Title of the Study: Technology-Based Objective Measures for Gait and Postural Assessment in Parkinson Disease Patients with Orthostatic Hypotension: Feasibility and Effect-Size Finding Study.

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BACKGROUND:
Neurogenic orthostatic hypotension (OH) is a frequent and disabling complication of Parkinson's disease (PD), with an estimated prevalence of 30-50% [1-3], and a significant impact on the quality of life (QoL). OH may be associated with potentially serious complications, such as postural instability, gait impairment, and falls, which directly or indirectly (e.g., fractures) represent the most frequent cause of hospitalization in PD [4-6].
The lack of objective measures for the assessment of OH disability, however, represents a clinical challenge in the management of this complex hemodynamic condition. Although different scales have been developed for the assessment of orthostatic intolerance in PD [7], their application is limited by the substantial proportion of patients not reporting "classic" OH symptoms, namely dizziness, lightheadedness, or "feeling like you might black out while standing" [7]. Up to 50% of OH patients may complain symptoms such as weakness, vertigo, and difficulty concentrating, which may be erroneously diagnosed, underestimated, and thus undertreated. In a recent study, we demonstrated that OH might cause a 3-fold risk of gait impairment and functional disability in PD, regardless of the presence/absence of postural lightheadedness [8].

Clinical assessment and monitoring of OH symptoms relies on inaccurate and highly subjective clinical measures based on quantification of symptoms that are frequently ambiguous and not specific. In a recent study where we assessed the impact of autonomic dysfunction in 121 consecutive PD patients, OH was independently associated with gait impairment and functional disability, regardless of the symptomatic or asymptomatic status [8]. These data support the hypothesis that clinical scales currently available for quantifying the severity of OH are not adequate for capturing the full complexity of this frequent yet under-recognized PD complication.

Technology-Based Objective Measures (TOMs)

The introduction of TOMs in medical care represents one of the most promising aspects of modern medicine [14]. TOMs may quantify the severity of PD motor symptoms and increase the diagnostic accuracy of different challenging conditions. In addition, the growing access to high-speed internet connection may facilitate continuous communication and remote assessment of data collected via TOMs during normal activities of daily living, providing accurate monitoring of patients in their home environment. Possible advantages will include the reduction of placebo effect due to in-clinic evaluations, higher sensitivity in the accuracy of outcome measures, and a substantial decrease in sample size and duration of clinical trials.

Future Directions

Currently, TOMs application in clinical trials is limited by the lack of validation studies proving the feasibility and reproducibility of measuring therapeutic outcomes via technological sensors. Preliminary data collected in this study will prove the feasibility of using TOMs for assessing the effects of anti-OH

treatment, informing the design of a major proposal aiming to evaluating the beneficial effects of an early treatment for the prevention of OH complications in PD.

Experimental Design and Patient Population

The main objective of this study is to evaluate the feasibility of using TOMs in the assessment of OH-associated postural stability, both "in-clinic" and "at-home". Twelve consecutive PD patients with OH about to start pharmacological treatment with vasopressor agents prescribed by their neurologist will undergo gait and postural assessments (Protokinetic Zeno Walkway) before and after treatment with vasopressor agents (Droxidopa). Patients will also use wearable motion sensors (WMS) (Apple Watch® - Apple, Cupertino, CA, USA) for monitoring their normal activities of daily living. Gait analysis will measure the improvement in stride length and velocity, double-support time (percentage of time spent with both feet in contact with the ground), and postural sway on the anteroposterior and lateral axis, both at baseline (before treatment with Droxidopa) and after 6 weeks of therapy (2 weeks of dose-titration plus 4 weeks of maintenance therapy).. Data collected by TOMs (a) before and (b) after treatment with Droxidopa, will be correlated with changes in conventional scales of postural stability (Tinetti balance scale) [10], OH questionnaire (OHQ) [7], quality of life measures (39-Item Parkinson's disease questionnaire, PDQ-39)[11], and cognitive functions (Cambridge neuropsychological test automated battery – CANTAB - Connect Research, Cambridge Cognition Ltd., UK - and CERAD-NAB).[12, 13]

Our **central hypothesis** is that TOMs will result in higher detection power and lower variability than conventional clinical assessments, also minimizing interferences due to the placebo effect. If confirmed, these findings will improve the treatment in PD by using TOMs, instead of standard subjective outcome measures.

AIMS OF THE STUDY

The two aims of this study are:

Aim #1: To evaluate the feasibility and effect-size of using gait and postural tests to quantify OH related postural stability during in-clinic evaluations:

PD patients with newly diagnosed OH (n = 12) will be assessed at baseline and after 1 month of anti-OH treatment with the following tests:

Clinical tests: OHQ score (OH Symptom Assessment, OHSA and Orthostatic Hypotension Daily Activities Scale, OHDAS), Tinetti score, PDQ-39 score.
Gait analysis: stride length, single leg stance time, dynamic stability index, and gait velocity
Postural analysis: postural sway on the X and Y-axis.

Hypothesis: Gait analysis and Postural analysis will accurately capture changes in gait and postural stability associated with OH treatment, with higher sensitivity and lower variability than standard clinical tests.

Aim #2 To evaluate the feasibility and calculate the effect size of using WMS to quantify OH related postural instability during at-home activities of daily living

Gait and postural stability will be evaluated in the home environment by means of the following outcome measures:

Clinical assessment: Self-assessed clinical diary (OHDAS-based score) evaluating the subjective sensation of postural instability and number of episodes of postural instability.
WMS assessment**:** WMS (Apple Watch®) evaluating functional parameters, namely a) number of steps per day; b) number of hours of standing per day; c) total calories and active calories per day.

Hypothesis: TOMs will provide an accurate measure of functional parameters in the home setting, thus allowing an indirect measure of the patients' quality of life, with higher sensitivity and lower variability than self-reported clinical diaries.

INVESTIGATOR EXPERIENCE: Please see attached Bio sketch.

CLINICAL EVALUATIONS

Screening Assessment (Day 0)

12 consecutively consenting PD patients with OH about to start pharmacological treatment with a vasopressor agent (Droxidopa), as prescribed by their treating physician from the Gardner Family Center for Parkinson's Disease and Movement Disorders, will be screened for the following inclusion/exclusion criteria:

Inclusion criteria: (a) Diagnosis of idiopathic PD, meeting UK Brain Bank criteria [15] for at least 3 years; (b) Hoehn and Yahr (H&Y) stage I-III; (c) Age between 30 and 80 years old (both inclusive); (d) Stable dosage of dopaminergic medications for at least 4 weeks; (e) OH, defined as a fall in systolic BP $\geq$ 20 mmHg or diastolic BP $\geq$ 10 mmHg within 3 minutes of standing [16]; (f) Willingness and ability to comply with scheduled visits.

Exclusion criteria: (a) Diabetes mellitus or other diseases potentially associated with autonomic dysfunction [17]; (b) Treatment with antihypertensive drugs or with alpha-adrenergic antagonists; (c) Cognitive impairment, defined as a score < 24 at the Montreal Cognitive Assessment (MoCA) [18]; (d) Any atypical signs lowering the diagnostic certainty for PD; (e) Lack of postural reflex defined as a score > 2 at the MDS-UPDRS [13] item 3.12 [recover at the pull test]; (f) Severe levodopa induced dyskinesia, defined as a MDS-UPDRS item 4.2 > 2 [functional impact of dyskinesia].

Pharmacological Therapies

Changes in medications or dosages that may affect blood pressure, other than Droxidopa, will not be allowed for the entire duration of the study (6 weeks).

Study Assessment/Procedures

Screening Visit: The PI or a member of the study team will explain the purpose, procedure, potential risks and benefits of this study, obtain the informed consent, and screen patients for Inclusion/Exclusion criteria.

Visit 1: This evaluation will be performed at least 1 hour after the first dose of dopaminergic medications, when patients are expected to be at their most optimized level of motor function. BP assessment, as per autonomic laboratory protocol, will be performed with a beat-to-beat BP monitor (Caretaker 4, Caretaker, VA, USA) and confirmed by an automated sphygmomanometer (HEM-7200 Omron Healthcare, Japan) placed at heart level on the left arm, evaluating patients in the following conditions: a) sitting in a chair

after at least 10 minutes of rest; b) after a minimum of 10 minutes of supine rest; and c) after 1 and 3 minutes of standing. These measurements will serve to (1) confirm the diagnosis of OH, and (2) evaluate for the presence of SH, defined as systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg in the supine position [19]. Arm-cuff BP measurements will be performed with the upper arm positioned at the heart level with the feet flat on the floor. Patients will also receive training to self-monitoring BP with automated arm-cuff sphygmomanometer, which will be provided at Visit 1, and will serve to monitor BP during Droxidopa titration plan.

Clinical Assessments: Motor severity as per the MDS-Unified Parkinson's Disease Rating Scale (MDS UPDRS) [20]; OH symptoms severity as per the full OHQ (OHSA and OHDAS) scale [7]; quality of life as per the PD questionnaire (PDQ-39) [11]; Cognitive assessment as per the Cambridge automated neuropsychological test battery (CANTAB) [12] and CERAD-NAB [13].

Clinical Diary: Patient will be instructed to score the severity of the OH-related episodes of postural instability and the number of episodes of postural instability a day before starting titration with droxidopa, 1 day after V2 and 1 day after V3; using a self-assessed clinical diary based on the OHDAS (a section of the OHQ assessing the impact of OH symptoms on standing and walking).

Gait Assessments (average of two measurements): In order to evaluate variables of interest (stride length, single leg stance time, dynamic stability index, and gait velocity), patients will be assessed walking on the 20 feet-Protokinetics Zeno Walkway. Patients will be instructed to "walk from the mark (red tape) before the mat to the mark after the mat, turn around and walk back". After a preliminary review for acquisition errors, the data will downloaded into a Matlab-based software platform prepared ad-hoc for this study (Matlab, Mathworks, CA, USA) by the Department of Bioengineering of the University of Cincinnati (Prof. Jeff Johnson).

Postural Assessments (average of two measurements): In order to evaluate variables of interest (postural sway on the X and Y-axis, as measured by the center of mass estimated X and Y range), patients will be asked to perform a modified Clinical Test of Sensory Interaction on Balance. Patients will stand on the mat for 30 seconds under the 2 following conditions: eyes open/rest and eyes closed/rest, with their feet 1"-2" apart and arms at their side. For the eyes open condition, he/she will be asked to focus on a point in front of him/her at eye level to control for visual distractions. Data will be collected and stored into the software platform described above.

WMS Assessment: Patients will be provided an Apple Watch® with dedicated app (e.g., the Activity app®), able to measure number of hours of standing per day, and total calories and active calories per day. The Apple Watch® will be connected with an iPhone and will be given to each subject together with dedicated instructions to fill out the OH-related diary. More in details, patients will be instructed to charge the Apple Watch® and the iPhone® every night before going to bed, and to wear the watch the day after when they wake up. Total number of hours in which the patients will wear the watch will be counted at the end of the study, based on the data provided by the Apple Watch®. Data collected by the Apple Watch® will be downloaded after the end of the study and will provide information related to number of steps per day, number of hours of standing per day, and total calories and active calories per day.

Droxidopa Titration Plan

Droxidopa will be started after 2 days of baseline data collection at the dosage of 100 mg 3 times a day (TID). Dose-optimization will be titrated over a 2-week period in 100- mg TID increments every 2 days until at least one of the following criteria is met:

- Self-rating score of 0 at the item 1 of the OHQ, plus an increase in standing systolic BP ≥10 mm Hg, compared with the baseline value, as measured 3 minutes post-standing (and 3 hours after a Droxidopa dose).
- Reaching the maximum permitted dosage of 600 mg TID.
- Sustained BP >180 mmHg systolic or >110 mmHg diastolic while standing, sitting, or supine.

Visit 2: Patients will receive a complete BP assessment following the same procedure detailed in Visit 1 (see above), and a standard neurological examination. Adverse events and side effects associated with Droxidopa treatment will also be addressed, adjusting the dosage of Droxidopa if needed. Technical issues related to the use of Apple Watch® will also be discussed, if present.

Visit 3: This evaluation will be performed in the morning, at 8:00 AM before breakfast and at least 1 hour after the first dose of dopaminergic medications, 4 weeks after Visit 2. Patients will undergo a complete clinical, gait, postural and BP assessment, as per the protocol described in Visit 1.

Data collected from Apple Watch® will be downloaded and analyzed in three steps. (1) Each patient will receive a unique identification code for entry into the computer database to ensure patient confidentiality. By means of a semi-automated algorithm, the software will score the main variables of interest. (2) Data recorded from the questionnaires will be logged (in a blind fashion) in a REDCap database designed in consultation with Dr. Dwivedi (a professional biostatistician from Texas University) as per the need of data analysis. (3) The REDCap data file would be transferred into SAS data file and combined with Matlab data for statistical analyses and report preparation. Dr. Alok Dwivedi will process the data.

Study Timeline

Months 0-1 Administrative preparation

Months 1-2 Creation of the Software Platform for data analysis (Matlab-based platform prepared ad-hoc for this study, which will analyze and score with a semi-automated algorithm the postural data downloaded from (1) the WMS and (2) the Gait and Postural Analysis system

Months 2-10 Recruitment of Patients

Months 10-11 Completing Data Collection and Analysis – Manuscript Development

Months 11-12 Manuscript Completion and Submission

Bioengineering and Statistical support

In order to guarantee the success of this application and the correct analysis of signals derived by TOMs, adequate support will be provided by the department of Bioengineering, University of Cincinnati, with particular regard to the phase of data analysis. For the statistical needs, we will be assisted by the experience

of Dr. Dwivedi, Assistant Professor at the Division of Biostatistics and Epidemiology at TTUHSC-El Paso, and active member of our research team. He will provide statistical assistance and active participation in the analysis of data for the entire duration of the study, ensuring that data will be collected and analyzed using the most appropriate statistical methods.

Data Analysis

Aim #1 To evaluate the feasibility and calculate the effect size of gait and postural TOMs to quantify OH related postural instability during in-clinic evaluations

Data will be described with appropriate summary measures (mean and SD, or median and interquartile range) at Visit 1 (before Droxidopa treatment) and Visit 3 (after 4 weeks of Droxidopa maintenance therapy). Changes in the main clinical (PDQ-39, Tinetti, OHQ and related subscales), gait (stride length, single leg stance time, dynamic stability index, and gait velocity) and postural (postural sway on the X and Y axis) outcomes will be compared between Visit 1 and Visit 3 using the paired t-test/ non parametric Wilcoxon signed rank test depending on the distribution of change outcome. Effect size (mean or median change and percent change) will be reported along with 95% confidence interval (CI). In addition, data collected with TOMs before and after treatment with Droxidopa will be correlated with changes in the PDQ-39, OHQ, CANTAB and CERAD-NAB by means of the Pearson correlation/Spearman rank correlation analysis.

Hypothesis: Gait analysis and Postural analysis will accurately capture changes in gait and postural stability associated with OH treatment, with higher sensitivity and lower variability than standard clinical tests.

Aim #2 To evaluate the feasibility and calculate the effect size of using WMS to quantify OH related functional parameters during at-home activities of daily living

Postural data collected from WMS (Apple Watch®) and evaluating: (1) Number of steps per day; (2) number of hours of standing per day; and (3) total calories and active calories per day, will be analyzed and compared with episodes of subjective (OHDAS-based diary) postural instability recorded during the follow-up period using a paired t-test/Wilcoxon signed rank test. In addition, we would also evaluate the changes from pre-baseline to post baseline of subjective measure of postural stability and correlate with objective measures of postural stability using Pearson correlation/Spearman rank correlation analysis. Statistical analyses will be carried out using SAS 9.3.

Hypothesis: WMS will provide an accurate measure of functional parameters in the home setting, thus allowing an indirect measure of the patients' quality of life, with higher sensitivity and lower variability than self-reported clinical diaries.

Missing data on the scores will be handled by a two-step approach. Less than 20% missing data on any variable for an individual will be imputed using the mean of the final score of that question. Greater than 20% missing data for any participant on any instrument will be handled by a multiple missing imputation approach. Missing data on BP related variables will be imputed using multiple missing imputation approach.

Sample Size Calculation: Given the exploratory nature of this pilot study, the sample size calculation is inevitably limited by the lack of previous data. We used a study analyzing the effect of levodopa in PD with

a gait analysis [21], which reported a 30% improvement in the stride length (SD 31.3%), to pre-specify a threshold of minimal improvement of 10% between baseline and follow-up. With these assumptions, we estimate that a sample of 12 patients will be more than sufficient to detect significant differences using a paired t-test, with more than 80% power and at 5% level of significance (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

Innovation

Although TOMs are unanimously thought to represent the future of medical assessments, their routinely application is limited by the lack of validation studies proving their efficacy and reliability in clinical trials. The current proposal will provide more sensitive standards for the assessment of OH complications in PD, with the main innovation of developing and validating an innovative outcome measure based on a mobile (WMS) and in-clinic (gait analysis) technology.

DATA STORAGE AND CONFIDENTIALITY:

All records from this study will be maintained in a secure setting. We will be using REDCap (Research Electronic Data Capture) as the secure web-based application to store data for this research study. Records will not have any patient health information (PHI) associated with them. These records will be kept indefinitely to allow for re-analysis of data, if needed. The data will never be accessible without a secure password.

RISKS AND BENEFITS:

This study is considered more than minimal risk as per FDA guidelines [19], and involves the use of Droxidopa, a FDA approved drug for Parkinson Disease and Orthostatic Hypotension and evaluation of Technology objective measures. It does not involve the use of any other invasive procedure, but the patients would not normally have these evaluations as part of their standard PD clinic visits. Subjects could risk falling while completing the walking assessment, though they will not be asked to walk beyond their daily norm and a researcher will walk beside the patient as they perform the walking assessment. By collecting data on their responses, we will be able to determine an objective evaluation of postural stability and risk of falling for these patients. Patient could also present side effects from using Droxidopa (Patient Brochure attached). The adequate dose titration and potential side effects will be explain by the principal investigator before starting medication. The information gathered from this study will provide a basic understanding how technology objective measures (TOMs) are a more reliable measure of OH than compared to standard subjective measures. If confirmed, these findings will improve the treatment in PD by using TOMs, instead of standard subjective outcome measures.

PATIENT COSTS/PAYMENT

There will be no cost to participants for participating in this study. The patients will not receive payment for their participation in this study.

CONSENT

A separate document is attached.

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