PROTOCOL

Study Title
Varenicline for the treatment of postural and gait dysfunction in Parkinson Disease (PD).

Objectives
To determine if varenicline is effective for abnormalities in balance and posture in PD.

Design and Outcomes
The design is a randomized, double-blinded, placebo-controlled study conducted at one center. The primary outcome is the change in the Berg Balance Scale. Secondary outcomes include the Activities-specific Balance Confidence Scale, Parts I-III of the MDS-UPDRS, the Timed up and go test, the Folstein Mini Mental Status Exam (MMSE), the Beck Depression Inventory, the Beck Scale for Suicidal Ideation, the Frontal Assessment Battery (FAB), and total number of falls.

Interventions and Duration
Subjects will be randomized to placebo or varenicline with an escalation phase of one week (0.5 mg daily for three days, 0.5 mg twice daily for four days, then 1 mg twice a day to begin at week two). The rating scales will be performed before initiation of the drug, and then the subject will remain on drug for eight weeks after which outcomes will be reassessed.

Sample Size and Population
Sample size is estimated to be 38 patients; however 42 will be recruited to allow for attrition. All patients will have been diagnosed with PD using the UK Brain Bank Criteria. There will be no stratification of randomization.

STUDY OBJECTIVES

Primary Objective

The hypothesis tested is that varenicline will result in improvement of balance and postural instability after eight weeks of treatment compared to placebo. The null hypothesis is that there will be no difference in tests of balance between subjects on placebo compared to those on varenicline using the Berg Balance Scale as the primary outcome. The primary and secondary outcomes will be performed by the site investigator who will be blinded to treatment.

Secondary Objectives

There are two secondary hypotheses. First, we hypothesize that subjects with the postural-instability-gait disturbance (PIGD) subtype of PD will be more responsive to treatment compared to the tremor-predominant subtype. Patients will be categorized with tremor-predominant PD if the ratio of the mean tremor score to the mean PIGD score is 1.5 or higher and as PIGD predominant if the ratio is 1 or lower. The mean PIGD score

will be defined as the sum of an individual's baseline falling, freezing, walking, gait and postural stability UPDRS scores divided by five.

The second hypothesis is that varenicline will improve cognitive functioning in PD subjects. This hypothesis will be tested by comparing the results from the MMSE and the FAB at the beginning of the study, at four weeks, and at eight weeks.

BACKGROUND

Rationale

Parkinson disease (PD) is a clinical entity characterized by bradykinesia, rigidity, tremor, and postural instability. Current treatments primarily focus on replacement of dopamine to compensate for the degeneration of the substantia nigra pars compacta dopaminergic neuronal population. Though dopamine treats many of the motor symptoms of PD, postural instability (which often leads to falls) typically is least responsive to therapy. PD affects 2,000,000 people in the United States. It affects 49.7 per 100,000 person-years for those over age 50.[6] The incidence of falls is estimated to be as high as 69% in PD patients.[7] Clearly falls in this population can lead to significant sequelae of fractures, prolonged hospitalization, and associated medical complications.

Varenicline (Chantix) is a novel partial α4β2 agonist and full α7 agonist developed as an aid for smoking cessation and has been shown in initial studies to improve imbalance in patients with inherited spinocerebellar ataxia. Recently, the degeneration of the cholinergic system arising from the pedunculopontine nucleus (PPN) in the brainstem has been implicated in gait dysfunction in PD. Striatal cholinergic inputs are supplied from the PPN both via the intralaminar complex of the thalamus and through direct inputs. The primary subtypes of cholinergic receptors present in the striatum are nicotinic and include α4β2, α6β2, and α7 receptors. Varenicline has been reported in case reports to be effective in ataxia for patients with Spinocerebellar Ataxia types 3 and 14, the Fragile-X Associated Tremor/Ataxia syndrome (FXTAS), as well as improving subjective proprioception in Friedreich's Ataxia. Varenicline was given at 1mg twice a day and showed improvement on the Scale for the Assessment and Rating of Ataxia (SARA) scale. Other medications used for balance and prevention of falls in PD have not been shown to be helpful and thus the mainstay of treatment involves physical therapy.[8]

The dosage escalation medication regimen in this protocol is similar to those studies conducted for smoking cessation and for ataxia. The active medication will be dosed twice daily (1 mg BID) due to convention, though the half-life of the drug is listed as 24 hours. A week of dose escalation will allow for maximal tolerability. The worsening of neuropsychiatric symptoms reported in some patients with other disorders on varenicline appears to be isolated in patients with prior psychiatric conditions, but this has not always been the case. In order to monitor for this potential side effect and to screen for potential sub-clinical depression, the Beck Depression Inventory will be given to all subjects and followed during the course of the study. Suicidal ideation and attempt has also been reported in patients taking varenicline, so the Beck Scale for Suicidal Ideation will also be administered to participants during the course of the study. There are no aspects of the proposed dosing schedule that are not FDA-approved for other indications. This study is

of high priority due to the absence of any proven medications to treat imbalance in this disorder.

STUDY DESIGN

This is a randomized, double blind, placebo controlled parallel-designed study. Varenicline was chosen because of its novel mechanism of action and its preliminary success in treating some forms of hereditary ataxia. This will be the first clinical trial testing varenicline in patients with Parkinson Disease. The specific nicotinic cholinergic receptors varenicline targets are located in the human striatum with afferent cholinergic input arising from the brainstem where the locomotor center of the brain is thought to originate. The direct and indirect effects on these receptors may provide a mechanism to improve postural instability and imbalance in this patient population.

SELECTION AND ENROLLMENT OF SUBJECTS

Inclusion criteria:

- Subjects will be diagnosed with Parkinson Disease (PD) by the UK Brain Bank criteria.
- Subjects will have to be at least stage 2 on the Hoehn and Yahr staging system of PD and have a history of at least 1 fall or near fall in the last 6 months.
- Subjects must have a stable medication regimen.
- All subjects will be over the age of 40 in an attempt to exclude inherited forms of parkinsonism.
- Serum creatine kinase, complete metabolic panel, complete blood count, liver function tests, renal function tests, platelets and EKG are within normal limits (results obtained from primary care physician and dated within the past 6 months or obtained at screening visit).

Exclusion criteria:

- Hoehn and Yahr stage 5 subjects.
- Subjects with a history of major psychiatric disorder, deep brain stimulation surgery, recent cerebral trauma, cardiac arrhythmia, or renal insufficiency.
- a cardiovascular procedure in the last 5 years (eg, percutaneous transluminal coronary angioplasty) or have cardiovascular instability (including myocardial infarction or unstable angina). Other cardiovascular exclusions include uncontrolled hypertension, significant neurological sequelae of cerebrovascular disease, peripheral vascular disease with prior amputation, or severe congestive heart failure (New York Heart Association class III or IV).Concurrent treatment with any MAOIs, bupropion (Wellbutrin), or nicotine patches.
- Dementia or other psychiatric illness that prevents the patient from giving informed consent (MMSE score less than 25).
- Concurrent treatment with trihexyphenidyl (Artane) or benztropine mesylate (Cogentin).
- Significant degree of dysphagia, by history.

- Legal incapacity or limited legal capacity.

- Presence of severe renal disease (BUN 50% greater than normal or creatinine clearance <60 mL/min) or hepatic disease.

- Abnormal creatine kinase and/or platelet count in the past 6 months (as determined by lab reports obtained from primary care physicians or conducted at baseline).

- Use of varenicline within the previous 30 days.

- Women of childbearing potential who are pregnant at the time of screening or who will not use adequate contraception during participation in the study.
- Allergy/sensitivity to the drug or its formulations.
- Concurrent participation in another clinical study.
- Active substance or tobacco use or dependence.
- moderate or severe chronic obstructive pulmonary disease
- Serious illness (requiring systemic treatment/or hospitalization) until the subject either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least 60 days prior to study entry.
- Inability or unwillingness of the subject or legal guardian/representative to give written informed consent.

Study Enrollment Procedures

Patients with Parkinson Disease (PD) will be recruited through the Movement Disorders clinic located at the Neuroscience Institute at Rush University Medical Center. There are eight movement disorders attending physicians and three fellows who see approximately 4800 new and follow-up PD patients per year. Recruitment goals are expected to be predominantly achieved through the cohort of individuals seen at Rush, but advertising may also be conducted through monthly PD support group meetings or newsletters to enhance enrollment. Potential subjects may be identified by their treating physician in the Movement Disorders Clinic at Rush or referred to Rush from elsewhere. If a patient is interested in enrolling in this study, he/she will be invited to an initial study visit, at which time he/she will provide informed consent after a full explanation of the study.

Documentation of inclusion and exclusion criteria will occur if the patient is interested in enrollment. Eligible subjects who refuse participation will be given the option of later enrollment if desired.

Much of recruitment will occur from physicians who have a treatment relationship with the patient. Prior to the consent process, the Mini Mental State Examination will be performed to determine the patient's level of comprehension. If the potential subject scores less than 25, the patient will be excluded from the study. Consent will be obtained by the primary investigator and the potential subject. All investigators are trained in the conduct of human research. A copy of the consent form will be provided to all subjects.

The independent medical monitor will be responsible for obtaining group assignments. The assignment will be masked to the PI, the treating physician, the

subject, and all other staff conducting the study. The medical monitor will be responsible for correct drug dispensing for each subject based on randomization.

STUDY INTERVENTIONS

Interventions, Administration, and Duration
42 subjects will be randomized to receive 1 mg twice daily of oral varenicline or matched placebo. The therapeutic dose will be escalated over the first week as 0.5 mg daily for three days, and then increased to 0.5 mg twice daily for the next four days. Thereafter, subjects will continue on 1 mg twice daily for the remaining eight weeks. The outcome measures will be assessed at the end of week 5 and then repeated at the conclusion of the study. Side effects will be monitored at each of the encounters with the subject, either in person or by telephone. The most common expected side effects include nausea, insomnia, abnormal dreams, or headache. Subjects will be evaluated in the outpatient Movement Disorders Clinic at Rush University at the initiation and conclusion of the study. All patients may remain on other medications for neurologic signs (with the exception of those mentioned in the exclusion criteria), but the dose of these medications must remain stable during the duration of the study.

The Handling of Study Interventions
The drug and placebo will be manufactured by Pfizer. Placebo has similar taste and color to the active drug. The drug and placebo will then be shipped to Rush University, and dispensed to the study team who will distribute them to the subjects as described above. The medication will be stored at room temperature in a climate-controlled room which will be secured by lock. The pills will be dispensed to the subjects in pill bottles. For the escalation phase, subjects will receive one pill of 0.5 mg daily for three days, then two pills daily for the next four days, then two pills of 1 mg for the remaining 56 days. Subjects will be asked to return any unused medication after nine weeks to Rush University. Study intervention accountability records will be completed according to the Manual of Operations. The subject, investigators, and study staff will be blinded to the treatment arm of each subject. The study team dispensing the drug and the independent medical monitor will disclose the randomization to the investigators after the database has been locked at approximately three months.

Concomitant Interventions
Medications for neurological signs of Parkinson Disease must remain stable during the nine weeks of this study. The only contraindicated intervention is deep brain stimulation surgery.

- Required Interventions: oral varenicline 1 mg twice daily or placebo twice daily.
- Prohibited Interventions: concomitant use of trihexyphenidyl (Artane) or benztropine mesylate (Cogentin).
- Modifications to the study intervention can only occur during the open label escalation phase.

Adherence Assessment

Adherence will be assessed by pill counts and adherence questionnaires that will be completed at each of the study visits. Because the study is using an intent-to-treat analysis, adherence will be reported using descriptive statistics.

CLINICAL AND LABORATORY EVALUATIONS

Timing of Evaluations

Subjects will be consented and have initial laboratory studies and rating scales at the entry visit. Once on the study medication, they will be contacted by phone at three weeks for questions regarding side effects, clinical issues, and to answer any questions. The subject will be reassessed after five weeks for depression or suicidal ideation, and they will continue with the intervention or placebo. Again, they will be contacted by phone at week seven to assess for safety and tolerability. They will be seen at nine weeks and outcome measures will be performed.

Table 1. Timing of Evaluations

Evaluation	**Screening**	**Entry**	**Week 3**	**Week 5**	**Week 7**	**Week 9**
Informed Consent		X				
Documentation of PD	X					
Medical/Treatment Hx	X					
Inclusion/Exclusion	X					
Clinical Assessment		X				
Neurological Exam		X				
Adherence Assessments			X	X	X	X
Questionnaires						
MDS-UPDRS and other rating scales		X				X
Beck Depression/suicide scales		X		X		X
Mental Status exam		X				X
FAB		X				X
EKG		X				

Pre-Randomization Evaluations

These evaluations occur prior to the subject receiving any study interventions.

- Screening

At the screening visit, the diagnosis of Parkinson disease will be confirmed and medical history will be reviewed. Inclusion and exclusion criteria will be completed.

- Pre-Entry

Screening and pre-entry may occur concurrently. Consent will be obtained. EKG and blood tests will be completed at the visit and randomization will occur.

On-Study Evaluations

Blood chemistries, liver function tests, and hematology laboratory tests will be performed at two times during the study. Rating scales for movement disorders and cognitive disturbances will be performed twice during the study. The allowable time window is Schedule of Evaluations ± 7 days.

- Entry

The entry visit will occur at least two weeks after the screening visit to allow for adequate drug supply. Study drug will be dispensed at the entry visit.

- Intervention Discontinuation Evaluations

Evaluations done at the time of discontinuation include blood chemistry, hematology, and the rating scales. In addition, an adherence assessment will also be done.

- Post-Intervention Evaluations

Neurological examinations will be performed according to the standard of care by the treating neurologist/investigator.

- Final Evaluations

The final visit will consist of blood chemistry and hematology, neurological examination, rating scales (BBS, MDS-UPDRS, TUG, ABC, MMSE, FAB, BDI, and BSSI), and adherence assessment.

Special Instruction and Definitions of Evaluations

The source document will include all of the following listed below:

- Informed Consent: The patient will have an opportunity to review the consent form and ask any questions prior to signing the form. If the patient has dementia, he/she will be excluded from the study. A copy of the signed consent form will be given to the subject, and copies will be maintained in the study chart and the hospital record.
- Documentation of PD: Diagnosis of PD will be documented in the patient's chart prior to study entry.
- Medical History: The subject's history regarding PD will be obtained or a record of this history will be secured for the study chart. A complete social history, family history, and review of systems will also be performed.
- Treatment History: Allergies will be reviewed. Prior and current medications and other treatments will be reviewed and documented.
- Clinical Assessments: Clinical assessment procedures will be reviewed at the entry visit and the neurological examination will be performed. Clinical assessments to review safety, tolerability, and effectiveness will be conducted at each face-to-face visit or over the phone. Neurological examination will occur at the face-to-face visits only. Change in neurological signs or symptoms, adverse events, or tolerability issues should be recorded on the CRFs.
- Laboratory Evaluations: Blood chemistry and hematology will be performed and the resulting laboratory result forms will be placed in the study record.
- Questionnaires and Rating Scales: Scoring for each item on the Berg Balance Scale will be recorded in the scoring grid. Scoring for the MDS-UPDRS, TUG, ABC,

MMSE, Beck Depression Inventory, Beck scale for suicidal ideation, and FAB will be recorded in the CRF.

- Adherence Assessments: Pill counts and questionnaires will be filled out at every phone or in-person visit.

Off-Intervention Requirements

Recording of adverse events for subjects after the study will occur in the setting of regular care with the treating neurologist.

The Berg Balance Scale

The BBS was designed to measure changes in functional standing balance over time. This is a 14-item scale that rates each function from 0 (worst) to 4 (best). This scale measures balance abilities seen during tasks involving sitting, standing, and positional changes. Total scores are indicative of overall balance abilities, with scores interpreted in the following manner: 0 to 20, wheel-chair bound; 21 to 40, walking with assistance; and 41 to 56, independent. The BBS is relatively safe and simple to administer. It uses a quantitative scale format that has strong internal consistency and good inter- and intra-rater reliability with different patient populations, including brain injury, stroke, and geriatric patients. It has specifically been clinically validated for evaluating postural instability in PD patients.[9]

For this study, improvement will be defined as an 8 point improvement of the scale which has been found in one study to be required to reveal a genuine change in function among older people who are dependent in activities of daily living and living in residential care facilities.[10]

MANAGEMENT OF ADVERSE EXPERIENCES

The four most common adverse events with varenicline in adult studies are nausea, insomnia, abnormal dreams, and headache. Other side-effects include: constipation, dry mouth, flatulence, and dizziness. Psychiatric side effects have been reported and will be strictly monitored. The four most common placebo side-effects also include: nausea, insomnia, abnormal dreams, and headache. Adverse events will be documented on the adverse event form and sent to the independent medical monitor.

CRITERIA FOR INTERVENTION DISCONTINUATION

Criteria and rules for stopping subject treatment include: new toxicological findings or serious adverse events, patient withdrawal of consent without need for justification, inability of the patient to participate for medical reasons (such as surgery), violation of eligibility criteria, development of significant neuropsychiatric symptoms such as suicidal ideation or psychosis, subject failure to comply with the protocol, development of cardiovascular symptoms, new cardiovascular diagnosis, or a cardiovascular event. Subjects who stop treatment will still be asked to complete a final visit with rating scales and blood work.

STATISTICAL CONSIDERATIONS

General Design Issues

The primary and secondary outcomes will be analyzed using SPSS. The independent medical monitor will review adverse event data and the final analysis. There will be no interim analysis performed. The independent medical monitor will not be blinded to treatment arm. There will be no stratification.

Outcomes and Data Analysis

- Primary outcome (Aim 1): The primary hypothesis will be tested using a paired *t*-test using means of the total Berg Balance Scale score before and after treatment. Linear regression will be used to determine if there is an association among outcome, gender, age, race, or ethnicity. This outcome will be determined by the rating of patients from a blinded movement disorders neurologist.
- Secondary outcomes (Aim 2): Secondary hypotheses will be tested using paired *t*-tests on the full MDS-UPDRS, the TUG, and the ABC scale. For side effect analysis, logistic regression will be performed with the treatment arm as the dichotomous outcome and the MMSE and FAB as covariates. In addition, gender and age will also be included as covariates.
- Side effects (Aim 3): Adverse events will be recorded and classified as to seriousness of the side effect and likelihood that the side effect is related to the drug. Adverse events in the treated group versus the untreated group will be compared and any events that are significantly more frequent in the treated group will be identified.
- Sample Size and Accrual: Sample size was estimated using published means and standard deviations of the BBS in PD subjects[6]. The mean of the rating scale is 40.22 with a standard deviation of 8.48. Based on a published effect size of a change of 8 points, and using a power of 0.80 and a significance of 0.05 with a two sided test, a sample size of 19 subjects for each group would be needed for a parallel design. To allow for attrition, 42 subjects will be recruited. Intent to treat analysis will be performed. The number of subjects lost to follow-up is likely to be low due to the relative lack of efficacy of other forms of treatment for this particular symptom of PD. Power for calculating secondary outcomes is lower than 0.8.

Data Monitoring

An independent medical monitor will be established to monitor this study. An interim safety analysis will not be performed. Guidelines for stopping the study would include new toxicological findings of varenicline or serious adverse events reported from the subjects on active medication. The independent medical monitor will meet with the PI as needed during the protocol.

DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

Records to Be Kept

All study forms will be kept at Rush University. The records will be stored in a locked office of the site investigator. At the main site, data on the CRF will be entered into a

password-protected database. Access to the database will be restricted to the host site CRA, PI, and biostatistician.

Quality Assurance
The PI will meet with the study coordinator once monthly to review records, consent forms, protocol compliance, and data quality. All of the investigators will meet once every four months to review issues related to quality.

Adverse Experience Reporting
Adverse events will be recorded on the adverse event CRF and reported within three days. Serious adverse events will be reported within 24 hours. Detailed definitions of adverse experiences, a table for grading their severity, and details of how clinical sites are to report them, appear in the Manual of Operations.

HUMAN SUBJECTS

Institutional Review Board (IRB) Review and Informed Consent
This protocol and the informed consent documentation and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form will be obtained from the subject. Subjects who cannot consent for themselves cannot be included in the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, or legal guardian and this fact will be documented in the subject's record.

Subject Confidentiality
All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using the SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

Study Modification/Discontinuation
The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor (Pfizer), the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

PUBLICATION OF RESEARCH FINDINGS
Publication of the results of this trial will be governed by the policies and procedures developed by the Principal Investigator.

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