Anxiety in Parkinson's: Use of quantitative methods to guide rational treatment

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JHM IRB - eForm A – Protocol

Anxiety in Parkinson's: Use of quantitative methods to guide rational treatment

1. Abstract

a. Provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Anxiety in PD aggravates physical disability and independently contributes to poor health-related quality of life. Clinically significant anxiety occurs in up to 40% of patients with PD, a markedly higher prevalence than healthy or comparably disabled persons without PD. Anxiety in PD is complicated by atypical presentations, comorbidity with depression, and phenomenological overlap with other non-motor and motor symptoms of PD. As a result, anxiety syndromes in PD are often poorly characterized. In my previous work, 22% of anxious patients with PD had clinically significant anxiety syndromes that failed to meet criteria for the established Diagnostic and Statistical Manual (DSM) anxiety diagnoses. These 'non-DSM' anxiety syndromes were often associated with fluctuations in motor symptoms resulting from the 'wearing-off' of dopamine based treatments. However, even when anxiety occurs in association with motor fluctuations, it is not clear whether it is a reaction to the change in motor function and dopamine levels or an independent process. In order to better target and treat anxiety syndromes in PD the relationship between PD-specific features and anxiety needs to be better understood.

There have been no randomized controlled drug trials to treat anxiety in PD. Current management strategies are based on expert opinion and observational studies and recommend the anti-anxiety treatments typically used in the non-PD population. Yet, many of these anti-anxiety treatments may worsen motor function and increase fall risk in PD. Currently, there is no evidence-based standard to guide the pharmacologic treatment of anxiety in PD. The overlap between PD-specific features and anxiety suggests that certain anxiety syndromes may emerge from the neurodegenerative process of PD. The goal of this study is to, 1) investigate a system of classification for anxiety disorders that accounts for patterns of comorbidity with PD-specific features (e.g. wearing-off) and 2) to design and conduct an intervention that tests whether treating fluctuations in dopaminergic neurotransmission improves anxiety in an 8-week study of rotigotine vs. placebo.

2. Objectives (include all primary and secondary objectives)

(1) **Using latent class analysis, investigate whether a hypodopaminergic state, produced by a temporary interruption of dopamine medications, is associated with a distinct anxiety syndrome in PD in a cross-sectional study of 200 subjects with idiopathic PD.** *Hypothesis: Certain anxiety syndromes and PD have a shared causal mechanism. Demonstrating that certain anxiety symptoms are associated with motor fluctuations, that is both anxiety and motor fluctuations are increased in hypodopaminergic states and cluster together based on a latent variable will support this hypothesis*

(2) **Conduct an 8-week intervention study of rotigotine (n=30) compared to placebo (n=30) for the treatment of anxiety disorders in PD that will provide estimates of effect size and the impact of co-occurring motor fluctuations on the treatment of anxiety.** *Hypothesis: Treatment with rotigotine for anxiety associated with motor fluctuations will result in a greater reduction of anxiety as compared to treatment with placebo*

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Anxiety is common in PD and associated with motor fluctuations. Anxiety is one of the most common non-motor symptoms in PD, occurring in up to 56% of patients, often in association with PD-specific features.(1,2) Anxiety syndromes are more prevalent than in healthy or comparably disabled individuals without PD and result in greater disability and a lower quality of life.(3-6) Anxiety syndromes in PD are a heterogeneous group of conditions that are characterized by either episodic or persistent anxiety phenomena, frequent comorbidity with depression, and atypical presentations when compared to anxiety syndromes in the general population.(7-9) In a previous study, we found that 22% of PD patients had atypical anxiety syndromes not specifically described by the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision (DSM-IVTR).(10) The most common atypical presentation of anxiety in PD in our study and others is when anxiety occurs as an episodic symptom potentially related to the wearing-off of dopaminergic treatment and motor fluctuations.(3,10,11) "Wearing-off" is defined as a generally predictable recurrence of motor and non-motor symptoms as the effect of dopaminergic treatment declines over a given dose.(12) The loss of treatment effect leads to episodic reemergence or worsening of motor and non-motor symptoms typically referred to as "fluctuations". The pathophysiology of wearingoff is thought to be related to the progressive loss of dopamine in PD.(13) Wearing-off occurs in up to 40% of PD patients within 4-6 years of starting levodopa therapy, although it has also been reported to occur much earlier, within 5-6 months, in up to 30% of patients.(14,15) Other studies suggest that anxiety (and depression) may be a 'phenocopy' of autonomic dysfunction, another common non-motor symptom, and not associated with fluctuations or wearing-off of dopaminergic medications.(16) Whether wearing-off anxiety, autonomic dysfunction related anxiety, and other subtypes are specific to PD and represent subgroups with distinct etiologies and treatment is not known.

There are very few data on treatment of anxiety in PD. A recent study by the MDS non-motor task force concluded there are insufficient data on the treatment of anxiety in PD to establish evidencebased treatment standards. (17) Anxiety is associated with worse quality of life, greater motor impairment, more dyskinesias, and a greater frequency of motor fluctuations.(18,19) In a recent study, our data showed that anxiety associated with motor fluctuations was an independent predictor of lower self-perceived health status in PD.(10) Despite the distress and dysfunction caused by anxiety syndromes and their unusually high prevalence in PD there are no randomized controlled trials (RCTs) on which to establish evidence-based treatment. (17) In addition, many conventional anxiety treatments can be problematic when used in PD. Benzodiazepines and tricyclic antidepressants can increase the risk of falls and contribute to the risk of delirium and confusion in PD.(20,21) Even selective serotonin reuptake inhibitors(SSRIs), which are typically well tolerated in the general population, may worsen tremor and other motor symptoms in PD.(21,22) Therefore, a RCT of a non-traditional anti-anxiety agent that takes into account the potential association between anxiety and PD-related features, and a potential PD-specific vulnerability to side-effects is needed.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

For objective 1: Subjects will be assessed in both the "on" and "off" motor states following the clinical protocol from the Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD).(23) We use the CAPSIT-PD protocol routinely in the PDRC and movement disorder clinics and will include consenting individuals as part of this study. However, a portion of the subjects recruited will have the CAPSIT-PD protocol exclusively for this study and not as a part of routine clinical care. "Wearing-off" and the "off-motor state" in PD are defined as a generally predictable recurrence of motor and non-motor symptoms as the effect of dopaminergic medications stops.(12) Subjects will temporarily stop all dopaminergic medications for a minimum of 12-hours in order to be assessed in the "off" motor state in the morning. (Most individuals with PD do not take medications overnight and usually take their last dose between 5-9pm. Therefore most participants will only be off medications for a few hours more than they normally would be as the study will be conducted in the morning) The on- and off-state assessments are listed below. Subjects will then take their usual morning dopaminergic medications and after one hour, to allow them to return to their best "on" state, repeat the CAPSIT-PD on-off battery. In addition to the on-off testing battery, several PDrelated clinical features will be assessed, only in the on-state, using instruments recommended by the National Institute of Neurological Disorders and Stroke Common Data Element Project (NINDS-CDE)(24) for PD.

CAPSIT-PD on- and off-state testing battery

Each assessment will be conducted twice, once in the off-state and once after resuming PDmeds in the on-state

1. Anxiety: Hamilton Anxiety Rating Scale (HAM-A)(25)
2. Depression: 17-item Hamilton Depression Rating Scale (HAM-D)(26)
3. Motor and non-motor fluctuations: 19-symptom wearing-off questionnaire (WOQ-19)(27)
4. Physical Disability: Schwab and England Scale (SE)(28)
5. Motor symptom severity: MDS-UPDRS part III(30)
6. Symbol Digit Modalities Test(45)
7. Stroop Color and Word Test(46)

NINDS-CDE Recommended Assessments for PD-Specific Clinical Features (only for on-state)

1. Demographics
2. PD Medical History
3. PD Family History
4. PD and Non-PD Medication Log
5. Motor: MDS-UPDRS parts I-IV
6. Psychiatric: Structured clinical interview for DSM-IV-TR (SCID) axis I disorders, research version, non-patient edition (29)
7. Cognitive: Montreal Cognitive Assessment (MoCA)(31)
8. Other non-motor: Non-motor Symptoms Questionnaire (NMS-Quest)(35) and the Scales for Outcomes in Parkinson's disease autonomic dysfunction scale (SCOPA-AUT)(32,33)
9. Quality of life: 8-item Parkinson's Disease Questionnaire (PDQ-8)(34)
10. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease(QUIP)(47)

11. Neo Five-Factor Inventory(48)
12. Rapid Assessment of Physical Activity(RAPA)(49)

For objective 2:

The intervention will be 8 weeks in duration and include a 4-week dosage titration period and a 4-week maintenance period. Transdermal patch. Dosing will begin at baseline on day zero with either 1) placebo or 2) rotigotine at 2mg/24h and will be increased following the recommended dose escalation schedule for PD such that subjects will increase to 4mg/24hrs in week 2, and 6mg/24hrs in week 3. This dose of rotigotine is within the range shown to be safe and efficacious for the treatment of motor symptoms. 17,36,37) The timing of assessments is shown in Table 1. All assessments except for the physical exam, and the Clinical Global Impression for Anxiety Severity and change scales (CGI-S and CGI-C)(38) are part of the CAPSIT-PD on- and off-state testing battery, the table indicates administration points. Safety and tolerability will be assessed by recording adverse events.

b. Study duration and number of study visits required of research participants.
Objective 1 is one 3-hour cross-sectional visit, duration and visits for objective 2 are in Table 1

Table 1. Assessment schedule for objective 2

Visit Number	**Screening**	**Baseline**	**Follow-up visits**		
Time	**- - -**	**0**	**WK2**	**WK4**	**WK8: FINAL**
Diagnostic Interview or AIM 1 Battery	X				X
Physical Examination	X				X
MDS-UPDRS I-IV	X				X
MoCA	X				X
CGI-Severity	X	X			
CGI-Change			X	X	X
HAM-A	X	X	X	X	X
HAM-D	X	X	X	X	X
SCOPA-AUT, NMS	X	X	X	X	X

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

For the clinical trial in objective 2: double-blinded, randomized, placebo controlled, 8-week intervention study of rotigotine vs. placebo for the treatment of anxiety in PD. The study is double-blinded to reduce the risk of bias in rating anxiety response to treatment as both the subject and investigators will be rating anxiety using self-reports and investigator-administered scales.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Patients will receive routine care and will NOT have current therapy stopped.

e. Justification for inclusion of a placebo or non-treatment group.

Absence of current standard treatment for anxiety in PD justifies inclusion of a placebo group. Anti-anxiety drugs based on serotonin, norepinephrine, and benzodiazepine mechanisms are the current standard in non-PD populations and are used in PD without sufficient evidence of efficacy and may be associated with side effects.

f. Definition of treatment failure or participant removal criteria.

Rotigotine is an evidence based treatment for motor symptoms and motor complications of treatment in PD and deemed to be of "acceptable risk without specialized monitoring".(17) Rotigotine does carry the risk of nausea, vomiting, application site reactions, dizziness, anorexia, hyperhidrosis, insomnia, lower extremity edema, somnolence and dyskinesia. Rotigotine is a treatment routinely used as part of clinical care in PD. If impulse control disorders occur the subject will taper and stop the study drug, their treating neurologist will be notified, and they will be referred for psychiatric treatment. Subjects will be examined for lower extremity edema at screening and at each follow-up visit. If edema occurs subjects will be asked if they wish to discontinue the study drug. Subjects will be asked about excessive somnolence at each visit. If somnolence is severe and interferes with daily functioning, tapering and discontinuation of the study drug will be recommended.

Subjects in the intervention study will be medically screened prior to enrollment and will be monitored at the designated intervals for any adverse events. Subjects who are acutely suicidal or an imminent risk to themselves will be excluded. Subjects will be removed from the study if they request removal, if the team believes it is unsafe to continue, if they experience significant distress for any reason, or if the patient becomes imminently suicidal. Subjects will be monitored closely by an experienced clinical team, available 24-hours per day.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

After termination of the intervention study, prematurely or scheduled, a summary letter will be sent to the patient's treating clinicians detailing the patient's participation in the study, the patient's response, aftercare plans, and any other relevant information. The study medication or placebo will be tapered and stopped, unless, in the case of participant on study drug, their treating doctor wishes to continue rotigotine and take over prescribing it as part of their routine care. Subjects will be offered follow-up psychiatric care in our clinic as well as assistance in obtaining care elsewhere, including by providing consultation to their primary clinician/neurologist. All adverse events will be reported to the JHH IRB.

5. Inclusion/Exclusion Criteria

Subjects for both objectives will be English-speaking adult men and women including minority groups, ages 21 years or older, with idiopathic PD, based on UK Brain Bank Criteria.(39) Subjects with a diagnosis of dementia or a Montreal Cognitive Assessment (MoCA) (30) <23 will be excluded to reduce the chance of enrolling individuals with Lewy body dementia. Additional inclusion and exclusion criteria for objective 2 are in Table 2.

Table 2. Additional inclusion and exclusion criteria for objective 2 8-week intervention study
Inclusion Criteria

1. Diagnosis of DSM Anxiety Disorder and as part of this intervention study, we will include all anxiety subtypes provided treatment with medication is indicated in standard clinical psychiatric practice
2. Stable medical history and general health. If non-postmenopausal female, must be non-pregnant and using a medically acceptable form of contraception during the study if sexually active
3. On stable anti-parkinsonian therapy for 2 weeks before enrollment and expected to be able to remain on stable therapy for the 8-week study.
4. If treated for depression, must be on stable anti-depressant for 2 weeks before enrollment and expected to be able to remain on stable therapy for the 8-week study.
5. *[Not on anti-anxiety therapy (unless it is for another indication, i.e. REM Sleep Behavior Disorder) at time of enrollment OR able to be tapered safely off these medications as determined by the t ½ of prescribed medication at the time of screening]*

Exclusion Criteria

1. *[Exclude subjects with dementia as diagnosed by DSM criteria or MoCA <23 and subjects with less than a 1 year duration of PD to help exclude subjects who may have Lewy body dementia (62)]*
2. Lifetime diagnosis of schizophrenia, bipolar disorder, impulse control disorder (ICD), or major depression with psychotic features
3. Current alcohol or substance use disorder, as defined by DSM
4. Acute suicidality or need for inpatient psychiatric hospitalization
5. Psychotic symptoms so severe as to warrant treatment with antipsychotic medications in the opinion of the patient's physician
6. Medical conditions such as current malignancy or hematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or other non-PD neurological disease that is medically debilitating and/or CNS affecting (e.g., uncontrolled diabetes mellitus or thyroid disease). If there is a history of such disease and it has been stable for > one year, then subject may be included if investigator judges their participation as safe.
7. Patient currently treated with psychotherapy for anxiety/depression
8. Current treatment with another dopamine agonist

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Rotigotine is an evidence-based treatment for motor symptoms and motor complications of treatment in PD and deemed to be of "acceptable risk without specialized monitoring". Dosing will begin at baseline on day zero with either 1) placebo or 2) rotigotine at 2mg/24hrs and will be increased following the recommended dose escalation schedule for PD such that subjects will increase to 4mg/24hrs in week 2, and 6mg/24hrs in week 4.]* This dose of rotigotine is within the range shown to be safe and efficacious for the treatment of motor symptoms in PD.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable. Hamilton Anxiety Rating Scale(HAM-A)

b. Secondary outcome variables. 17-item Hamilton Depression Rating Scale (HAM-D), 19symptom wearing-off questionnaire (WOQ-19), Schwab and England Scale (SE), MDS-UPDRS part III

c. Statistical plan including sample size (n=200) justification and interim data analysis.

For objective 1: We will conduct a latent profile analysis (LPA) using the following observed variables (measured in the on-state) as latent profile indicators: age of PD onset, LEDD, HAMA, HAM-D, WOQ-19, SE, UPDRS part III, and MoCA score, to model unobserved (i.e. latent) profiles. LPA is a type of latent class analysis that uses continuous indicator variables. Using LPA we will determine 1) the number of classes/profiles that best fits symptom profiles of observed values, 2) the proportion of the sample that belongs in each class/profile (e.g. class prevalences), and 3) the means of each latent profile, conditioned upon membership in each class. We will then test whether specific subject characteristics (age, gender, variability of symptoms between on- and off-states (as change scores), and motor fluctuations), from the battery above predict differential membership in the identified latent profiles via latent profile regression. With latent profile regression, predictors of latent profile membership are modeled via multinomial logistic regression. Statistical power for latent profile regression was determined via monte carlo simulation,(42) assuming 3 classes/profiles with prevalences of 30%, 10%, and 60%. We would have 80% or greater power to detect a log odds ratio for an association between a standardized predictor and latent profile membership of 1.17 for profile 1 (prevalence of 30%) and 1.71 for profile 2 (prevalence of 10%), with profile 3 as the reference class. Antidepressant, anti-anxiety, and other psychiatric medication use will be controlled for in the analysis.

For objective 2: The primary outcome variable is the HAM-A. Power was calculated based on an enrollment of 60 subjects total, equally distributed between treatment and control groups, with a 10% dropout by the final time-point, and a standard deviation of 8.55 (which is a pooled estimate calculated from different anxiety subtypes in PD patients assessed using the HAMA.(43) The within subject/between time-point correlation was assumed to be 0.5 with a compound symmetric correlation structure, and the alpha level was set at .05. Power calculations were based on the formula of Jung and Ahn,(44) which calculates power for the difference in slope (i.e. the difference in response trajectory) between treatment and control groups for a longitudinal clinical intervention. Based on the assumptions specified, we would be able to detect an effect size of .69 from baseline to 8 weeks for the two groups with 80% power. This proposal is for a proof of concept study that will provide important initial estimates which may be used to 1) assess the potential efficacy of this novel anxiety intervention and thus provide necessary data for a "go-no-go" decision for a more definitive hypothesis-testing trial, and 2) provide estimates of effect size and variance needed to properly design such a trial.

Screening for objective 1: Screen failures are expected to be rare for objective 1 as there are only 3 criteria for exclusion: 1) UK Brain Bank criteria for PD, 2) English speaking, and 3) nondemented. In our longitudinal study of Parkinson's disease, which has autopsy confirmation at study end, the rate of accurate clinical diagnosis of PD is approximately 90%. The presence of dementia has a similar accuracy and will be further screened using the MoCA with a cut off of <23. The drop-out rate is also expected to be low as objective 1 takes place in one 3-hour visit. Screening for objective 2: Objective 2 will require 60 subjects who *can* be recruited from the n=200 from objective 1. Based on our preliminary data, 30% of subjects with a DSM anxiety disorder and comorbid depression and up to 53% with anxiety disorders only will not be

on any treatment for anxiety. In addition, we have included a protocol for enrolling individuals whose anxiety is not adequately controlled on their current therapy.(item 4 inclusion criteria)

Subjects for objective 2 will be preferentially recruited from objective 1 for maximum efficiency. In the unlikely event that none of the subjects for objective 2 come from objective 1 the total number of subjects needed for both is n=260. We will be conducting post consent screening and will allow for ~15% screen fail rate and estimate that the maximum number of subjects consented will not exceed 300.

d. Early stopping rules.

Participants will be removed from the study if they request removal, if the team believes it is unsafe to continue, if they experience significant distress for any reason, or if the patient becomes imminently suicidal. Subjects will be monitored closely by an experienced clinical team, available 24-hours per day.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

All members of the research team will make every effort to implement the protocol procedures in a sensitive and supportive manner. Only subjects who are medically stable will participate in these studies. Dr. Pontone will provide close clinical monitoring during all aspects of the study.

Clinical assessments and questionnaires: Subjects will be informed prior to beginning the evaluation to please notify the examiner if they experience any distress. If this occurs, the examiner will stop the evaluation. To minimize the chance of this happening, subjects will be provided breaks and positive feedback and research staff will provide assistance with form completion if needed. We will conduct psychiatric and motor assessments in a standardized fashion. These approaches are standard for patient assessment in clinical practice and are generally not associated with more severe complications. Frequency: rare

On- and off-motor state testing: As mentioned above we will follow the standard clinical protocol established in the Core Assessment Program for surgical Interventional Therapies in PD.(66) Subjects will be closely monitored for discomfort or distress. For subjects who experience distress the off-state testing will be stopped and their usual Parkinson's medications will be resumed. For subjects unable to tolerate the full 12 hour off-state, it is recommended that the longest tolerable wash-out be determined and to use this period for all subsequent assessments. For our study, subjects who fail to tolerate washout of 8 hours or more will be excluded to minimize the potential for patient distress while preserving the goal of optimal washout of dopaminergic medication. Frequency: rare

Rotigotine drug treatment: Rotigotine carries the risk of impulse control disorders, lower extremity edema, and excessive somnolence. Prior to enrollment in the intervention study subjects will be screened for impulse control disorders and subjects with any current or past impulse control disorders will be excluded from the study. During the course of the study subjects will be specifically asked about impulse control disorders at each visit. If impulse control disorders occur the subject will taper and stop the study drug, their treating neurologist will be notified, and they will be referred for psychiatric treatment. Subjects will be examined for lower extremity edema at screening and at each follow-up visit. If edema occurs subjects will be asked if they wish to discontinue the study drug. Subjects will be asked about excessive

daytime somnolence at each visit. If daytime somnolence is severe and interferes with daily functioning, tapering and discontinuation of the study drug will be recommended.

Subjects in the intervention study will be medically screened prior to enrollment and will be monitored at the designated intervals for any adverse events. For females of childbearing age, negative urine pregnancy test prior to study will be required. Subjects who are acutely suicidal or an imminent risk to themselves will be excluded. Subjects will be removed from the study if they request removal, if the team believes it is unsafe to continue, if they experience significant distress for any reason, or if the patient becomes imminently suicidal. Subjects will be monitored closely by an experienced clinical team, available 24-hours per day.

We will have direct contact with the patient's neurologist and will convey clinically relevant information in a summary report or by direct phone or personal contact, as is our standard practice for our other PDRC clinical research protocols. If the screening exam is negative or the participant declines, this will be indicated. Dr. Pontone will also review the patient's responses for evidence of any information that should be addressed immediately by the patient's treating clinicians. In particular, this would include suicidality or other severe psychiatric symptoms. After termination of the intervention study, a summary letter will be sent to the patient's treating clinicians detailing the patient's participation in the study, the patient's response, aftercare plans, and any other relevant information. Subjects will be offered follow-up psychiatric care in our clinic as well as assistance in obtaining care elsewhere, including by providing consultation to their primary clinician/neurologist. All adverse events will be reported to the JHH IRB. Frequency: 10% of subjects on rotigotine experience impulse control issues at some point during treatment, daytime somnolence severe enough to be clinically significant is not common, and edema is rare.

b. Steps taken to minimize the risks.

Answered in item a above.

c. Plan for reporting unanticipated problems or study deviations.

All adverse events and study deviations will be compiled and reported quarterly to the IRB. Serious Adverse Events (defined as those which are life-threatening, or require hospitalization) will be reported within 24 hours to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

We will comply with applicable laws and regulations regarding subject data privacy. We will use the health information only as permitted in accordance with the provisions of the Health Insurance Portability and Accountability Act and the regulations promulgated thereafter. If necessary, we will revise our protocol to meet those regulations. Patient identifications will remain anonymous to study staff until the patient indicates willingness to participate. With approval from the participant, medical and neurological records will be reviewed by the investigator or research assistant in order to complete and confirm aspects of the database. Research data will be kept in locked files and information on computer databases will be coded to protect patient identity. Subjects will not be identified in publications.

e. Financial risks to the participants. N/A

9. Benefits

a. Description of the probable benefits for the participant and for society.

Potential benefits to participants is better recognition of anxiety disturbances that can occur in PD. Benefits also include awareness that participation in the study is a significant contribution toward finding a better understanding of the mechanistic underpinnings of anxiety syndromes that may be specifically associated with PD and to the development of an evidenced based treatment for anxiety in PD. Clinically relevant information that would otherwise have remained undetected but is revealed through this assessment will be conveyed to their treating clinicians.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Objective 1: Participants will be provided $10 for travel costs or valet parking (valued at $10).

Objective 2: Participants will be provided $25 at completion plus paid valet parking or travel costs ($10) for each visit.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to the participants.

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