patients by Clinical Global Impression Severity/Improvement Scale for parkinsonism (CGI-S parkinsonism and CGI-I parkinsonism) and for psychiatric symptoms (CGI-S psychiatric disease and CGI-I psychiatric disease).

Cases with uncertain EPS were video-recorded and discussed with a neurologist with expertise in movement disorders (AA) who also screened all cases with parkinsonism, reviewed all ^{123}I-FP-CIT SPECT by visual-qualitative-method and managed patients during the follow up.

STATISTICAL ANALYSIS

We estimated prevalence rates of EPS overall and of every EPS.

A univariate statistical analysis was performed to find association between EPS and all above-mentioned demographic and clinical variables by chi-square test or Fisher exact test (for qualitative variables) and by Wilcoxon rank sum test (for quantitative variables).

Statistical significance was assumed if $p \leq 0.05$.

CGI scores were described by median scores. We did not perform statistical analysis because of the small size of the subsample.

RESULTS

The sample consisted of 285 patients out of 325 admitted in the 18 months of the study. Data were missing in 40 patients because of short hospital stay or lack of consent.

Mean age was 46 ± 17 years, with normal distribution and range between 14 and 92 years. Gender was equally distributed (50% male). About half of patients (51.6%) had familiarity for psychiatric disorder, 16.5% had familiarity for EPS, 60% had medical comorbidities (14% neurological, 20% endocrine-metabolic, 26% cardiovascular, and 37% others). Regarding psychiatric diagnoses, 26.7% had psychosis, 27.7% bipolar disorders, and 26% major depression. Other diagnoses (isolated or as psychiatric comorbidity) were personality disorders (17.8%), substance use disorders (14.4%), and intellectual disabilities (3.2%). Mean duration of psychiatric disease was 33 ± 18 years. The majority of patients (75.8%) were treated with APS (5.6% FGAs, 71% SGAs), 41.8% with mood stabilizers (22.5% valproic acid, 9.1% lithium salts, and 10.2% other anticonvulsants), 46% with antidepressants (24.2% SSRI, 1.4% tricyclic, and 20% others), and 66.3% with benzodiazepines. A very small portion of patients (3.9%) were on anticholinergic or dopaminergic drugs. Polypharmacy was given in most cases. About half of the sample was given additional non-psychotropic drugs, but none of them were given medications at risk for inducing EPS (antiemetics, calcium-channels inhibitors, chemotherapics, immunosuppressants, and antimalarials) (9, 17–19). Characteristics of the sample are summarized in **Table 1**.

Prevalence of EPS overall was 50.5% (144 cases). The most frequent EPS was tremor (94 cases, 33% of the total sample, and combined form in most cases). The second EPS was parkinsonism (38 cases, 13.3%). Other EPS showed the following prevalence rates: akathisia (2.1%), tardive dyskinesia (1.4%), and acute dystonia (0.7%) (**Figure 1**). Patients with uncertain motor alterations (20.2%) were not considered in the overall prevalence. The two most frequent motor symptoms

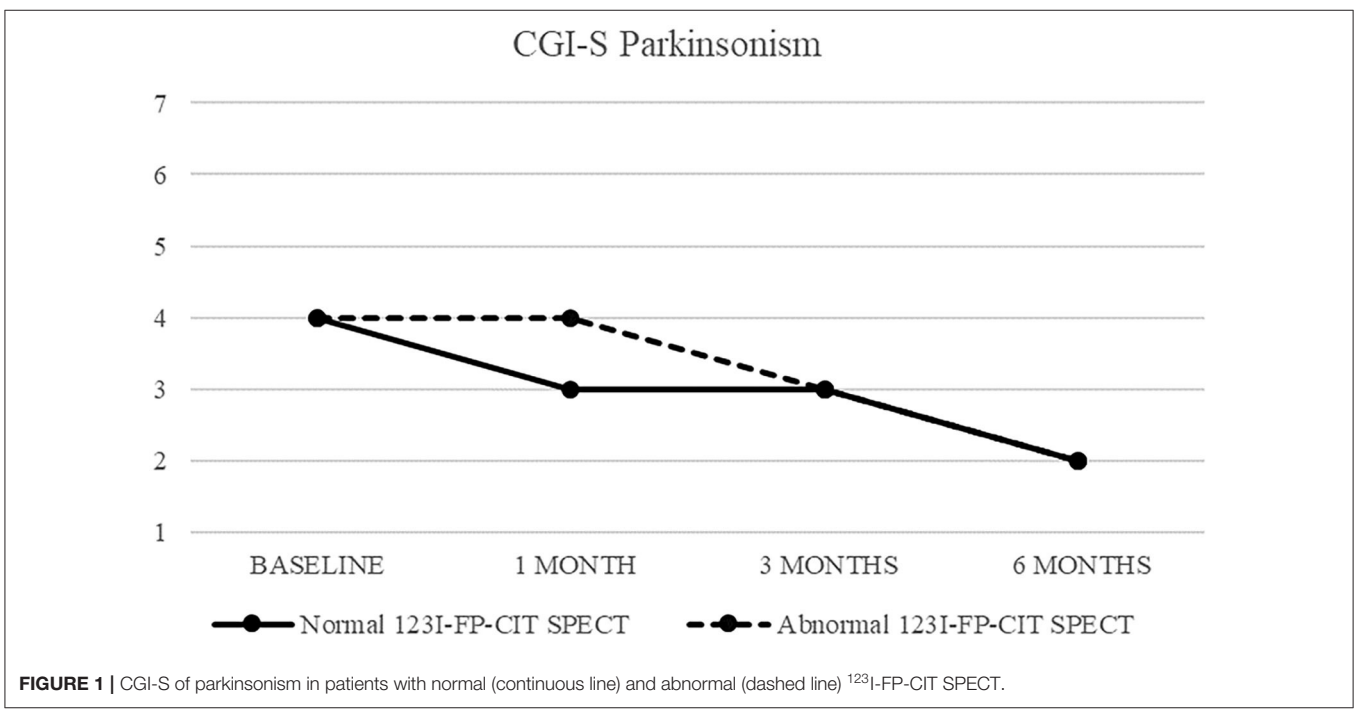

FIGURE 1 | CGI-S of parkinsonism in patients with normal (continuous line) and abnormal (dashed line) ^{123}I-FP-CIT SPECT.

were isolated bradykinesia (18%) and isolated extrapyramidal rigidity (10%).

We compared patients with and without EPS for groups with sufficient sample size: "EPS overall," "tremor" and "parkinsonism." We found no differences between patients with and without "EPS overall." Patients with and without parkinsonism showed significant differences in age (respectively, median age 60 [48, 69] vs. 44 [31, 54], $p = 0.001$), medical comorbidity (respectively, 82% vs. 58%) ($p = 0.01$) and medical therapy (respectively, 86% vs. 46%) ($p = 0.0001$). Ongoing treatment with FGAs was significantly different in patients with and without EPS overall (respectively, 72.7% vs. 27.3%) ($p = 0.04$) and with and without parkinsonism (respectively, 77.3% vs. 40.2%) ($p = 0.03$). Patients with and without tremor showed significant differences in ongoing treatment with mood stabilizers (respectively, 59% vs. 40%) ($p = 0.04$). These results are summarized in **Table 2**.

Twenty-six patients (68.4% of patients with parkinsonism) showed clinical features suggestive of PD and underwent ^{123}I-FP-CIT SPECT to confirm presence of striatal dopaminergic deficits. This group was characterized by almost equally distributed sex (52% males), age over 50 years (range 51–81), mean age 65 (±9) years, prevalence of affective (65.4%) over psychotic disorder, and long duration of psychiatric illness (mean duration 23.2 ± 16.8 years). At baseline, all 26 patients were taking APS (SGAs: 73%, FGAs: 27%), 9/26 cases in combination with mood stabilizers (lithium salts or valproic acid). Eleven out of 26 patients (42.3%) had normal ^{123}I-FP-CIT SPECT striatal binding. Nonetheless in four cases it was decided to gradually reduce dose or switch to another APS (clozapine).

Fifteen patients (57.7%) showed abnormal ^{123}I-FP-CIT SPECT striatal binding (mostly limited to the posterior putamen) and 12 of them were prescribed either levodopa (11 cases) or pramipexole (one case) 1 month after APS reduction.

Clinical response to treatment of these 26 patients is showed in **Figure 2**.

Both patients with normal and abnormal SPECT showed a progressive decrease in median CGI-S-parkinsonism scoring, from four (moderately ill) at baseline to two (borderline ill)

TABLE 2 | Comparisons between patients with and without EPS, with and without tremor and with and without parkinsonism.

			EPS overall			Tremor			Parkinsonism		
			yes	no	*p*	yes	no	*p*	yes	no	*p*
Age (year)		Median	47	44	ns	46	45	ns	60	44	0.001
		25°, 75° perc min-max	36, 57 14-92	31, 55 15-83		37, 56 15-92	31-57 14-84		48, 69 25-82	31, 54 14-92	
Gender		% male	50.3	50	ns	50	50.3	ns	42.8	51	ns
Familiarity for psychiatric disorder		%	48.2	55.5	ns	47.7	53.6	ns	44	52.4	ns
Familiarity for EPS		%	18.4	14.2	ns	20.7	14.4	ns	17.4	16.4	ns
Medical comorbidity	Any	%	65.7	55.2	ns	64.1	59.1	ns	82.1	58.3	0.014
	Neurological	%	17.9	10.4	ns	16.3	13.5	ns	28.6	13	ns
	Endocrine	%	22.1	19.1	ns	23.9	18.9	ns	32.1	19.4	ns
	Cardiovascular	%	26.2	26.9	ns	27.2	26.2	ns	39.3	25.1	ns
Medical therapy		%	55.2	44.4	ns	57.6	46.3	ns	85.7	46.1	0.0001
Psychiatric disorder	Schizophrenia and other psychosis	%	27.2	25.8	ns	27.7	25.9	ns	35.7	25.5	ns
	Depressive Disorders	%	25.8	25.8	ns	21.3	28.2	ns	39.3	24.3	ns
	Bipolar Disorders	%	27.2	28.1	ns	25.5	28.3	ns	14.3	29.2	ns
	Personality Disorders	%	18.4	17.2	ns	21.3	16.0	ns	3.5	19.4	ns
	Substance abuse	%	12.9	16.4	ns	12.8	15.5	ns	10.7	14.9	ns
	Others	%	12.9	11.7	ns	17	9.9	ns	14.3	12.2	ns
APS (any)		%	54.1	46	ns	64	55.1	ns	89	60	ns
FGA		%	72.7	27.3	0,04	59.1	41	ns	77.3	40.2	0,03
SGA		%	52.8	47.2	ns	64.6	39.5	ns	90.8	85.3	ns
SSRI		%	58.2	41.8	ns	62.7	50.2	ns	87.3	75	ns
MOOD STABILIZERS		%	59.1	40.8	ns	59.1	40.9	0.04*	70	65.1	ns
Duration of psychiatric disorder (years)		Median	28	27	ns	23	28	ns	33	27	ns
		25°, 75°	19, 40	20, 42		18, 40	20, 40		20, 60	19, 40	

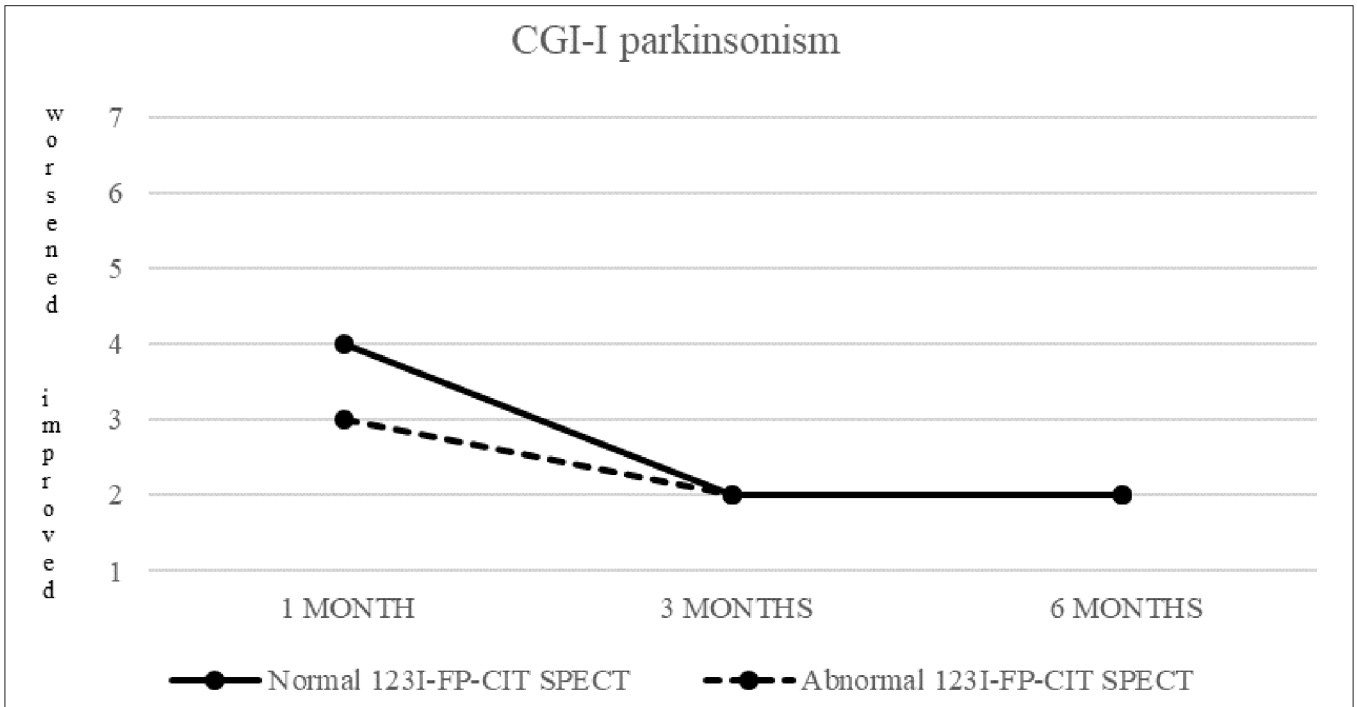

FIGURE 2 | CGI-I of parkinsonism in patients with normal (continuous line) and abnormal (dashed line) ^{123}I-FP-CIT SPECT.

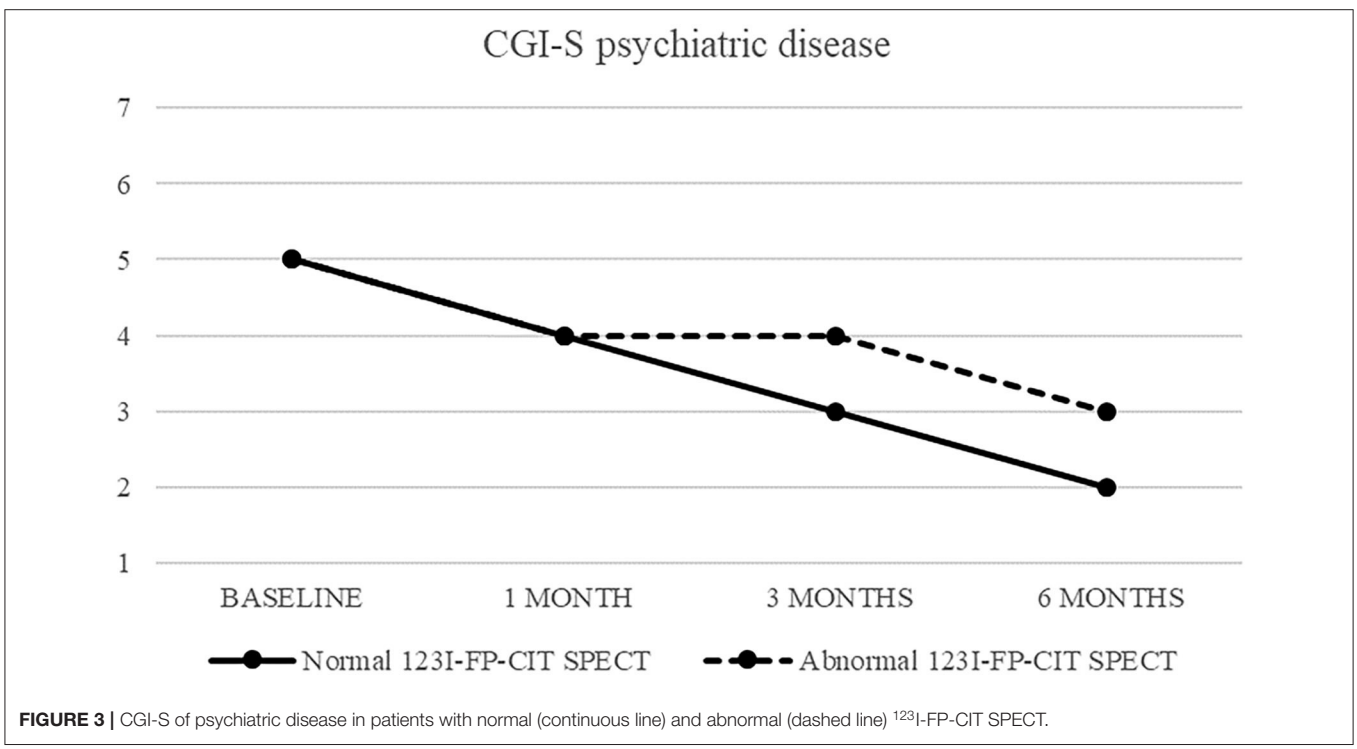

FIGURE 3 | CGI-S of psychiatric disease in patients with normal (continuous line) and abnormal (dashed line) ^{123}I-FP-CIT SPECT.

at 6 months. Patients with normal SPECT showed no change (median CGI-I = 4) after 1 month, but a significant improvement (CGI-I = 2) after 3 and 6 months, while patients with abnormal SPECT showed improvement already at 1 month follow up.

Also CGI-S scoring about psychiatric disease progressively decreased, from five (markedly ill) to two after 6 months. CGI-I confirmed an improvement, although less pronounced (minimally improved after 3 and 6 months in both groups) (**Figures 3**, **4**).

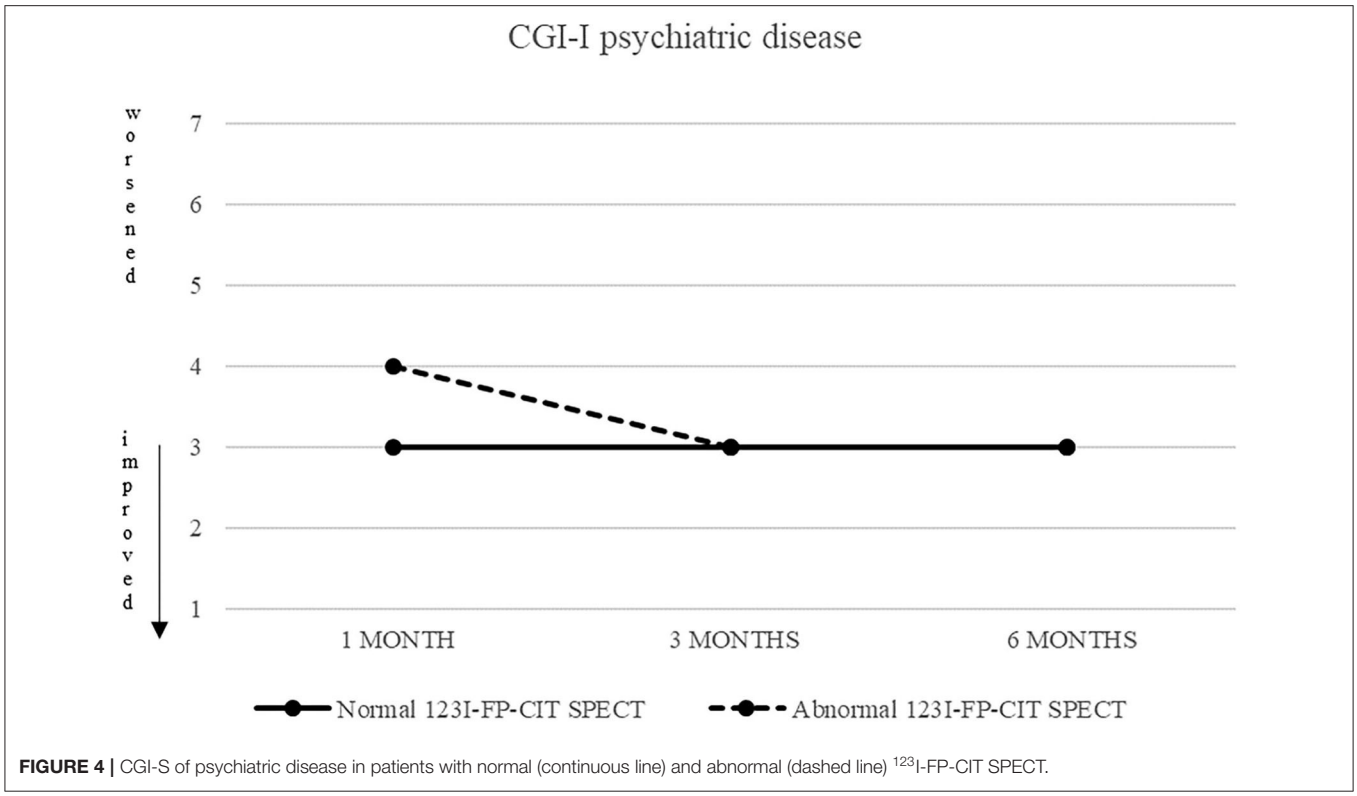

FIGURE 4 | CGI-S of psychiatric disease in patients with normal (continuous line) and abnormal (dashed line) ^{123}I-FP-CIT SPECT.

DISCUSSION

We reported high prevalence of EPS (50.5%), particularly tremor and parkinsonism, in psychiatric patients routinely managed in our Psychiatric Hospital Unit, which is almost double of that reported in other series (28%) (20).

To our knowledge, there are no other studies on overall prevalence of EPS among psychiatric inpatients. Available studies regarded mainly patients with schizophrenia treated with APS, selected for type and time of exposure, or focused on one specific EPS. Other studies found that parkinsonism is often under-recognized and that, in patients treated with APS, its prevalence varies between 20 and 35%, which is similar to that of akathisia and tardive dyskinesia (10–30% and 20–40%, respectively) (15, 21, 22). Prevalence rates of parkinsonism (13.3%), akathisia (2.1%), and tardive dyskinesia (1.4%) was lower in our study than literature.

Discrepancies may be attributed to various reasons. First, we used a structured assessment for detection of EPS in a hospital setting. Second, our sample consisted of a wide range of psychiatric disorders with different propensity to be associated to EPS. Third, most patients were prescribed new generation APS (greater use of SGAs) which have lower risk to induce EPS. Lastly, isolated bradykinesia (17.8% of total sample) or extrapyramidal rigidity (9.8%) were not considered as full-blown EPS according to DSM 5, which may have resulted in slight underestimation of EPS prevalence.

It should be stressed that our cross-sectional design did not allow to identify any causal relationship between all variables considered: evaluation of prevalent cases was a limit of the study because we could not assess past pharmacological treatment. We only reported psychopharmacotherapy in general terms because most patients were taking a long-term polypharmacy, so we were not able to know cumulative doses and times of exposure, both involved in the genesis of EPS. However, significant differences were found in ongoing treatment, particularly higher prevalence of FGAs in patients with EPS overall and parkinsonism compared to patients without, and higher prevalence of mood stabilizers in patients with isolated tremor compared to patients without.

We found that only a minority of patients fulfilled criteria for possible PD and an even smaller proportion presented reduced striatal DAT binding. Patients with parkinsonism were on average 20 years older and had more comorbidities, which is in line with previous studies (23, 24). This might suggest greater vulnerability in elderly subjects but also greater likelihood to develop dopaminergic dysfunction in that age range. It should also be underscored that patients with parkinsonism had a very long duration of psychiatric illness, predominant bipolar disorder as well as exposure to various APS and mood stabilizers over the years. Nonetheless the severity of parkinsonism was moderate at first visit, with some improvement during follow up possibly due to APS dose adjustment or change. In those subjects we introduced primarily levodopa with one exception where we opted for pramipexole since patient presented tremor and apathy. The positive outcome of these patients is in line with previous studies (14).

This study confirmed the clinical and epidemiological relevance of EPS among inpatients with SMI, mainly tremor

and parkinsonism. A small percentage of patients with EPS have features compatible with possible PD and presence of reduced striatal DAT binding, resulting in treatment modification.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee for Clinical Trial (CESC) - Padova - Prot. AOP0300-DDMEDP-3323/AO/14. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BR and GP drafted the work. AA revisited it critically. All authors gave substantial contributions to the conception and design of the work and to the acquisition, analysis or interpretation of data, and provided approval for publication of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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METHODS
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PasoDoble, a Proposed Dance/Music for People With Parkinson's Disease and Their Caregivers

Lydia Giménez-Llort[1,2]* *and Lidia Castillo-Mariqueo*[1]

[1] *Department of Psychiatry and Forensic Medicine, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain,* [2] *Institut de Neurociències, Universitat Autònoma de Barcelona, Barcelona, Spain*

Managing the heterogeneity of Parkinson's disease symptoms and its progressive nature demands strategies targeting the hallmark disrupted neurotransmission but also the comorbid derangements and bolstering neuroprotection and regeneration. Strong efforts are done to find disease-modifying strategies, since slowing disease progression is not enough to hamper its burden and some motor symptoms are resistant to dopamine-replacement therapy. The inclusion of non-pharmacological strategies can provide such a multitarget umbrella approach. The silent long-term biological process that precedes the clinical onset of disease is a challenge but also an opportunity to reinforce healthy lifestyle known to exert preventive/therapeutic effects. These non-pharmacological strategies are foreseen as able to reduce the prevalence and the global impact of long-term diseases demanding strong management of patient-caregiver quality of life. In this regard, European guidelines for Parkinson's disease recommend physical-related activities such as aerobic exercise and dancing known to improve functional mobility and balance in patients. Here, we propose "PasoDoble," a novel dance/music patient-caregiver intervention with additional preventive value. The rationale is founded on evidence-based therapeutic benefits of dance/music therapy and the singular features of this widely extended Hispanic dance/music targeting motor symptoms, mood/cognition, and socialization: (i) As a dance, an easy and simple double-step pattern (back-and-forward and lateral movements) that evolves from a spontaneous individual dance to a partnered dancing, performed in social groups and involving dancing-figures of increasing complexity; (ii) "PasoDoble," as a music that can be sung, has musical rhythmicity with high groove and familiarity that will help to synchronize the steps to the rhythm of music; (iii) Widely extended (Spain, Mexico, Puerto Rico, Colombia, and USA) and easy-to-learn for others. As a regular dancing "PasoDoble" can improve and preserve function, mood and socialization, as an intervention the method is structured to improve gait and balance; facilitate movement, reaching and grasping; muscle power and joint mobility; reduce of risk of falls, and increase of aerobic capacity. Finally, this easy-to-implement into patient care and free-living environments (elderly social centers,

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***Correspondence:**
Lydia Giménez-Llort
lidia.gimenez@uab.cat

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home care) rehabilitation programs can promote positive emotions and self-esteem, with added general improvement of social attachment and recognition, thus improving the quality of life of patient-caregiver.

Keywords: Parkisnon's disease, prevention, rehabilitation, quality of life, caregiver, dance and movement psychotherapy, family-centered care, home care

INTRODUCTION

Parkinson's disease (PD), as most aging associated neurodegenerative pathologies, has a heterogeneous presentation. Besides the hallmark motor symptoms, sensorial, cognitive, and psychiatric alterations can also be developed (1, 2). Managing such a diversity of symptoms and progressive nature demands strategies targeting the hallmark disrupted neurotransmission but also the comorbid derangements and the bolstering of neuroprotection and regeneration (3). Currently, there are various treatment strategies to address the symptoms and progression of PD but pharmacotherapy is the treatment of choice (2–4).

The dopaminergic therapy targets the prominent loss of dopaminergic neurons in the substantia nigra that caused a deficiency of dopamine and results in the main clinical symptoms that characterize the disease: tremor, bradykinesia, rigidity, and postural instability (4–6). Besides, other typical motor symptoms can be observed, such as an altered gait pattern, freezing of walking steps and deficits in coordination, directly impacting general motor control, and mobility of the entire body of the individuals who suffer from it (7). Thus, these motor disorders are dramatically evidenced in the gait of the individual as the disease progresses, recognizing an "akinetic-rigid gait" when these alterations are accentuated (8). Gait disturbances include decreased steps speed with decreased length as well, a narrow support base, and a hunched posture that affects the neck, shoulders, and trunk. Also, the oscillation of the arms and the rhythmic movement of the upper and lower cingulum are reduced, causing the arms to remain in an adducted position and flexed toward the trunk. In the lower extremities, the feet are raised less than normal, which can lead to walking intermittently causing greater variability in each step and therefore the gait time spent increases (4, 7, 8). Freezing usually occurs at the start of the gait but can also appear when turning or approaching an obstacle. It develops from early stages and usually decreases with medication in less severe stages. While the adaptation mechanisms and postural adjustments along with the dynamic balance are altered during the execution of the steps in the gait (6).

With regards to non-motor symptoms (NMS) of PD, growing number of literature (3, 9) consistently describes REM sleep behavior disorder and constipation; mood and affect disorders with anxiety and depression; sensory disfunction with hyposmia and taste loss, as early non-motor features preceding onset of motor symptoms of the disease (10). Excessive daytime sleepiness, fatigue, pain, apathy, and dysfunction of other autonomic responses such as urinary dysfunction and orthostatic hypotension, excessive sweating, are also commonly reported in the early-stage PD. Neuroimaging of NMS in PD showing early affectation of monoamine and cortical systems beyond the nigrostriatal dopaminergic pathway supports these broad spectrum of symptoms that during the progress of the disease will also involve cognitive domains, with executive dysfunctions (11), deficits in procedural learning (12, 13), visual hallucinations and dementia, as well as complex behavioral disorders (14). Executive functions and attention seem to be associated with gait and balance, a relationship that is conspicuous in normal aging and in neurodegenerative diseases that affect cognition and/or motor functions (15). However, other reports found no correlation between NMS burden and motor severity, age, or gender (10).

At the therapeutical level, strong efforts are done in order to find disease-modifying strategies, since slowing disease progression is not enough to hamper the burden of disease and some symptoms are resistant to dopamine-replacement therapy (1–4, 16). The above mentioned prodromal stages unveiled by NMS point at new scenarios for early intervention, but inability to make a conclusive diagnosis at the earliest stages as well as difficulties in the management of symptoms at advanced stages of the disease are still important clinical challenges (1). In this sense, the inclusion of non-pharmacological strategies and managing PD with a multidisciplinary perspective can contribute to provide such a multitarget umbrella approach. Thus, the silent long-term biological process that precedes the clinical onset of disease is a challenge but also an opportunity to reinforce healthy lifestyle known to exert preventive/therapeutic effects. For its part, non-pharmacological treatment requires the intervention of several disciplines, among which is therapeutic exercise, use of auditory, visual and somatosensorial stimuli, care strategies and complementary therapies, which reflects the wide range of options and alternatives of choice. These non-pharmacological strategies are foreseen as able to reduce the prevalence and the global impact of long-term diseases demanding strong management of patient-caregiver quality of life. In this regard, European guidelines for Parkinson's disease recommend physical-related activities such as aerobic exercise and dancing known to improve functional mobility and balance in patients (17).

"PASODOBLE", A PROPOSED DANCE/MUSIC INTERVENTION FOR PEOPLE WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS

PD rehabilitation programs for people with PD include combined multimodal exercises of strength, balance, coordination, and/or aerobic training for the improvement of physical and motor condition (18, 19). It is possible to create circuits with a great variety of exercises, for example, those used in walking and overcoming obstacles that can provide benefits in patients with mild and moderate PD, reducing intrinsic fragility and providing greater possibilities for the control of dynamic balance in the performance of the steps in each stride (20, 21).

In this context, pasodoble is a type of ballroom dance that is characterized by its base step consisting of walking, so integrates many features of therapeutic exercise. In this traditional dance, the couple is of great importance since figures of eight are made in eight steps in a coordinated and harmonious way to the rhythm of the music (2 × 4). The important thing is to perform the dance steps with the upright posture, raising the chest and contracting the abdomen for proper control of the trunk. Some of the basic figures that can be performed include walking back and forth on the same site, making turns, and incorporating lateral movements. Then it progresses to separation and return of the couple, walk of the woman and crossed steps at different times. Finally, fast turns are made with forward, backward, and lateral movements in 8 times.

Based on this traditional pasodoble dance/music, here, we propose "PasoDoble," a novel dance/music patient-caregiver intervention with additional preventive value. We also want to highly its potential value for maintenance of physical well-being as a regular dancing in the lifestyle of the Hispanic elderly. We aim to provide a methodological scenario (see **Figure 1**) and the theoretical fundaments (see **Box 1**) for the benefits of this dance and method (see **Box 2**) improving gait, balance, and functional disturbances in people with Parkinson's disease but also patient-caregiver quality of life, as a family caregiving intervention. However, the investigation of this approach as an intervention targeting PD is still a work that is currently in progress (see **Figure 2** for Measures and Tools).

The rationale of our proposal "PasoDoble" as a PD intervention is founded on evidence-based therapeutic benefits of dance/music therapy that will be discussed below. Also, it is based in the singular features of this widely extended Hispanic popular dance/music targeting motor symptoms, mood/cognition and socialization (see **Box 2**).

Rehabilitation programs for PD should be "goal-based" (aimed at practicing and learning specific activities in core areas), but it is necessary to identify a number of practical variables (intensity, specificity, complexity), as well as adaptations related to the individual characteristics of the patients according to the degree of involvement and severity that the disease has caused with its clinical manifestations of motor disorder.

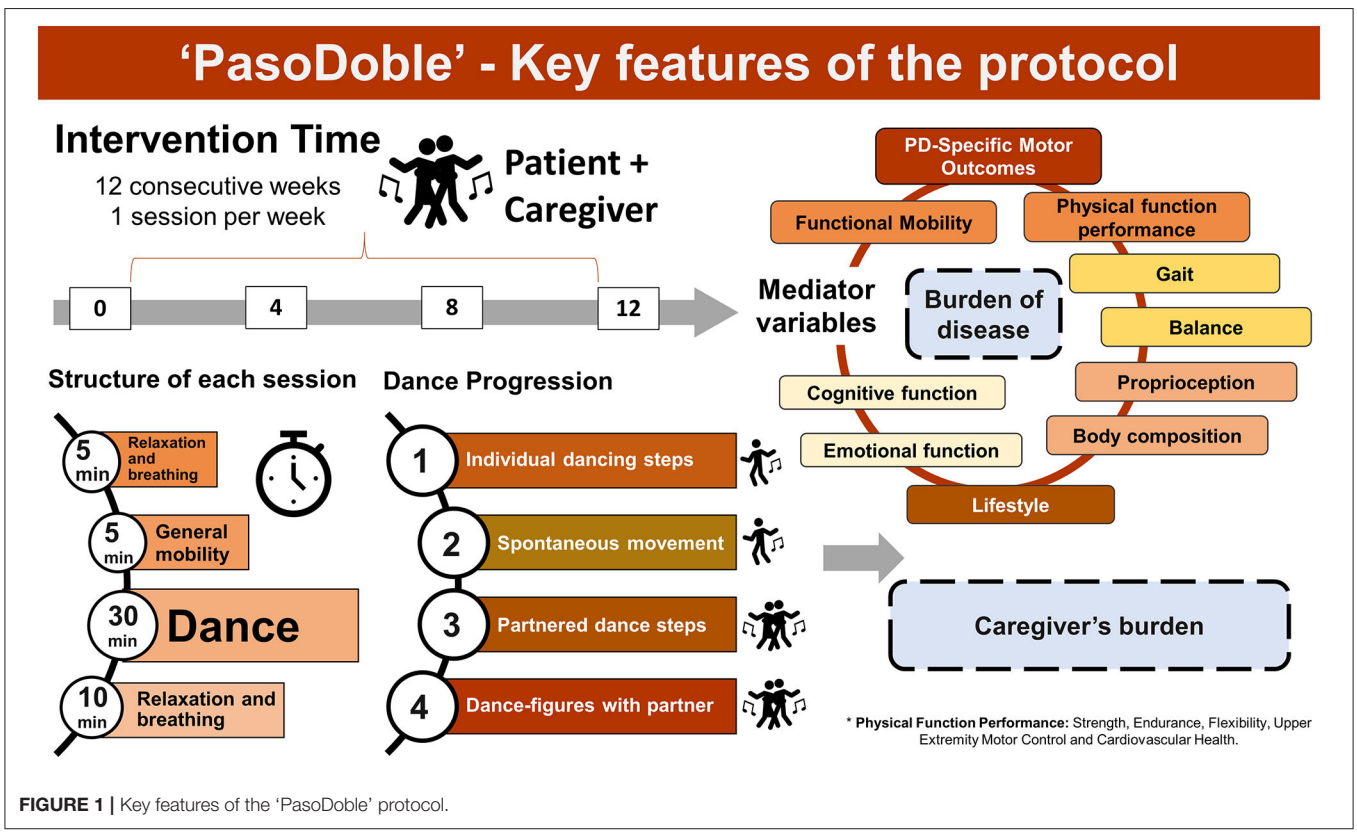

FIGURE 1 | Key features of the 'PasoDoble' protocol.

BOX 1 | Scientific rationale of "PasoDoble."

The evidence-based therapeutical benefits of dance/movement therapy and the singularity of PasoDoble features. The European physiotherapy guideline for Parkinson's disease recommends dance as "a meaningful approach to improve functional mobility and balance" (17). According to the stage of progression of the disease, the proposed **time-line of intervention** relays on four **key areas**:
1) Cueing strategies to improve gait,
2) Cognitive movement strategies to improve transfer,
3) Exercises to improve balance and
4) Training of joint mobility and muscle power to improve physical capacity (22).
In fact, since the early work by Westbrook and McKibben (23), **dance/movement therapy** has been reported been more effective than exercise in the outpatient treatment of patients with Parkinson's disease. Underlying **neural mechanisms** are a research area of growing interest (24) and it has been speculated that regular dancing practice may facilitate activation of sensory-motor areas impaired in the brain of people with PD (25). On parallel activation by means of **music** of brain areas such as amygdala, nucleus accumbens, hypothalamus, hippocampus, insula, cingulate cortex, and orbitofrontal cortex are pointed out as those providing emotional benefits (26). Besides, in **partnered dancing,** dance partner and music may exert additive effects on achievement of **rhythmicity** since they both provide **spatial external cues and timeframes** that may facilitate movement initiation and execution in a PD-brain with impaired basal-ganglia that leads not only to movement disturbances but also worse rhythm perception as compared to controls (27). Motor control, expertise and action-perception links, sensory cues for physical contact, synchronization of the steps to the rhythm of music, **familiarity** with the music, **groove** that compels the body to move, and motor learning processes are also considered among key factors in neurocognitive control of dance perception and performance (24, 28). Furthermore, partnered dancing as a **social dance practice** in **community settings** has been described as an effective and attractive form of entertaining for patients with PD due to the level of physical interaction and amusement between partners and the social group.

BOX 2 | **The 5 key fundaments of the "PasoDoble" Method** The "Pasodoble" methods is based on the 5 key features, that can be summarized as follows:

i) As a dance, an **easy and simple double-step pattern** (back-and-forward and lateral movements) that evolves from a **spontaneous individual dance** to a **partnered dancing**, performed in social groups and involving dancing-figures of increasing complexity; Based in a simple walking pattern (2 beats, 8-to-8 steps, 2 × 4 rhythm), easy to translate into a training program. Its basic performance is spontaneous and flexible, not predefined routine from start to end, but guided by the rhythm of the music, with the directionality of movement including the **facilitatory effect of the partner**.
ii) "PasoDoble," as **a music that can be sung**, has musical rhythmicity with **high groove and familiarity** that compels the body to move, overcoming the difficulties and tiredness that the parkinson's patient encounters with each movement. It also helps to synchronize the steps to the rhythm of music with the extra-guidance of the dance partner (caregiver);
iii) **Widely extended** (Spain, Mexico, Puerto Rico, Colombia, and USA) and **easy-to-learn** for others.
iv) While **as a regular dancing** "PasoDoble" can improve and preserve function, mood and socialization, **as an intervention** the "PasoDoble" method is structured to improve gait and balance; facilitate movement, reaching and grasping; muscle power and joint mobility; reduce of risk of falls, and increase of aerobic capacity.
v) Finally, this **easy-to-implement into patient care and free-living environments** (elderly social centers, home care) **rehabilitation program** can promote positive emotions and self-esteem, with added general improvement of **social attachment and recognition**, thus improving the **quality of life of patient-caregiver**.

The implementation and realization of the protocol "PasoDoble" include the following methodological aspects: firstly, where the dance takes place, it must provide the participants first security. It must have the physical requirements that provide a spacious and illuminated space to develop each of the sessions. The environment can be adapted for video-recordings and train the professional team (neurologist, nurse, occupational therapist, psychologist, kinesiologist, and professional dancers). According to precedent data in other dance/movement therapies, 1 h session, twice a week, 12 weeks, pre-test (Evaluation 0) and follow-up evaluation at 3, 6, 9, and 12 months would be the proposed duration by which an individual must engage in the intervention to elicit a therapeutic benefit. Here, we have designed the intervention also considering how dancing is scheduled in social clubs elderly people. The protocol lasts 12 consecutive weeks (a seasonal trimester) with a frequency of therapy of once a week with a structure and duration of each session as follows (see **Figure 1**): duration of 50 min (a total duration of 1 h if considering get started/get over) with an opening with relaxation and breathing (5 min), general mobilization (5 min), PasoDoble dancing (30 min), and a closing with relaxation and breathing. The dance progression during the weeks considers 4 phases of intervention or stages of training. Initially, simple and less complex movements will be performed until reaching the dance performance in pairs (1. spontaneous movement rhythmicity and 2. sequence of dance steps), then 3. partnered dance and finally 4. dance-figures with partner. That is, an intervention program would fit with a trimester proposal, and 1 session per week. In the context of Hispanic population, but not restricted to them, a widely extended habit of elder people is to enroll to social clubs, when once a week (usually Sundays) life music is performed and elderly dance with their own partners or other elderly attending the social event. Family associations for PD also have their own spaces were rehabilitation programs are performed. Here, the intervention time was designed to be perfectly adapted to this natural timings and habitudes, but under a structured protocol where decisions have been made by the therapist, not the participants. An important question in the inclusion criteria to be part in the program is to do a functional evaluation (pre-test) to determine the stage of PD (I, II, and II of the Hoehn and Yahr scale) so that the person can be allocated to the corresponding level. Age of participants should not be a criteria. Control of drug therapy must be done. The inclusion of a regular partner in this partnered dance provides an internal control group, at least for most functional variables. However, since the proposed method is also aimed to improve quality of life of caregivers, enrolling as the partners in the dance,

Measures	Instrument / Test · Normal Aging – PD Patient & Caregivers
Progression of PD symptoms	Hoehn and Yahr scale
PD-Specific Motor Outcomes	UPDRS – III (Unified Parkinson's Disease Rating Scale)
Functional Mobility	TUG (Timed up and go test)
Physical Function Performance	Strength: Arm Curl test - Chair stand test Endurance: 2 minutes step test Flexibility: Chair-sit and reach-test - Back scratch test. Upper Extremity Motor Control: 9HPT Nine-Hole Peg Test Cardiovascular Health: Six-minute walk and waist–hip ratio
Gait	Six-minute walk Gait performance: speed, stride time, stride length, basis support
Balance	BBT – Berg balance test: tandem, semi-tandem, and side-by-side stands
Proprioception	Different joint position sense - kinesthesia
Body composition	BMI (Body mass index)- Measurements and calculations including body weight, percentage of fat and muscle
Lifestyle	PDQ-39 (Parkinson's disease questionnaire – 39)
Cognitive function	MMP (Mini-Mental Parkinson) – MMS-F (Mini-Mental State Examination of Folstein)
Emotional function	GDS (Geriatric Depression Scale of Yessavage)- Self-Report
Caregiver's burden	Caregiver burden interview of Zarit

FIGURE 2 | Measures and tools to evaluate the effects of 'PasoDoble' in normal aging, the PD patient and the caregivers.

self-reliant older adults would be the best control group, for burden of disease in PD patient and caregiver's burden as the partner. As in many other proposals, blind evaluators, and pilot studies in real settings, are also advised.

Although non-pharmacological therapy has gained great importance, there is still little consensus on how to measure the analysis of therapies, being a wide and interesting field of research to address (29–31). The current ongoing research using this PasoDoble protocol is focused on clinical measures of PD and caregiver's health, such as motor symptoms, mood/cognition, and socialization (UPDRS, BBS, TUG, 6MWT, FOG, DGI, Sit-to-stand test, Beck, Zarit QoL). The instruments and specific tests for each variable are as mentioned in illustration 2. The expected result in a pre- post- analysis and as compared to control standard physical activity, include: improvement of gait and balance, facilitation of movement through external cues and specific movements, better coordination and stability with the partner, reaching and grasping, muscle power and joint mobility, reduction of risk of falls, increase of aerobic capacity (see **Figure 1**). This rehabilitation program will be easy to implement into patient care but also in already socially established free-living environments (community setting such as elders social centers, home) improving patient-caregiver quality of life by means of promotion of positive emotions and self-esteem with additional general improvement of social attachment and recognition.

Finally, limitations of the proposal, most of them in common with other non-pharmacological strategies, must also be mentioned here. Studies in older adults have shown that exercise

outcomes, such as improved self-efficacy, are more strongly predicted by the social cognitive factors associated with exercise. In fact, in spite of being a common shortcoming, PasoDoble has an advantage, as the naïve ballroom dance (pasodoble) is already popular in elderly social centers, and part of its strength to be implemented as a preventive or rehabilitation program (with a schedule or protocol) relies on this "familiarity" or "social" aspect. So, social cognitive factors are part of the virtues of this dance and looked for, with purpose, as an intervention. The small number of participants, lack of partner for the interventions or dancers unfamiliar with PD can be also foreseen as a critical point. However, this kind of dance is so popular but also intimate, that it can be implemented to the minimum of one patient and his/her therapist. Regarding the time schedule, a 3-month duration of the intervention may be too short to see strong effects upon participation, and commitment over a 10-week period may be difficult, in this and other programs. As mentioned before, the initial proposal is established in 12 weeks (3 months) as it is a formula that fits trimestral (seasonal) activity proposals and easier to be committed with. With regards to the severity of PD, it may vary within the sample. Thus, heterogeneity in the level of impairment requires a prior accurate evaluation of the motor impairment, could affected participation but could be solved with the establishment of different groups or levels. The last, but not least, randomized controlled trials are necessary to better understand the effects of programs of dance therapy for older adults with and without PD, and this also applied to this proposed method that is currently under study.

"PASODOBLE" AS A FORM OF THERAPEUTIC EXERCISE FOR PD AND PROTECTIVE STRATEGY FOR CAREGIVERS

In the following paragraphs we will provide further discussion on the benefits that can be derived as a form of therapeutic exercise programs for rehabilitation in PD, thereafter those that are in common with other dances, and finally we'll present the scenario of PasoDoble in this 2020–2030 Decade of Healthy Aging where family-centered care models are among the most important needs pointed out by UN.

The main objective of therapeutic exercise and rehabilitation is to improve and maintain the quality of life of people with PD. This is done by helping to improve or increase mobility, balance, gait, coordination, and thus maintaining the functional autonomy of the patient for a longer time. Educating their environment, family, caregivers, and community will also contribute to finally promote an active role in the rehabilitation process (18, 32). The benefits of exercise and physical activity are widely known and have led researchers to become interested in the possibilities it offers as a therapeutic resource of rehabilitation. It has its own characteristics and multiple physiological benefits, according to the "dosage" used, which is why it attracts even more to differentiate its effects in diseases such as PD (18). At the brain level, exercise increases synaptic strength and influences neurotransmission, thus enhancing the functional circuits involved in PD. Furthermore, exercise is a fundamental element of motor learning, influencing, and modifying motor deficit parameters in neurodegenerative diseases (29). The exercise is a fundamental element of motor learning, influencing and modifying motor deficit parameters in neurodegenerative diseases. In PD, the exercise increases synaptic strength and influences neurotransmission, thus enhancing the functional circuits involved in PD (29, 33).

Engagement of PD patients in different types of physical exercise, such as walking on a treadmill, is reported to reduce gait disturbances, to improve executive functions and motor learning (15, 30). Still, gait improvements seem to be specific to the type of motor activity practiced during exercise, whereas improvements in cognitive inhibition are not. This suggests indirect action mechanisms such as enhancement of cardiovascular capacity to. These results are also relevant for the development of targeted aerobic exercise training interventions to improve functional autonomy in PD patients (15). In this sense, regarding exercise dosage, there are various exercise guidelines that generally have a training duration of 4 to 48 weeks and a total of 4 to 96 h, which vary according to the therapeutic objectives and the selected training modality (21). The exercise is usually performed under moderate to high intensity for a long term (34). Mak et al. (19) point out that a training period of at least 6 months is effective to achieve a clinically significant improvement in UPDRS-III scores as well as improvements in gait and walking ability. Here, an intervention time of 12 consecutive weeks is proposed as it is a schedule feasible to be implemented as seasonal "trimestral" (alone or repetitive in an annual schema) schedules in most elderly social center settings (i.e., Winter PasoDoble Program).

As specific resources, improving gait parameters, workouts with differentiation of surfaces, weight support, among others, have also been described (21). These have been combined with signaling strategies, which provide external signals to facilitate the initiation and/or continuation of movement, so patients are instructed to pay attention to signals and to step on the line or markers, or to go to the rhythm of an auditory or somatosensory signal (20, 35). Some examples include visual cues (lines or markers on the floor and on the treadmill), rhythmic auditory cues, metronome rhythms, or music at a preset frequency, somatosensory cues–tactile sensation given to a part of the body as in Tai Chi (a repetitive bodyweight martial art that shifts from one foot to the other, taking a step and turning in different directions) (33, 36, 37).

In this context, Pasodoble is a type of ballroom dance and high groove music. Dance has been incorporated as a rehabilitation strategy since it has sequenced movements performed with music (31, 36). The treatment of neurological diseases is complex due to emotional factors, so dance/movement therapy is of potential benefit in such circumstances. Dance therapy for the rehabilitation of PD (dance/movement) would be more effective than exercise in the outpatient treatment of patients (25, 38) (Hackney and Earhart, 2010). An example is Tango, which improves aerobic capacity, coordination, and balance (26). The benefits observed in dance as therapy can be explained through several mechanisms such as external signals, which can be derived from the music or the couple, as well as the specific

movements incorporated in the form of the dance (39, 40). Music provides auditory cues to the premotor cortex through the cerebellum and to the supplemental motor area via the thalamus, allowing the use of these auditory cues to impact individual's gait (35). Some studies indicate that speed, start of gait and cadence are favored with this type of therapy in PD (41, 42). The rhythm of the music and the dance partner can facilitate the coordination of the steps, increase balance and postural stability (43). In turn, signals such as a change in weight and direction of movement given by the dance partner can help initiate the movement and increase or maintain the length and cadence of the steps (Hackney and Earhart, 2010). The dance provides specific patterns of guided movement, as well as proprioceptive and tactile signals in interaction with the auditory signals that the music gives off, facilitating the integration of key elements for rehabilitation in this disease. The current evidence indicates dance, as a complementary therapy, can contribute to the improvement of various symptoms of the patient, both motor, cognitive, and emotional (26, 44, 45).

Dance is a pleasurable and captivating activity that involves motor, cognitive, visuospatial, social, and emotional engagement (39). It is contributing to the configuration of the body schema, the perceptual organization, favoring coordination. Increase body awareness and movement awareness through musical rhythms and melodies (35). It requires spatial integration, rhythm, synchronization with external stimuli, balance, and coordination of the whole body, which makes it a highly useful therapeutic resource for the rehabilitation of PD (25, 35). Furthermore, the dance and movement has a psychotherapeutic, which aims to integrate the individual physically and emotionally, increase the level of personal and body perception, which allows for wide movements and encourages the individual to express himself authentically through the integration of the unconscious (40). The dance rhythmic stimulation may be used to improve gait automation since it helps cognition in the emotional domain, requiring reinforcement in the connections of the frontal cortex and the amygdala (39, 46). In addition, the dance allows participants to establish positive emotional aspects and valence that they experience and store, facilitating knowledge about postures and movements in the most optimal way (47, 48).

Previous studies of dance therapy (Tango, Ballroom, Valls) have shown beneficial results on some gait parameters, as well as an increase in the perception of time, modifying the altered elements for displacement. In turn, improvements in postural balance and motor adjustments for general stability have also been included (46). Dancing in PD promotes greater dynamic balance, increased walking speed, longer step length, positive effects that can be sustained over time (49–51).

Pasodoble is a ballroom where both the person with PD and his/her caregiver (spouse, most of the times) can be involved, although the partner can be another subject or the therapist, too. In this aging population, the role of caregivers for the well-being of the elderly, especially of those affected by neurodegenerative disorders, is crucial (52). In most cases, the spouse or a family member becomes the informal caregiver, holding a demanding full-time responsibility that will worse with the progress of disease with the consequent burden of care (53). The disease severity and duration are determinant factors for caregiver burden, with sleep problems, autonomic dysfunction and psychiatric symptoms amplifying the burden of care in PD (53, 54). Thus, family caregiver burnout in PD is been considered primarily dependent on patient's NMS, requires considerable time investment and can trigger depression in the spouse /family member (53). For the good quality of caregiving and also the quality of life of the physically, emotionally and psychosocially exhausted informal caregiver, early and continued collaboration and support is essential (55). Caregiver unmet needs trigger the requirement of professional care at home or the early institutionalization of the beloved person with PD and the beginning of a new period for family members that may experience anticipatory grief (53). More importantly, increasing number of studies aware of the need to recommend protective therapies for caregivers already in those caring early stages of PD (56). Thus, there's a clear need to provide family-centered care as it is done in oncology (57). As mentioned before, guidelines for family caregiving intervention in PD point at non-pharmacological strategies that include physical-related activities known to improve functional mobility and balance in patients while at the neuronal level exert brain plasticity and neuroprotective effects (17, 58). A comparison of dance interventions in people with PD and older adults points out substantial and wide-ranging benefits but also aware that, as compared to what is known in older adults, more efforts are needed to investigate the growing literature for dance in PD (59).

Dance as part of lifestyle is important, for both patients and caregivers. Prevalence of physical activity in some countries (i.e., the United States) has become a behavioral risk factor (60). The studies aware that an important number of people over age 65 do not meet physical activity recommendations and this situation is worsened in PD (61). In such a case, promotion of social activities that involve physical activities and are part of culture and tradition, like dancing during weekends in elderly social centers or in public areas during festivities, can be more easily implemented. In this sense, dance is presented as a promising intervention because it requires the integration of multiple sensorial information, namely auditory, vestibular, visual, and somatosensory. Besides, any dance style can induce functional adaptations in older adults, especially related to balance as it involves the fine-grained motor control of the whole body (62). Behavioral studies have already provided evidence of better performance in balance and memory tasks in elderly dancers (63–65). The psychotherapeutic use of movement, which aims to integrate the individual physically and emotionally, increase the level of personal and body perception, which allows for wide movements and encourages the individual to express himself authentically through the integration of the unconscious (40). Dance contributes to the configuration of the body schema, the perceptual organization, favoring coordination. Increase body awareness and movement awareness through musical rhythms and melodies. It requires spatial integration, rhythm, synchronization with external stimuli, balance and coordination of the whole body, which makes it a highly useful therapeutic resource for the rehabilitation of PD (25,

35). A recent compilation of research work on sound, music, and movement in PD provided new scientific evidences and arguments highlighting the benefits of therapies using visually, acoustically, and somatosensorially enriched environments (66) but most importantly how the intact ability of PD's patients to pick up and use external sensory information to initiate and time movement would encourage them to actively seek out programs that use sound, music, and movement so that they can lead more active and fulfilling lives (46).

CONCLUSIONS

In summary, founded on evidence-based therapeutic benefits of dance/music therapy we present "PasoDoble," derived from the widely known Latin ballroom dance traditionally danced in family celebrations and festivities, as a dance/music intervention suitable for family-centered Parkinson's Disease care. As a regular dancing at home, satisfactory "PasoDoble" dance practice can improve and preserve function and mood in the elderly, while in community settings will also promote and improve socialization. The same singular features can be beneficial through rhythmic auditory stimulation and signing for patients with PD since a gait training plan is performed with rhythmic and groove sound stimulation that marks each of the steps in company with the guide of the dance partner, usually the spouse (and family caregiver). The dance partner can help the mastery of balance and displacement by contributing to the control of dynamic balance, controlling external disturbances. We provide "PasoDoble" the methodological proposal and the key features of our protocol, an intervention the method which is structured to improve gait and balance; facilitate movement, reaching and grasping; muscle power and joint mobility; reduce of risk of falls, and increase of aerobic capacity. "PasoDoble" can address each of the four key areas in people with PD on which the benefits of physical exercise in PD are based: to improve gait, cognitive strategies to improve transfers, exercises to improve balance, and exercises to increase joint range and muscle strength to improve physical capacity. Depending on the intensity of the requested exercise, "PasoDoble" can also contribute to improving physical capacity and all its components. Besides, "Pasodoble" is also a music *per se*, with familiarity and groove that compels to move which can serve as an external reference to facilitate specific movements. We consider that this easy-to-implement into patient care and free-living environments (elderly social centers, home) rehabilitation program can promote positive emotions and self-esteem, with added general improvement of social attachment and recognition, thus improving the quality of life of patient-caregiver as a patient and family caregiving intervention that can be tailored to the individuals. The comparison with other ballroom dance and/or rehabilitation circuits and with regards to different stages of disease, will contribute to fully describe its benefits, but also limitations, in different rehabilitation programs and settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LG-L: concept. LG-L and LC-M: development of the concept and review, protocol of intervention and graphical abstract, and review and approving final version of manuscript.

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Effect of Levodopa Initiation on the Gut Microbiota in Parkinson's Disease

Natalia Palacios[1,2,3†], Anas Hannoun[4†], Julie Flahive[5], Doyle Ward[6,7], Kelsey Goostrey[8], Anindita Deb[8] and Kara M. Smith[8*]*

[1] Department of Public Health, University of Massachusetts Lowell, Lowell, MA, United States, [2] Department of Veterans Affairs, Edith Nourse Rogers Memorial Veteran's Hospital (ENRM VA) Hospital, Bedford, MA, United States, [3] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [4] Department of Neurology, Geisel School of Medicine at Dartmouth, Manchester, NH, United States, [5] Department of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, United States, [6] Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA, United States, [7] Department of UMass Center for Microbiome Research, University of Massachusetts Medical School, Worcester, MA, United States, [8] Department of Neurology, University of Massachusetts Medical School, Worcester, MA, United States

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***Correspondence:**
Natalia Palacios
natalia_palacios@uml.edu
Kara M. Smith
kara.smith@umassmemorial.org

[†] These authors have contributed equally to this work

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Background: The impact of Levodopa on the gut microbiota of Parkinson's disease (PD) patients has not been sufficiently addressed.

Methods: We conducted a longitudinal study to examine the impact of Levodopa initiation on the gut microbiota composition of 19 PD patients who had not previously been exposed to Levodopa. Patients provided two stool samples prior to and two samples 90 days after starting Levodopa. Motor impairment (MDS-UPDRS Part III), diet, and other patient characteristics were assessed. 16S rRNA gene amplicon sequencing was used to characterize the microbiota. We examined, cross-sectionally and longitudinally, the associations between Levodopa use and alpha and beta diversity and performed feature-wise, multivariate modeling to identify taxa associated longitudinally with Levodopa use and with improvement in motor function after Levodopa administration.

Results: We did not observe significant differences in alpha or beta diversity before vs. after initiation of Levodopa. In longitudinal feature-wise analyses, at the genus level, no taxa were significantly associated with Levodopa use after false discovery rate (FDR) correction ($q < 0.05$). We observed a marginally lower relative abundance of bacteria belonging to *Clostridium* group IV in PD patients who experienced a medium or large improvement in motor impairment in response to Levodopa compared to those with a small response [$\beta = -0.64$ (SE: 0.18), p-trend: 0.00015 p-FDR: 0.019].

Conclusions: In this study, Levodopa was not associated with changes in microbiota composition in this longitudinal analysis. The association between abundance of *Clostridium* group IV and short-term motor symptom response to Levodopa is preliminary and should be investigated in larger, longer-term studies, that include a control group.

Keywords: Levodopa, microbiome, motor function, Parkinson's disease, Unified Parkinson's Disease Rating Scale

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by aggregation of the protein alpha-synuclein in Lewy bodies and neurites, leading to dopaminergic neuron loss in the substantia nigra (1). PD is typically associated with motor symptoms such as bradykinesia, tremor and rigidity, but the importance of non-motor aspects, particularly gastrointestinal problems, is increasingly appreciated. Constipation is a well-recognized risk factor for PD (2), and increased intestinal permeability and inflammation have been described in PD (3). Due to the growing evidence for gastrointestinal involvement in PD, as well as support for the hypothesis that alpha-synuclein may propagate from the gut, along the vagus nerve to the brain (4, 5), the gut microbiome holds promise as a source of biomarkers as well as for potential therapeutic intervention in PD.

To date, a number of studies have reported differences in the gut microbiota composition of PD patients compared to controls (6–18). There has also been significant heterogeneity of results. Only a single study considering disease progression has far been conducted, reporting that low counts of *Bifidobacterium* may be associated with faster PD progression over 2 years (19).

Medications have been shown to explain a large proportion of variance in the gut microbiota composition (20) and the microbiome has been suggested to impact medication efficacy (21–23). Specific to PD, the microbiome may explain the heterogeneity in the efficacy and side effects of Levodopa, which is not clearly linked with clinical factors (17). A recent report identified *E. faecalis* as potentially responsible for Levodopa decarboxylation, and potentially, the differential Levodopa response among PD patients (24). It has been shown that bacteria in the rat small intestine express genes encoding for the enzyme tyrosine decarboxylase (TDC) that decarboxylates Levodopa to dopamine, potentially suggesting a role for the microbiome in the pharmacokinetics and effect of Levodopa in individuals with PD (25).

Recent studies have suggested that some of the reported differences in gut microbiota composition of PD patients compared to controls could potentially be related to Levodopa use. In a small study that compared drug naïve ($n = 12$) and treated ($n = 26$) PD patients, Levodopa use was significantly associated with the abundances of *Bacillaceae* (9). In another study, Levodopa dose was inversely associated with abundance of genera *Dorea* and *Phascolarctobacterium* (18). A decrease in genus *Faecalibacterium* was reported in a cross-sectional analysis of microbiota composition of PD patients using Levodopa (26). Notably, in a recent study comparing the microbiota composition of PD patients vs. controls (27), adjustment for Levodopa use, in addition to other covariates, resulted in attenuation of most findings, highlighting the importance of considering medication use in analyses (27).

Understanding the impact of Levodopa on the gut microbiome is crucial to separate disease-related from medication-related impacts on the microbiome. However, to our knowledge, no study to date has examined the impact on the microbiome of starting Levodopa longitudinally in *de novo* PD. In this study, we evaluated the gut microbiota composition *de novo* PD patients prospectively and longitudinally, before and after starting Levodopa therapy. We also evaluated associations between the microbiota composition and Levodopa response in PD patients.

METHODS

Enrollment and Study Participants

Fifty patients with idiopathic PD were approached for enrollment, and 21 were enrolled (**Figure 1**). Patients did not qualify for the study, if they were already on or have previously taken any Levodopa or Levodopa equivalent brand name treatment prior to the study such as Sinemet, Sinemet CR, Rytary, or Duopa gel infusion. Participants were allowed to be stable on other PD medications during the study (dopamine agonists, mono-amine oxidase inhibitors, and NMDA antagonists).

We excluded those on antibiotics, antifungals, antivirals, or antiparasites, cytokines, any immunosuppressants or immunomodulators, large or FDA approved doses of probiotics in any form, at the time of recruitment or within 6 months of stopping, as well as those who had a recent gastrointestinal inflammatory condition or major gastrointestinal surgery. Other exclusion criteria included unstable vital signs upon enrollment, acute infectious disease at the time of the sample obtaining, unstable dietary history, recent history of chronic alcohol consumption, positive HIV, HBV, or HCV infection, confirmed state or condition of immunodeficiency, pregnancy or lactation.

All study participants were enrolled through the movement disorders clinic at the University of Massachusetts Medical School and the movement disorders clinic at Brown University. Idiopathic PD diagnosis was made by a movement disorders specialist based on their best clinical judgment following the UK Brain Bank Criteria (28). After appropriate evaluation and discussion with the patient, a clinical decision to start Levodopa was made.

MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was captured both upon enrollment and 90 days after starting Levodopa. Both body mass index and a dietary questionnaire were collected at enrollment and study completion. Upon enrollment, other demographic and clinical parameters were collected including Hoehn and Yahr (H&Y) Stage (29), PD duration, comorbidities, medications, and alcohol or smoking history.

Stool Samples Collection and Storage

Samples were collected in OMNIgene•GUT collection tubes (OMR-200, DNAgenotek) and stored at −80°C until extraction. Each patient provided a total of four samples: two samples were collected directly prior to starting Levodopa, 5–7 days apart. Ninety days after starting Levodopa, the third and fourth samples were collected, an average of 7 days apart.

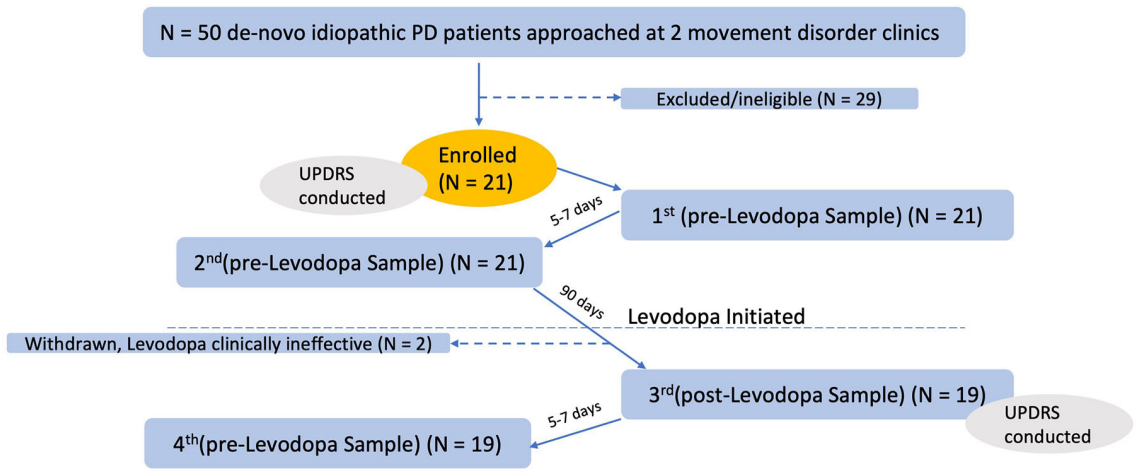

FIGURE 1 | Participant enrollment, testing, and collections.

DNA Extraction and 16S rDNA Sequencing

Approximately 400 µl stool aliquots were extracted using the PowerMag® Soil DNA Isolation Kit (27100-4-EP, MO Bio Laboratories, Inc.) on an epMotion® 5075 TMX Liquid Handling Workstation. The 16S rRNA gene was sequenced following methods previously described (30) using the 341F and 806R universal primers to amplify the V3–V4 region. Three hundred nt paired-end sequences were generated on the Illumina MiSeq platform. Reads were assembled and clustered, and an OTU table was generated using the UPARSE pipeline (31). Taxonomic classifications were determined using SINTAX (31) and RDP training set v16 (with species names) (https://drive5.com/usearch/manual/sintax_downloads.html).

Statistical Analysis

All statistical analyses were performed in R version 3.6.0 and SAS version 9.4 (SAS Institute Inc., Cary, NC). We used false discovery rate (FDR) for multiple comparisons correction.

Omnibus Testing

We used the Vegan package in R to calculate the Shannon Alpha Diversity index. Faith's Phylogenetic diversity was calculated in QIIME2 (32). In descriptive analyses, we used the first pre-Levodopa sample from all patients to characterize the associations between microbial alpha diversity, using one way Analysis of Variance (ANOVA), and the covariates assessed in the study, including age, BMI, and diet prior to starting Levodopa. These comparisons were made for alpha diversity and Permutational Analysis of Variance (PERMANOVA) for beta diversity metrics. Subsequently, we performed a longitudinal analysis with linear mixed models, treating subject as a random effect, to examine the association between sample status (post- vs. pre-Levodopa) and the two Alpha diversity metrics (Shannon and Faith's Phylogenetic) adjusting for age, sex and BMI in all four samples from all 19 patients.

Beta Diversity

Beta diversity comparisons were performed using four metrics: Bray-Curtis dissimilarity, Jaccard similarity, weighted UniFrac, and unweighted UniFrac. First, to examine which predictors contribute to beta diversity before initiation of Levodopa, we used the first pre-Levodopa sample and conducted a set of univariate PERMANOVA analyses to examine whether any of the covariates contributed strongly to beta diversity, using the "adonis" command in R with 999 permutations. Subsequently, to examine whether initiation of Levodopa impacts beta diversity, we computed the dissimilarity, using the four metrics above, between the first two (pre-Levodopa) samples and compared this dissimilarity to that between the second and third (pre-to-post) and the third and fourth (post-post) samples, using the Wilcoxon signed rank test. Finally, we performed a longitudinal PERMANOVA, using all four samples, treating subject as a random effect and examining the association between Levodopa use and each of the beta diversity metrics, adjusted for age, sex and BMI.

Feature-Wise Analyses

We used MaAsLin2 (Multivariate Association with Linear Models 2 (Version 1.4.0): https://huttenhower.sph.harvard.edu/maaslin2), a modified general linear model for feature-wise multivariate modeling, to identify differentially abundant taxa associated with Levodopa use. The MaAsLin2 model was fit with data from all four time points, treating subject as a random effect, and adjusting for age, sex, and BMI. We used the default parameters in MaAsLin2 (https://github.com/biobakery/Maaslin2).

Longitudinal Analyses to Identify Taxa Associated With Motor Response to Levodopa Treatment

Pre- and post-Levodopa MDS-UPDRS Part III (motor examination) was available for 16 patients. We stratified patients according to three categories of response to Levodopa, using the change in MDS-UPDRS III at 90 days compared with

baseline. A small response was defined as no or minimal change: a decrease in MDS-UPDRS III or an increase <1 point. A medium response was defined as MDS-UPDRS III improvement of 1 to <12 points, and large response was defined as an improvement of difference of 12–35 points. These cut-points were based on visual inspection of MDS-UPDRS III data in order to create categories with relatively balanced numbers of patients ($n = 5$, 5, and 6 per group, respectively).

We used MaAsLin2 on all four longitudinal samples with random effects for subject to identify taxa associated with change in MDS-UPDRS III after Levodopa treatment. These analyses were conducted using change in UPDRS as a categorical (small/medium/large) outcome, and p-trend was calculated across categories.

Sensitivity Analyses

While the mean disease duration among our study participants was 3 years, one patient had PD for 17 years. We thus conducted sensitivity analyses excluding this participant.

Ethics

All study procedures, documents, and advertisement methods were performed according to the rules and regulations of the Institutional Review Board (IRB) of the University of Massachusetts Medical School (Docket #H00013990). HIPAA authorization for review of medical charts for research purposes were signed by all participants.

RESULTS

Twenty-one patients successfully provided the first two stool samples, prior to starting Levodopa. Two patients stopped Levodopa use because it was clinically ineffective and were thus withdrawn from our study. The remaining 19 patients returned the two post-Levodopa samples (**Figure 1**), for a total of four stool samples per patient (two pre-Levodopa and two post-Levodopa). Demographic, clinical characteristics, and Levodopa daily dose (LDD) of the patients under study are shown in **Table 1**. The Levodopa daily dose at 90 days was available for 17 of the 19 patients. The majority (11 of 17) participants were taking 300 mg Levodopa per day. Other doses were as follows: 900 mg ($n = 1$), 600 mg ($n = 2$), 450 mg ($n = 2$), and 200 mg ($n = 1$). As shown in **Table 1**, 8 of 19 participants were stable on non-Levodopa PD medications during the study (dopamine agonists, mono-amine oxidase inhibitors, and NMDA antagonists). Participants did not initiate any other PD medication during the study.

TABLE 1 | Demographic characteristics of study participants.

Age [years, mean (SD)]	71 (5.3)
Sex [*n* (%) female]	9 (47)
Race [*n* (%) white]	100
Ethnicity [*n* (%) non-Hispanic]	100
BMI [mean (SD)]	28 (5.8)
PD duration (years) [mean (SD)][a]	3 (3.7)
Smoking [*n* (%)]	0
Alcohol (drinks/week) [mean (SD)]	1.6 (2.9)
Comorbidities [*n* (%)]	
Hypertension	7 (37)
Hyperlipidemia	9 (47)
Diabetes	3 (16)
Medications [*n* (%)]	
Dopaminergic medications	8 (42)
Metformin	2 (11)
Statins	7 (37)
Antidepressants (SSRIa and SNRIs)	3 (16)
MDS-UPDRS Part III-pre [mean (SD)]	39 (18)
MDS-UPDRS Part III-post [mean (SD)]	29 (19)
MDS-UPDRS Part III-difference [mean (SD)]	10 (12)
Levodopa daily dose [mean (range)]	382.9 (200–900)

[a] *One participant had PD duration of 17 years.*

Alpha Diversity

In linear regression analyses in pre-Levodopa samples, Shannon alpha diversity was positively associated with age ($\beta = 0.05$; $p = 0.005$) and marginally inversely associated with BMI ($\beta = 0.03$, $p = 0.07$). Faith's Phylogenetic diversity was positively associated with PD duration ($\beta = 11.16$, $p = 0.05$) as well-alcohol use ($\beta = 0.91$, $p = 0.04$), and inversely associated with BMI ($\beta = -0.23$, $p = 0.04$), and marginally inversely associated with age ($\beta = 0.49$, $p = 0.09$) (**Table 2**). In longitudinal linear mixed model analyses, examining the association between Levodopa status (sample taken before Levodopa vs. after Levodopa) after adjustment for gender, age, PD duration, BMI, treating subject as a random effect, and alpha diversity metrics, we did not observe significant associations between Levodopa status and Shannon Alpha Diversity ($\beta = -0.02$, $p = 0.74$) or Faith's ($\beta = -0.21$, $p = 0.64$) (**Figures 2A,B**). Excluding the participant with longer (17 y) disease duration did not substantially impact the alpha diversity results.

Beta Diversity

In descriptive analyses within the first, pre-Levodopa sample, daily intake of nuts ($R^2 = 0.12$, $p = 0.047$), BMI ($R^2 = 0.12$, $p = 0.040$), alcohol use ($p = 0.07$, $R^2 = 0.11$), and age ($p = 0.09$, $R^2 = 0.10$) explained the most variance in terms of Bray Curtis dissimilarity in univariate PERMANOVA analyses. Likewise, when considering Jaccard distances, PD duration ($p = 0.004$, $R^2 = 0.30$) and daily meat consumption ($p = 0.07$, $R^2 = 0.24$) explained the most variance. When considering weighted and unweighted UniFrac, none of the metadata were significantly associated with beta diversity.

In longitudinal analyses, weighted UniFrac distance was significantly greater when comparing the 2nd vs. 3rd samples (when Levodopa was initiated) then it was comparing the samples collected during the 1st vs. 2nd visits (pre-Levodopa), indicating an increase in weighted UniFrac associated with Levodopa initiation ($p = 0.02$ using Wilcoxon rank sum test comparing Pre-Post and Pre-Pre groups). Bray Curtis dissimilarities, Jaccard or unweighted Unifrac comparing the first to second (both pre-Levodopa), second to third (pre- vs.

TABLE 2 | Associations between alpha and beta diversity and study covariates at baseline.

	Alpha diversity[a] (*p*-value)		Beta diversity[b] R^2 (*p*-value)			
	Shannon	**Faith's**	**Bray-Curtis**	**Jaccard**	**Weighted UniFrac**	**Unweighted UniFrac**
Hoehn and Yahr stage (per 1 unit)	0.06 (0.60)	0.99 (0.52)	0.046 (0.63)	0.09 (0.10)	0.05 (0.50)	0.05 (0.53)
Age (per 1 year)	**0.05 (0.02)**	0.49 (0.09)	0.10 (0.09)	0.07 (0.24)	0.09 (0.14)	0.09 (0.15)
BMI (per 1 unit)	−0.03 (0.07)	−0.23 (0.04)	**0.12 (0.047)**	0.06 (0.45)	0.08 (0.20)	0.08 (0.22)
PD duration (pear 1 year)	0.26 (0.47)	**11.16 (0.05)**	0.10 (0.62)	**0.30 (0.004)**	0.10 (0.64)	0.10 (0.62)
Sex (F vs. M)	0.12 (0.58)	3.11 (0.31)	0.030 (0.91)	0.04 (0.81)	0.05 (0.53)	0.05 (0.53)
Dopaminergic medication use[c]	0.006 (0.97)	−1.79 (0.58)	0.046 (0.59)	0.07 (0.24)	0.01 (0.99)	0.01 (0.99)
Antidepressants[c]	0.27 (0.36)	−0.62 (0.89)	0.046 (0.61)	0.06 (0.35)	0.08 (0.18)	0.08 (0.19)
Statins[c]	0.06 (0.79)	1.25 (0.69)	0.055 (0.45)	0.06 (0.43)	0.05 (0.64)	0.05 (0.68)
Metformin[c]	−0.31 (0.37)	−4.41 (0.32)	0.077 (0.19)	0.04 (0.83)	0.08 (0.23)	0.08 (0.24)
Diabetes[c]	−0.44 (0.13)	−1.79 (0.64)	0.039 (0.75)	0.06 (0.36)	0.05 (0.63)	0.05 (0.63)
Yogurt[c]	0.30 (0.16)	3.33 (0.28)	0.046 (0.62)	0.06 (0.35)	0.05 (0.65)	0.05 (0.63)
Whole grains daily[c]	0.01 (0.95)	1.79 (0.58)	0.05 (0.48)	0.06 (0.37)	0.05 (0.58)	0.05 (0.58)
Meat daily[c]	−0.03 (0.90)	−3.21 (0.29)	0.06 (0.42)	0.24 (0.07)	0.06 (0.43)	0.06 (0.44)
Nuts daily[c]	0.33 (0.15)	2.43 (0.45)	**0.123 (0.048)**	0.05 (0.67)	0.07 (0.30)	0.07 (0.30)
Fruits and vegetables daily[c]	−0.17 (0.63)	−4.24 (0.34)	0.05 (0.57)	0.04 (0.70)	0.05 (0.53)	0.05 (0.54)
Alcohol use weekly[c]	0.05 (0.19)	**0.91 (0.04)**	0.11 (0.07)	0.06 (0.29)	0.10 (0.08)	0.11 (0.09)
Caffeinated beverages daily[c]	0.05 (0.83)	2.52 (0.42)	0.06 (0.33)	0.03 (0.98)	0.04 (0.80)	0.04 (0.81)

[a] *Univariate linear regression model with alpha diversity measure as the outcome.*
[b] *Permutational Multivariate Analysis of Variance (PERMANOVA).*
[c] *Binary (yes/no) indicators. Values with $p \leq 0.05$ are bolded.*

post-Levodopa), or the third to fourth (both post-Levodopa) samples were not significantly different. In longitudinal PERMANOVA analysis incorporating all four longitudinal samples, treating subject as a random effect and adjusting for age, sex, and BMI as fixed effects, Levodopa use was not associated with any of the dissimilarity metrics (**Figure 2C**).

Feature-Wise Analyses

In longitudinal feature-wise analyses in MaAsLin2 adjusted for age, sex and BMI, treating subject as a random effect, no taxa were significantly associated with Levodopa use after FDR correction ($q < 0.05$). Excluding the participant with longer (17 y) disease duration did not substantially change the association between Levodopa initiation and weighted UniFrac distance ($p = 0.04$ using Wilcoxon rank sum test comparing Pre-Post (2nd vs. 3rd) and Pre-Pre (1st vs. 2nd visit) groups). The results of other analyses were also not substantially altered by the exclusion of the participant with longer PD duration.

The Role of Microbiota Composition in Levodopa Response

In longitudinal PERMANOVA analysis, permuting within patient, Levodopa status and time, and adjusting for age and BMI, change in MDS-UPDRS score use was not associated with Bray Curtis dissimilarity ($R^2 = 0.093$, $p = 0.84$). In longitudinal feature-wise analyses in MaAsLin2, adjusted for age, sex, and BMI, we observed a marginally lower abundance of bacteria belonging to the genus *Clostridium* group IV in patients who experienced a large response to Levodopa compared to those with the smallest response [$\beta = -0.64$ (SE: 0.18), p-trend: 0.0056, p-FDR: 0.36] This association was strengthened when excluding the participant with 17 y disease duration [$\beta = -0.64$ (SE: 0.18), p-trend: 0.00015, p-FDR: 0.019] (**Figure 3**).

DISCUSSION

There is growing evidence that the gut microbiome plays a role in PD (6, 8, 9, 11–16). Despite the increasing interest in this field, most of the studies conducted thus far have focused on microbiota comparisons between medicated PD patients and controls, using a cross-sectional approach (6, 8, 9, 11, 12, 14, 15). To our knowledge, no study to date has addressed, using a prospective and longitudinal design, whether initiation of Levodopa in *de novo* PD patients might alter the microbiome or whether the microbiome of PD patients might impact the improvement in motor function in response to initiation of Levodopa by PD patients.

In this longitudinal investigation of *de novo* PD patients who provided stool samples before and after initiation of Levodopa, we examined whether Levodopa administration alters the PD gut microbiota composition and whether composition of the gut microbiota in PD patients can predict response to Levodopa. In our baseline sample, age, and BMI were the factors most strongly associated with the microbiota (both alpha and beta diversity), which is in agreement with other studies (20). We observed an increase in weighted UniFrac distance, but not other metrics of alpha or beta diversity, when comparing the 2nd vs. 3rd samples, between which Levodopa was initiated, with the

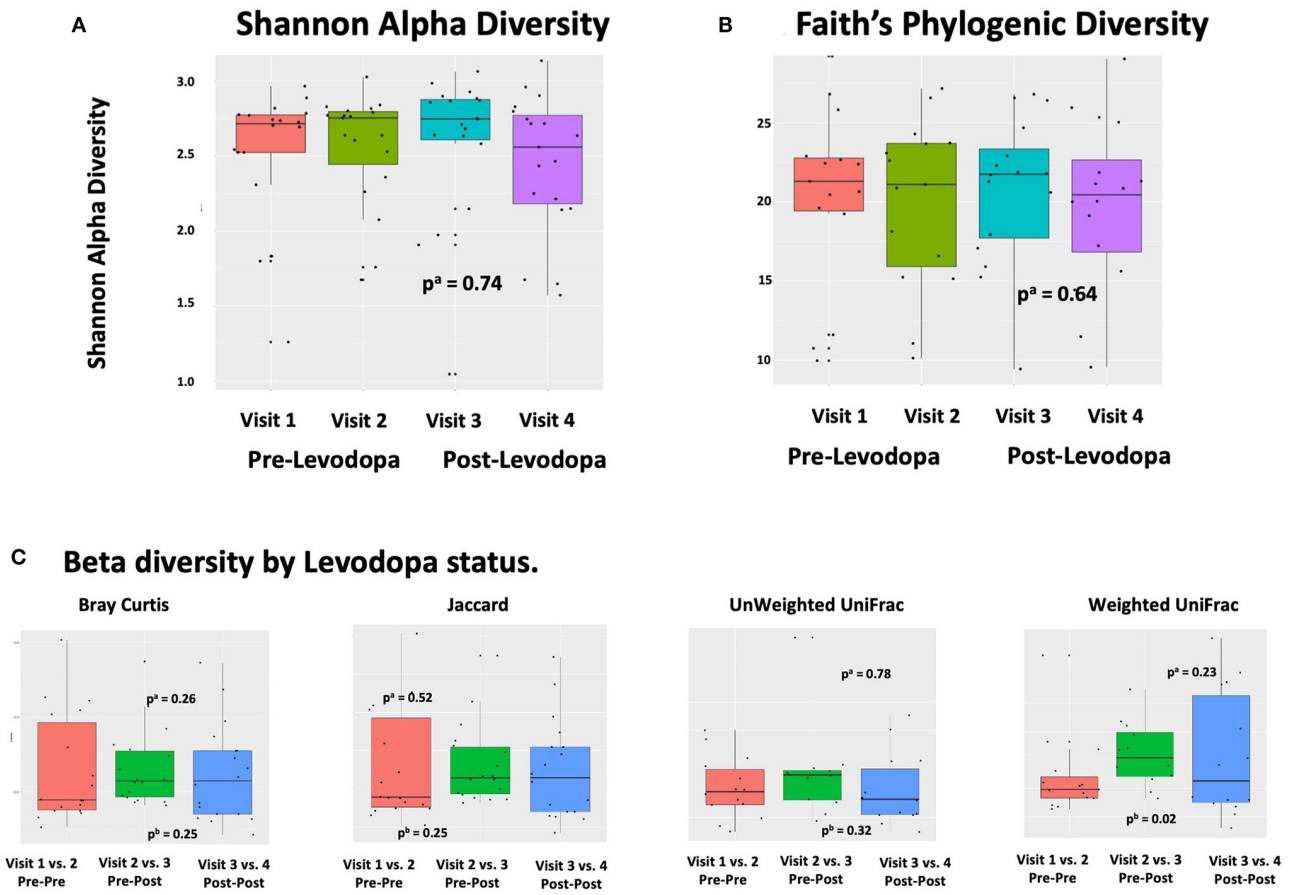

FIGURE 2 | Alpha and Beta Diversity of the gut microbiome in relation to Levodopa use. **(A,B)** Alpha diversity metrics (Shannon Alpha Diversity and Faith's Phylogenic Diversity) in relation to sample and timing of Levodopa use. *P*-values were calculated based on [a]linear mixed model (LMM) with alpha diversity (Shannon or Faith's Phylogenetic Diversity) as the outcome and Levodopa status (pre vs. post) as predictor, adjusted for gender, age, PD duration, and BMI, treating subject as a random effect. "Visit" refers to study visit, where visits 1 and 2 took place prior to Levodopa administration and visits 3 and 4 took place after. **(C)** Beta diversity metrics (Bray Curtis, Jaccard, unweighted UniFrac, weighted UniFrac) in relation to sample and timing of Levodopa use. Comparisons are made for each of Bray Curtis, Jaccard, unweighted Unifrac, and weighted Unifrac, comparing the dissimilarity between sets of samples from visit 1 vs. visit 2 (both pre-Levodopa samples), to dissimilarity between visit 2 vs. visit 3 (spanning initiation of Levodopa), and to that between visit 3 vs. visit 4 (both post-Levodopa samples). *P*-values were computed with [a]longitudinal PERMANOVA incorporating all four longitudinal samples, adjusting for age, BMI, and treating subject as a random effect and [b]Wilcoxon rank sum test comparing Pre-Post (dissimilarities of samples 2, 3) and Pre-Pre groups (dissimilarities of samples 1, 2) groups.

distance between 1st vs. 2nd samples (both pre-Levodopa). This suggests that Levodopa initiation is potentially associated with an increase in weighted UniFrac distance. Levodopa initiation was not associated with short-term taxonomic changes in longitudinal analysis. Our finding that only Weighted UniFrac distances, but not other metrics of beta diversity were associated with Levodopa initiation, is not necessarily conflicting with the null results for other metrics, but suggests that these effects may be more nuanced. Both Bray-Curtis and Jaccard consider discrete taxonomic groups. The limitation of Bray-Curtis and Jaccard is that taxonomic groups are equally weighted even though the phylogenetic relationships between taxonomic groups are not equal. UniFrac considers phylogenetic groups, with Unweighted UniFrac emphasizing the presence or absence of these groups and Weighted UniFrac additionally considering their abundance. Thus, Weighted UniFrac, which was the metric significantly associated with Levodopa initiation in our study, is unique among the four metrics used in that it considers the abundance of phylogenetic groups and the association we observed with this metric suggests that the abundance, more so than the presence/absence, of a phylogenetic group is contributing to statistically significant beta diversity differences.

In this study, we observed a marginally lower abundance of *Clostridium* group IV in PD patients with a good response to Levodopa. Bacteria belonging to *Clostridium* group IV are commensal, gram positive, and strict anaerobe bacteria. They play an important role in gut homeostasis and ferment dietary fiber to short chain fatty acids (SCFA), particularly butyrate, compounds that provide energy for colonocytes and play a key role in the health of the colon (33). They have also been shown to play an important role in the secondary

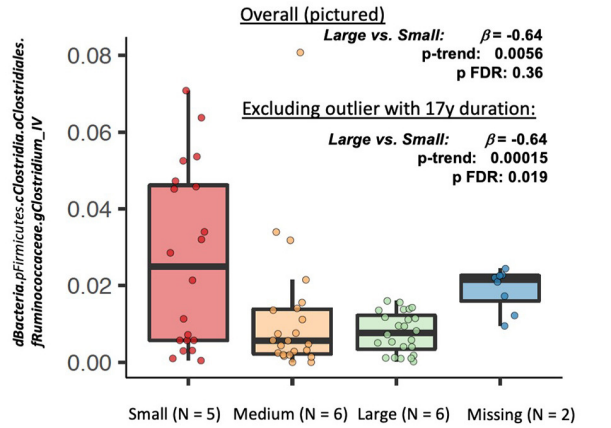

FIGURE 3 | Longitudinal feature-wise analyses of change in MDS-UPDRS Part III in response to Levodopa. MaAsLin2 (Multivariate Association with Linear Models, Version 2: https://huttenhower.sph.harvard.edu/maaslin2), was fit to identify differentially abundant taxa associated with Levodopa use. The MaAsLin2 model was fit with data from all four time points, treating subject as a random effect, and adjusting for age, sex, and BMI.
We used the default parameters in MaAsLin2 (https://github.com/biobakery/Maaslin2) .

metabolism of bile acids (34). Relevant to PD, prior work has implicated commensal *Clostridia* in the production of catecholamines, including norepinephrine and dopamine (35). *Clostridia* spp., are thought to impact host immunological signaling and immunological development, likely via production of metabolites such as SCFA and secondary bile acid metabolism (36). Specifically, *Clostridium* group IV have been shown to strongly induce of the accumulation of T regulatory cells, which are key to immune homeostasis, in the colon of mice (37). Immune system dysfunction involving neuroinflammation (38), T cell infiltration (39), and microglia activation (40) have been implicated in PD and suggested to play a role in the degeneration of dopaminergic neurons. The implication of *Clostridium* group IV in Levodopa response reported here, if confirmed in larger studies, supports the need to investigate the role of SCFA and secondary bile acids in PD. However, due to the very small sample size of this study, this result is preliminary and should be treated with caution.

Prior studies have linked Levodopa use to abundance of *Bacillaceae* (9) *Dorea* and *Phascolarctobacterium* (18). Our study did not identify any taxa significantly associated with Levodopa use but preliminarily implicated *Clostridium* group IV in Levodopa response, thus adding to an already heterogenous literature. Differences in study design size and patient population may explain some of the differences in findings from prior investigations. There may be several mechanisms by which microbiome changes can impact Levodopa response, including but not limited to impact on gastric emptying, gut mucosa local factors such as inflammation and metabolite concentrations, and direct metabolism of L-dopa via production of decarboxylases. Different mechanisms may be more important in different patients, potentially depending on patient characteristics, disease profile, and Levodopa formulation.

The longitudinal aspect of our study, and our focus on the impact of Levodopa initiation in the microbiota in *de novo* PD, is a major strength of our study. Examining microbiota composition changes within individuals longitudinally limits potential confounding due to between-person variation in diet, disease severity, and other factors that may impact studies relying on between-subject comparisons.

Our study is preliminary and was limited in power by the low number of patients, which reflected the challenge of identifying *de novo* PD patients at the time of Levodopa initiation. With adjustment for three covariates (age, sex, and BMI), with 19 total participants, each providing four samples, our study had 80% power to detect a 0.279—unit difference in common taxa (∼3,792 sequences and 0.0758421 relative abundance at 100% read usage rate), and a 0.108—unit difference in rare taxa (∼581 sequences and 0.0116187 relative abundance at 100% read usage rate). Most realistic microbiome effects are likely to be much smaller, and we had limited power to detect those. Larger, better-powered studies are thus needed to examine the microbiota changes after initiation of Levodopa in PD patients. Due to constrains on power, we kept our statistical models parsimonious, adjusting our analyses for age, sex, and BMI only. Several additional confounding or stratification factors could be of potential interest in future, better powered studies, including initial disease severity or disease phenotype, which could both influence extent of response to Levodopa. While this study could not take these factors into account, they would be important to consider in future analyses. Another important limitation of our study is that it did not include a healthy control group, and we were thus not able to reproduce results from prior case-control studies that made such comparisons.

Furthermore, the study focused on short-term Levodopa use and thus cannot address the question of whether longer term use Levodopa could be associated with changes in the gut microbiome. Although we did not have an untreated PD control group, it is less likely that substantial microbiota changes would have occurred, without treatment or intervention, during the 90-day study period. An additional limitation is the use of 16S sequencing, which can limit taxonomic identification. Larger, longer-term studies, with more detailed specimen analysis, such as metagenomics or multi-omic approaches are needed to validate our results and better understand the mechanism of the connections between the gut microbiome and PD pathophysiology, progression, and response to Levodopa and other PD medications.

In summary, we did not observe significant shifts in microbial alpha or beta diversity with Levodopa treatment in this short-term study of *de novo* PD patients. The lower abundance of *Clostridium* group IV in PD patients who had a good motor response to Levodopa compared to those who had no response is preliminary and should be confirmed in future studies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of the University of Massachusetts Medical School (Docket #H00013990). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AH conceived of the research project, organized and executed the project, including participant clinical and biospecimen data collection. He contributed to data analysis and interpretation, and contributed to writing the first draft and revising the manuscript. NP designed and executed statistical analyses, and reviewed and critiqued results, and contributed to writing the first draft and revising the manuscript. JF contributed to the design and execution of the statistical analysis. DW performed sample extraction, microbiome sequencing and analysis, and contributed to design and review/critique of the statistical analysis, and the revising of the manuscript. KG contributed to organization and execution of the research project, and revising of the manuscript. AD contributed to execution of the research project (participant recruitment), and review and critique of the results and the manuscript. KS contributed to study design and organization, participant recruitment and data collection, reviewed and critiqued results, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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