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Title: Effects of Cholinergic Augmentation on Measures of Balance and Gait

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Effects of Cholinergic Augmentation on Measures of Balance and Gait

Abstract. We will compare the effects of placebo and donepezil, a cholinesterase inhibitor that will enhance the effects of nicotinic and muscarinic cholinergic neurotransmission, on measures of standing postural sway, walking variability, and dual-task cost as indices of fall risk in Parkinson's disease (PD) subjects in a double-blind, placebo controlled, cross-over randomized clinical trial. In addition, short-latency afferent inhibition (SAI), a physiological index of central cholinergic function will be measured to determine if the deficits in balance and gait correlate with abnormalities of the SAI and if SAI is altered by donepezil as a measure of drug efficacy. The attention network test will be administered to determine if changes in gait and balance are mediated by changes in attention.

Hypothesis. Cholinergic systems contribute to mobility in Parkinson's disease (PD). Measures of gait and balance will improve in response to cholinergic augmentation with a cholinesterase inhibitor, donepezil.

Aim 1. Examine the effects of a cholinesterase inhibitor, donepezil, on physiological markers of mobility associated with falls in PD (postural sway in stance and gait variability).

Aim 2. Determine the effects of donepezil on dual-tasking during postural sway and gait variability and on attention using the Attention Network Test.

Aim 3. Correlate Short-latency Afferent Inhibition (SAI), a transcranial magnetic stimulation-induced marker of cortical cholinergic tone, with mobility deficits at baseline and with donepezil treatment.

The results of this study will be the most direct test of the hypothesized role of cholinergic neurotransmission in gait and balance. The study is exploratory because we do not know whether donepezil will affect gait, balance or attention, nor which measures of gait, balance or attention will be sensitive to drug manipulation. Our immediate goal is to determine the potential utility of cholinergic manipulation as a strategy for preventing or treating balance and gait dysfunction in PD. The findings of this trial are intended to lead to more sharply focused questions about the role of cholinergic neurotransmission in balance and gait and eventually to Phase II B trials to determine clinical utility of cholinergic manipulation to prevent falls and improve mobility.

Mobility disability and falls are common in PD and lack effective treatment. Gait and balance problems appear within 3 years of diagnosis and progress throughout the course of the disease.[1] Impaired mobility produces disability and reduces quality of life. Mobility depends on control of gait, balance and attention. Levodopa does not improve, and may worsen, several types of balance control. In general, as the disease progresses, levodopa is less efficacious for balance, likely because non-dopaminergic systems are impaired later in the disease course.[2] DBS is generally not effective for improving balance or reducing falls.

Cholinergic systems degenerate in Parkinson's disease and correlate with gait and balance impairments. The dopaminergic system is preferentially affected in PD, but there are also changes in the basal forebrain cholinergic complex that provides cholinergic innervations of the cortex. In addition, the pedunculopontine (PPN), part of the midbrain locomotor region (MLR), has a prominent cholinergic projection to the thalamus and it degenerates in PD.[3] PET imaging with[^{11}C]PMP, a substrate for acetylcholinesterase, identifies the integrity of cholinergic innervation. Loss of cortical cholinergic markers in PD representing degeneration of the basal

forebrain is associated with slower gait[4] and impairments in working memory, attention and executive function.[5] In addition, loss of thalamic [^{11}C]PMP, representing loss of PPN cholinergic innervation of the thalamus, is related to falls in PD.[6] In contrast, the extent of dopaminergic denervation of the striatum evaluated by PET imaging was not correlated with falls.[6] Finally, neurotoxin lesioning of the cholinergic neurons of the PPN induced gait and postural abnormalities in monkeys.[7] These observations support the need to examine cholinergic treatments in PD subjects with gait and balance difficulties.

The most direct test of the role of cholinergic systems in postural control to date are two small clinical trials. In a randomized, double-blind, crossover clinical trial of a cholinesterase inhibitor, donepezil, our group found that donepezil reduced falls in PD patients.[8] An open trial with another cholinesterase inhibitor, galantamine, also reported decreases in falls and freezing of gait (FoG). But these small clinical trials are not conclusive.

Intervention. Cholinesterase inhibitors such as donepezil are standard of care for PD patients with cognitive impairment.[9] We chose donepezil, an FDA approved drug, because it is possible to create a placebo for the donepezil tablet and it requires only once a day dosing. It is recommended to start donepezil at 5 mg per day to reduce adverse effects (FDA approved drug insert). We will increase the dose to 10 mg/day after 3 weeks, if tolerated, because that is the schedule used in our pilot study and this titration was well tolerated.[8] Donepezil has a half-life of 70 hours and it requires approximately 15 days to reach steady state. The maximum effects on cognitive measures occur within 3 weeks and loss of effect requires more than 3 weeks and less than 6 weeks (FDA approved drug insert). In our pilot study there were more falls at 3 weeks and 5 mg/day of donepezil than at 6 weeks and 10 mg/day of donepezil and 10 mg was more effective than 5 mg on cognitive measures in PD.[9] Washout between phases will be 6 weeks to minimize carry-over of effects.

Protocol. Subjects will be identified for potential recruitment through electronic medical record review; directly through OHSU's neurology clinics and through IRB approved advertisements. Subjects will receive the first study phase medications from the research pharmacy at the end of the baseline testing. The subject will be called weekly to ask about side effects or problems with the protocol. They will also be asked about falls. These contacts will be captured in case report forms. If there are problems, the investigator will call the subject or the subject will be brought into clinic to evaluate the problem. At 3 weeks, the subjects will have a phone call from one of the neurologists for safety; adverse events will be captured. At 6 weeks, the subject will return to the clinic for repeat testing with the measures captured at baseline and also the subjects will have ANT and SAI testing. The subject will be tested "off" their PD medications.

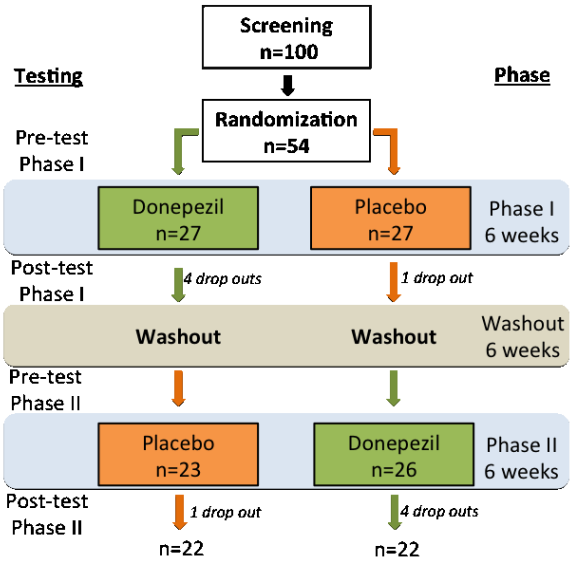

Figure 1. Study design

The subjects will then enter the 6-week washout period. Although the subjects will be on no experimental medications, they will continue to be called weekly to inquire about side-effects,

problems and falls. This is partly done to keep the subject involved in the protocol, as well as to collect data about falls. At the conclusion of the 6 weeks, the subjects will return to the clinic for repeat testing and to have medications dispensed for the final 6-week phase of the protocol. The final 6-week phase will be conducted exactly as was the first six-week phase with repeat testing at the end of the 6 weeks.

Subjects. Subjects will be 30 years or older, of either gender and any racial or ethnic origin. Women who are capable of child bearing must employ birth control. Pregnant women are not eligible to participate. The subjects will have idiopathic Parkinson's disease as determined from history and exam and lack of history or physical findings that would suggest another diagnosis or a parkinsonism-plus syndrome. Subjects may be Hoehn and Yahr stages II to IV. Subjects must be able to stand unassisted for a minute and to walk continuously for 2 minutes without assistance or assistive devices. The subjects must have a Montreal Cognitive Assessment (MOCA) of 23 or above and be judged to be able to appreciate the purpose of the research, give informed consent to participate, be able to cooperate with the testing and be compliant with taking the experimental medications.

Exclusion criteria include: significant tremor which would interfere with recording balance and walking; other factors affecting gait such as musculoskeletal disorders (particularly symptomatic hip, knee and lumbar osteoarthritis), uncorrected vision disturbance, vestibular problems or any other health problem judged to interfere with participation. Major depression, hallucinations or other psychiatric disturbances will be exclusions. Medical problems that might be worsened by donepezil are exclusion criteria and include tachycardia, bradycardia, arrhythmias, and peptic ulcer disease. Finally, use of anticholinergics for parkinsonism, cholinesterase inhibitors for cognitive problems, bladder antispasmodics for urinary urgency or tricyclic antidepressants for depression are contraindications because of their cholinergic actions.

Measures and Outcomes. Falls are a difficult endpoint for clinical trials because the data comes from patient self-reports and in most patients, falls occur infrequently. Falls also depend upon patient activity and falls may be reduced if patients are less active. Finally, falls are generally multi-factorial so that the environment and context, as well as posture, gait and attention play a role in falls. Because of these problems with falls as an index of disturbed mobility, we plan to use two physiological measures associated with falls as surrogate markers for fall risk rather than fall counts. These markers are: 1) increased sway while standing and enhancement of the sway by dual tasking, 2) increased gait variability and augmentation with dual-tasking.

Measurement Device. Balance and gait kinematic performance will be recorded by small, body-worn, inertial sensors, called 'Opals.'[10] The Opals consist of wireless, synchronized, triaxial accelerometers and gyroscopes that record body motion at 120 Hz. The Opals will be applied bilaterally to the ankles and wrists as well as to the sternum and pelvis with Velcro belts.

Postural sway is sensitive to mild PD and progression of disease. Thirteen early, untreated PD subjects with normal gait speed and no complaints of imbalance and 13 age-matched control subjects were tested with accelerometers on their belt while they stood with eyes open for 30 seconds. Of the 42 different measures of postural sway captured with the inertial sensors, mean velocity (MV), root mean square of sway frequency (RMS) and jerkiness of sway best separated PD from control subjects.[11] Postural sway measures were abnormal, even when neither the patient nor the treating neurologist noted balance problems. Thus, objective measures of postural sway may reflect small changes in neural control of balance. Five of these early PD subjects who did not start antiparkinsonian medication and the 13 healthy control subjects were followed for 12 months (Fig. 2). Postural sway velocity, jerkiness, and mediolateral sway range increased across the year in the untreated PD subjects but did not change in age-matched control subjects.[12]

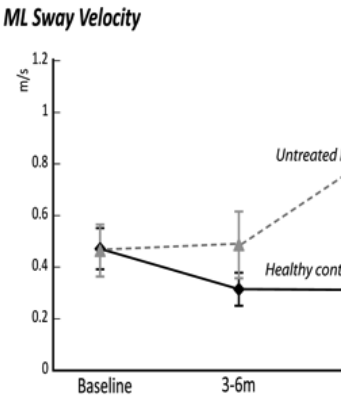

Figure 2. Group mean sway velocity across 12 months in Untreated PD and Control group.

Balance Protocol. Standing balance will be studied in six conditions: with subjects standing on the floor and on foam, with eyes open and eyes closed, and with or without dual tasking.

Gait variability is a sensitive measure of postural stability during walking. Gait variability is the fluctuation or variability from step to step in the time to step, stride length, stride velocity and double support time.[13] Variability of stride time reflects dynamic postural control during gait as lateral foot placement and double support time varies from step-to-step to compensate for excessive body center of mass (CoM) displacement.[13] Gait variability is larger in elderly fallers than non-fallers and is not related to fear and compensatory changes in gait.[14] Gait variability is present in PD and is related to severity of PD motor signs and is a surrogate for fall risk. [2,15] Variability of step time and double support time are independent of gait speed unlike variability of stride velocity and stride length.[16] Some aspects of gait variability are responsive to levodopa[15] but others are not, suggesting that gait variability may reflect disturbances in non-dopaminergic circuits as well.[2]

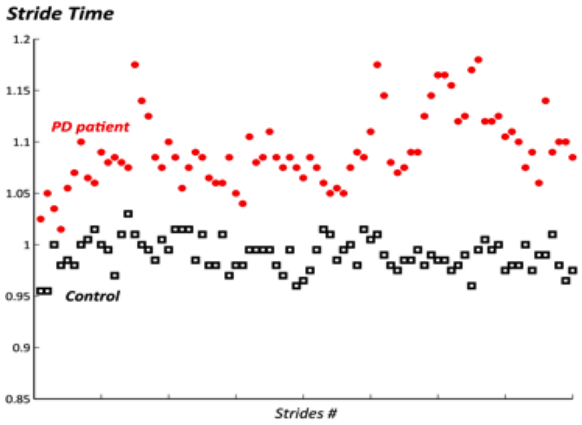

Figure 3. Example of coefficient of variation of stride duration from a representative PD and control subject.

We examined gait variability during a 2-minute walk in 20 PD subjects and 20 age-matched control subjects as part of an ongoing trial. The coefficient of variation of stride duration and cadence were significantly larger in the PD group. Figure 3 illustrates the variability in stride duration for each stride during a 2-minute walk for a representative subject with PD and an age-matched control subject. The PD subject's stride time was longer (1.04 vs 0.98 sec), representing slower gait and more variable with a larger coefficient of variation (3.26 vs 1.59) than the control subject.

Gait Protocol. Gait control measurements will rely upon the ankle gyroscopes for spatial and temporal gait measures with stride time variability the primary gait outcome. Subjects will walk

at their natural pace down a 20-meter long hallway, turn around at the end and return to the starting point and then continue walking back and forth for two minutes. The 180-degree turns during the walking are automatically detected and analyzed separately by Mobility Lab.

Dual Tasking Unmasks Instability. There is abundant evidence that gait and balance are under cortical control, requiring attention, as demonstrated in studies of gait and balance with concurrent mental tasks (dual-tasking).[17] Dual tasking increases measures of gait instability in patients with PD.[18] These observations indicate that cholinergic drug effects could be mediated by altering the ability to dual task and thereby influencing the risk of falling.

Dual Task Paradigm. The effects of dual tasking on sway and gait variability will be assessed with a mental task of counting backwards by 3s from various starting numbers. While performing the mental task, subjects will wear a small microphone connected to a small, custom-made computer with voice recording to record their performance on the mental task. Responses will be recorded for accuracy. Subjects will perform the counting backwards by 3s as a single task while sitting and then during standing and walking. This will allow calculating the dual-task costs on balance and walking.[18]

Attention. Deficits in attention are related to fall frequency.[19] Attention may be envisioned as having three separable aspects: alerting, orienting and executive control.[20] These aspects of attention can be tested with the Attention Network Test.[20] Our collaborator, Dr. Dimitrova examined the ANT in 9 normal and 16 non-demented (MMSE score >25) PD subjects in both the "on" and "off" state. All three attention networks were affected in PD ($p<0.05$). This observation indicates that the ANT is a sensitive method to detect attention dysfunction in non-demented PD.

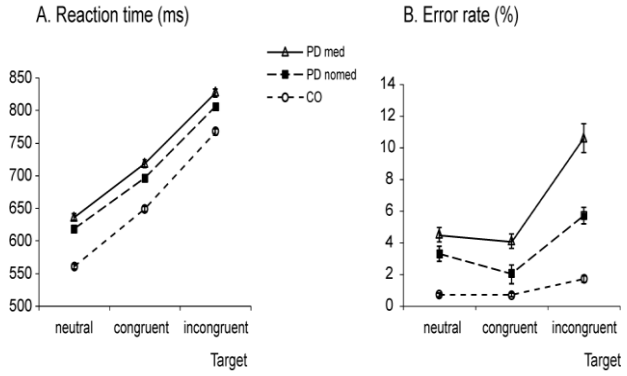

Figure 4A. Reaction time. Both PD_{med} and PD_{nomed} showed longer mean RT than the control subjects ($p < 0.001$). **B.** Error rates. PD_{med} had higher error rates than the controls for all three targets.

Attention Network Test. Attention will be tested with the Attention Network test, a 15-minute, computerized test that examines the effects of cues and targets within a single reaction time task to provide a means of exploring the efficiency of the alerting, orienting, and executive control networks involved in attention.[20]

Short-latency afferent inhibition (SAI). SAI will provide an estimate of the extent of cholinergic dysfunction in our subjects at baseline as well as the efficacy of our interventions on central cholinergic function. Median nerve stimulation 19 to 30 milliseconds prior to contralateral motor cortex stimulation with transcranial magnetic stimulation (TMS) attenuates the motor evoked potentials in hand muscles. This inhibition, termed short-latency afferent inhibition (SAI), has been related to cholinergic function by neurochemical and pharmacological studies. Alzheimer's disease (AD), Down's syndrome, dementia with Lewy bodies and Parkinson's disease with REM behavioral disorder, disorders associated with loss of cholinergic markers, have reduced SAI, whereas frontotemporal dementia, which is not associated with loss

of cholinergic markers, does not have alterations in SAI.[21] SAI is reduced or abolished by an acute dose of the antimuscarinic agent, scopolamine, in normal individuals. In AD subjects who had reductions in SAI, the response to a single dose of a cholinesterase inhibitor, 3 mg of rivastigmine, predicted the response to long-term anticholinesterase inhibitor treatment; those subjects who had an improvement in SAI with the single dose of cholinesterase inhibitor improved with long-term therapy.[22] These observations suggest that SAI may identify subjects in our study who have cholinergic deficits as well as be an indicator of the effects of our cholinergic interventions.

Monitoring Activity at Home. Monitoring activity at home will be accomplished with the small inertial sensors that the subject will be asked to wear on their belt and/or a limb.

Clinical Measures. UPDRS, MOCA, , ABC, PDQ-39 total index and mobility domain subscores and falls recorded during the study will be collected.

Data Analysis. A linear mixed model will be used to analyze a crossover with repeated measures design that includes treatment effects, random effects of treatment sequence within subjects and random effects of subjects within treatments. The observations on each subject are repeated measures (week 0 and 6) under different treatment conditions. Since in a typical experiment using repeated measures, two measurements taken at adjacent times are more highly correlated than two measurements taken several time points apart, we will use Bayesian Information Criterion (BIC) to explore optimal covariance structure for the model. The main focus of the study is to determine how the two treatments outcomes change over time, I.E. time by treatment interaction effect. Generalized least square (GLS) and restricted maximum likelihood (REML) will be used to estimate treatment effects and random effects, respectively. In crossover designs, missing data have much greater influence on the analysis than they would in a parallel groups design especially when missing data are not at random such as drop-outs due to the adverse effects of treatments. We will analyze two separate data sets in order to evaluate the impact of missing/non-response. One data set includes all patients who received at least one study drug and another data set only includes the patients who complete the complete treatment sequence.

Interpretation. We are especially interested in determining whether gait and balance are directly influenced by cholinergic manipulation or whether changes in attention capacity are primarily responsible for changes in balance and gait. If, for example, we find that ability to balance and walk during dual tasking is altered out of proportion to changes during standing and walking without dual tasking, it would suggest that cholinergic systems mainly contribute to attentional capacity required for balance and gait. Because of the evidence linking executive dysfunction with gait disorders, we expect that the executive attention which has been related to falls and to gait may be affected out of proportion to alerting and orienting aspects of attention although Posner and colleagues have linked alerting to cholinergic function.

Privacy, Confidentiality and Data Security. Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff is, and will continue to be, trained with regard to these procedures. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network and on encrypted

computers. Access to data/specimens is restricted to study personnel and requires OHSU ID/password authentication.
Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code.
Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN, etc.)
The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.
Data will be transferred to/from The Michael J. Fox Foundation in files using encryption. The data released to the Michael J. Fox Foundation will include only de-identified (coded) data.

Data Safety Monitoring Plan (DSMP). There are three safety issues.
1. Adverse effects of donepezil. Donepezil is widely used in PD at the doses proposed in this trial. We anticipate GI effects (anorexia, nausea, diarrhea and vomiting), muscle cramps, insomnia and mild worsening of tremor, which occur commonly but are mild. Serious but rare adverse events include exacerbation of peptic ulcer disease and bradycardia. Drs. Nutt and Chung will personally call each patient to discuss any reported side-effects and work with patients on strategies to reduce discomfort.
2. Fall risk during gait and balance testing. Subjects are chosen who can ambulate independently. Testing is conducted with a research coordinator who is trained to be able to assist subjects during testing. If a subject has precarious balance the research assistant will obtain backup assistance and use a safety belt for further safety.
3. Short-latency afferent inhibition is performed with transcranial magnetic stimulation. Subjects with a history of recurrent seizures will be excluded. TMS will occur in the hospital, close to emergency care if necessary. The short-latency afferent inhibition is measured at times that exceed the time for a stimulus at the wrist to reach the sensory cortex. Thus a somatosensory evoked potential will be measured at baseline.

Drs. Chung and Nutt will record adverse events and report to the IRB unexpected or serious adverse events. An independent neurologist will review the reported adverse events each six months and make recommendations to the trial leadership as well as the IRB about advisability of continuation of the trial, changing the protocol or other safety concerns. Dr. Steve Johnson, MD, PhD, a member of the OHSU movement disorder section but with no other connection to the clinical trial will serve as the Safety Monitoring Officer.

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