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Effects of Dance vs. Traditional Exercise on Cognitive Dysfunction in Parkinson Disease Patients with Mild Cognitive Impairment: A Randomized Trial

A. Study Purpose and Rationale

Idiopathic Parkinson Disease (PD), a progressive neurodegenerative disease most common in the elderly, is traditionally thought of as a movement disorder, defined by the four cardinal signs of tremor, rigidity, bradykinesia and postural instability. However, the cognitive effects of PD are increasingly recognized as common and debilitating features of the disease. These effects, while often mild and limited in the early stages of the disease, increase with time, and nearly 80% of Parkinson patients will develop dementia during the course of their disease. [1] Moreover, mild cognitive impairment (MCI) is seen in over one quarter of non-demented PD patients [2] and is associated with a higher risk of developing dementia. [3,4] At the time of diagnosis, patients with PD are twice as likely to have MCI as the general population. [5]

Cognitive deficits observed frequently in PD are manifold and heterogeneous, with the most common subtype of MCI being non-amnestic, single-domain impairment. [6] So-called "executive function" is commonly impaired, with deficits seen in working memory, planning, and flexible task-switching, all of which make use of frontostriatal dopaminergic pathways. [6,7] Other deficits commonly include memory, visuospatial function and attention. [8]These deficits have an impact on daily life, particularly on social and occupational function and on activities of daily living. [6,8]

Exercise in many forms is known to have positive effects on physical function, health-related quality of life, strength, balance and gait speed in PD patients. [9,10]A few studies have shown exercise to be a promising approach to counteract executive dysfunction in PD. For example, a 6-month aerobic exercise intervention produced a significant improvement on tests of executive function in 10 Brazilian PD patients. [11] In another small study, PD patients randomized to a 12-week exercise intervention that included strength and cardiovascular training showed improvements in neuropsychiatric tests of executive function. [12]

Dance is a well-established form of exercise that has been shown to improve health-related quality of life, balance and gait[13-19], even in patients with severe disease. [13] In addition to its known physical benefits, dance may have cognitive effects beyond those seen with typical exercise. While our understanding of dance as a cognitive activity is in its infancy, cognitive neuroscientists have proposed that dance makes use of the so-called "action-observation network" to affect not only motor expertise, but domains as diverse as learning and memory, emotion perception, and social cognition. [20]

As one example of a complex cognitive aspect of dance, expert dancers are able to quickly learn and recall complex sequences of movements, employing a variety of strategies to encode these sequences. [21] Motor sequence learning has been shown to involve "chunking" of sets of movements. [22] This chunk representation can help overcome working memory limitations, [22] one

of the prime deficits seen in PD executive dysfunction. Motor sequence learning is impaired in early PD, perhaps as a result of disruption of caudate nucleus function. [23] For this reason, motor sequence learning has been a focus of investigation into both motor and cognitive deficits in PD. [24-27]

We hypothesize that a tailored dance intervention, consisting of 12 weeks of twice-weekly 90-minute classes, will have a significant beneficial effect on cognitive dysfunction compared to a similar dose of traditional exercise classes. This effect, we hypothesize, will be due to the multiple cognitive domains integral to and explicitly engaged by dance training. We have chosen to study PD patients with mild cognitive impairment, because we hypothesize that the greatest improvement (or slowing of decline) may be seen in a group with known deficits at baseline.

If our results are positive, this study could have important ramifications in multiple areas. First, dance may prove to be an effective modality for both motor and cognitive neurorehabilitation (or even neuroprotection) in this very common and devastating disease. Second, by parsing out the cognitive domains particularly affected by dance, we may gain a better understanding of neural mechanisms underlying cognitive decline in PD. Therefore, while our primary outcome offers a global measure of cognition, many of our secondary outcomes aim to answer much more specific questions. Even if our study is negative, some of these secondary outcomes may help determine directions for future research. To our knowledge, there has been no clinical study to date examining dance's effects on cognition in Parkinson Disease.

B. Study Design and Statistical Analysis

We propose to conduct a prospective, randomized trial to evaluate the effects of a dance intervention versus traditional exercise on patients with known idiopathic PD (Hoehn & Yahr Stage 1-4) who exhibit mild cognitive impairment, defined by a score of 21-25 on the Montreal Cognitive Assessment. While the study will be a single-center trial based at the Neurological Institute at Columbia University Medical Center (CUMC), it will involve collaboration with the Columbia University Teachers College Department of Kinesiology, the Brooklyn Parkinson Group (a not-for-profit patient advocacy group), and Dance for PD, a program of the Brooklyn-based Mark Morris Dance Group (a not-for-profit modern dance organization).

Patients will be recruited from New York City and the surrounding tri-state area and undergo an initial screening by telephone, in which details of the study will be briefly explained to them. Patients will be told that investigators are studying the effects of different forms of exercise on patients with PD; they will not be informed of the study hypothesis in order to minimize placebo effects. Patients who desire to enroll in the study and meet initial screening criteria (see G., Study Subjects) will be further screened at CUMC by trained staff, to identify patients with mild cognitive impairment for inclusion, and exclude those with frank dementia, major depressive disorder, or other co-morbities that could confound the study results.

Patients who meet eligibility criteria will then be randomized to either the Dance group or the Exercise group. Randomization will be generated using an online random number generator. Baseline demographic information will be collected for each patient enrolled in the study, including age, race, length of diagnosis, highest level of education, and current medication

regimen.

After randomization, patients will undergo an initial evaluation by a neurologist and by research staff trained in administration of outcome measure tests (for example the Hamilton Depression Rating Scale), assessing all baseline characteristics for primary and secondary outcome measures. Evaluators will be blinded to patients' group assignments.

Primary outcome:
Change in baseline score on Mattis Dementia Rating Scale-2 (MDRS-2)*

We selected the MDRS-2 as primary outcome based on its being the only instrument for longitudinal monitoring of cognitive impairment to be recommended by the NINDS Parkinson Disease Common Data Element Working Group. This scale is noted to have good clinimetric characteristics for detecting cognitive impairment in PD, as well as the ability to sub-categorize cognitive impairment into different types. Furthermore, this scale is the only cognitive scale currently in use that has alternative versions, minimizing "practice" effects when following patients longitudinally.[28,29] The MDRS-2 must be administered by a clinician and typically takes 30-50 minutes to administer, making it impractical as a screening tool in daily clinical practice, but a reasonable research tool. Scores on the MDRS-2 range from 0-144, with higher scores indicating better cognitive function. A recent study recommends 139 as a cutoff score for mild cognitive impairment on the scale, although 140 has been used previously.[28] A score of 132 or below indicates dementia.

Secondary outcomes:
Global functioning: MDS-UPDRS* (Movement Disorder Society Universal Parkinson Disease Rating Scale)
Executive function: SCOPA-COG (Validated cognitive scale, designed for PD patients and measuring frontal/executive dysfunction)
Mood: Hamilton Depression Rating Scale-17 (HDRS-17)*
Apathy: Apathy Scale (AS)*
Gait: 6 Minute Walk Test, Timed Up and Go, Dual Task 6 Minute Walk Test
Falls: Daily fall calendar
Motor sequence learning: Motor sequence learning task as described in detail by Ghilardi et al. [25]

* "Strongly Recommended Instrument" for research purposes by National Institute of Neurological Disorders and Stroke (NINDS) Parkinson Disease Common Data Elements Working Group (PD CDE WG).

Outcome measures will be assessed at baseline, at the end of the intervention (3 months), and 6 months after the intervention ends, to assess whether effects persisted.

Between-group differences in baseline characteristics will be analyzed using a chi-square test for categorical variables and a one-way analysis of variance for continuous variables. We calculated that a sample size of 17 subjects in each group would give 80% power to detect a one-standard deviation between-group difference in the primary outcome (change in baseline score) using an unpaired t-test ($p=0.05$). Given a conservative estimate of 30% attrition rate in each group, we

aim to enroll 30 patients in each group, which would leave the study well-powered to detect between-group differences even with attrition. Data will be analyzed on an intention-to-treat basis.

30 subjects in each group would give us 80% power (p=0.05) to detect an absolute within-group change of 3.1 points, using a paired t-test, assuming a standard deviation of 5.9 points in baseline score (the SD seen in the most recent study of the MDRS-2)[28].

C. Study Procedure

The Dance intervention will consist of 12 weeks of twice-weekly, 90-minute dance classes modified for patients with PD and varying levels of disability. Classes will be taught by expert dance instructors trained in the Dance for PD method pioneered by David Leventhal of the Mark Morris Dance Group. Classes will take place in a large, wheelchair-accessible dance studio equipped with ballet barres and chairs to sit in, and will be accompanied by a pianist as is usual for professional dance classes. The class will be structured similarly to a typical professional modern dance class, and will consist of three parts: an initial group greeting and warm-up, seated in chairs, including stretching and strengthening of arms, torso and legs; a standing portion, during which participants stand at a ballet barre and perform more complex movements while self-stabilizing using the barre; and a final portion where participants move "across the floor," in the most complex part of the class. Classes will end with the traditional "reverence" when participants acknowledge each other, the accompanist, and the instructor. Consistent with typical dance training, classes will emphasize postural stability, alignment, symmetry of flexibility and strength, the learning of complex motor sequences (different for each class), and musicality.

The Exercise intervention will consist of 12 weeks of twice-weekly, 90-minute group classes, taught by expert physical trainers or therapists, tailored to the needs of patients with PD and varying levels of disability. Classes will include a group greeting at the beginning of the class; stretching, resistance training, and aerobic exercises, both seated and standing; and a final "cool-down" and relaxation phase. Recorded music will be played during the class, but exercises will not involve repetition of routines choreographed "to the music."

The Exercise intervention is specifically designed as a group class, accompanied by music, to help control for the positive social effects of meeting regularly in a group and the pleasure of exercising to music.

D. Study Drugs
No drugs will be administered as part of the study.

E. Medical Device
Not applicable.

F. Study Questionnaires

-Mattis Dementia Rating Scale-2
-SCOPA-Cog

-MoCA
-Apathy Scale
-HAM-D 17
-MDS-UPDRS

G. Study Subjects

Eligibility criteria:
Patients must submit written consent
Clinical diagnosis of idiopathic PD, disease severity rating Stage 1-4 on Hoehn and Yahr scale (range is from 1-5, with 5 indicating most severe disease)
Mild cognitive impairment, as indicated by a score of <26 on the Montreal Cognitive Assessment (MoCA) screening test[30]
Age 40-85 years
Stable medication use
Ability to stand and walk with or without an assistive device (cane, walker)
Medical clearance for participation
Willing to be assigned to either intervention

Exclusion criteria:
Dementia, indicated by a score of <21 on the MoCA [30]
Major depressive disorder, indicated by a score of >13 on the HAM-D
Participation in other instructor-led exercise program or interventional study (behavioral or pharmacological)
Debilitating co-morbid condition or vision impairment that would prevent full participation in the study
Unavailable during study period

H. Recruitment of Subjects
Patients will be recruited through newspaper advertisements, flyers at support groups, and referrals from internists, neurologists and physical therapists in Manhattan, Brooklyn and the tri-state area.

I. Confidentiality of Study Data
Participants in the study will be given a unique identifier linked to their name, home address and medical record number. Subjects will be identified only by this unique identifier for data analysis. Data will be encrypted and stored on secure, password-protected networks at all times. Paper records (e.g. questionnaires) will be kept in a locked cabinet accessible only to the investigators.

J. Potential Conflict of Interest
There is no conflict of interest to report.

K. Location of the Study
Dance classes will be held in wheelchair-accessible dance studios at Barnard College (at the Columbia University Morningside Campus). Traditional exercise classes will be held at the

Columbia University Teachers College Department of Kinesiology (Morningside Campus). Neurological and neuropsychiatric assessments will take place at the Neurological Institute at Columbia University Medical Center. Some gait assessments may take place at the Department of Kinesiology.

L. Potential Risks

Both dance and traditional exercise carry risks of minor injuries such as muscle soreness, strains and back pain. More serious risks include sprains and falls incurred during a class. These risks will be mitigated by structural supports (ballet barres, chairs, exercise equipment), as well as by assistants in the dance and exercise classes to help stabilize participants when needed. Furthermore, a prior exercise-based intervention (tai chi) actually showed a decrease in number of falls during and after the intervention. [31]

M. Potential Benefits

PD patients are troubled by cognitive dysfunction, both early in the disease and late when up to 80% develop dementia. [1] Cognitive dysfunction impairs quality of life significantly. [8] Exercise has been shown to improve cognitive function in PD patients in small studies[11,12]; therefore, we anticipate that both groups are likely to see some cognitive benefit. A 2008 systematic review and meta-analysis found that exercise interventions, including dance, led to significant improvements in physical functioning, health-related quality of life, strength, balance and gait speed in people with PD. [10] Therefore, even if the trial shows no effect on cognition, both groups may reap substantial benefits from participating in the trial.

N. Alternative Therapies

There are few treatment options for cognitive dysfunction in PD, with rivastigmine (a cholinesterase inhibitor) being the only medication currently deemed clinically useful for treatment of PD dementia; there is also some evidence for donepezil. [32] However, cholinesterase inhibitors have a number of adverse effects which patients may find bothersome, including worsening of tremor. While exercise may have cognitive benefits for PD patients[11,12], it is not standard therapy to prescribe exercise as a cognitive intervention.

O. Compensation to Patients

Patients will be reimbursed for costs of travel to and from classes and appointments, as well as parking costs.

P. Costs to Subjects

Costs include participants' time, as well as the costs of travel and parking for the classes and the neurological assessments. All classes will be free of charge. (See Compensation.)

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

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