Protocol Title:
L-DOPA vs. Placebo for Depression and Psychomotor Slowing in Older Adults

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N/A

Clinic:
Adult and Late Life Depression

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Not yet accepted

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Neurobiology and Therapeutics of Aging
Within the division/department, what Center or group are you affiliated with, if any?
Neurobiology and Therapeutics of Aging

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Anissa Abi-Dargham, MD

Stony Brook University

Mark Slifstein, PhD
Stony Brook University

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ PET/SPECT Scan
✓ MRI
✓ Off-label Use of Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency

NIMH
Grant Name
Targeting Dopaminergic Mechanisms of Slowing to Improve Late Life Depression
Grant Number
R61 MH110029
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)

Columbia University

Stony Brook University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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Individuals with Late Life Depression (LLD) often have cognitive problems, particularly problems with memory, attention, and problem solving, all of which contribute to antidepressant non-response. Our group and others have shown that decreased thinking speed is the central cause of functional problems in patients with LLD. Similarly, decreased walking speed is associated with depression and carries additional risk for falls, hospitalization, and death. Available evidence suggests that declining functionality in the brain's dopamine system contributes to age-related cognitive and motor slowing. The central hypothesis of this R61/R33 Phased Innovation Award is that by enhancing dopamine functioning in the brain and improvingcognitive and motor slowing, administration of carbidopa/levodopa (L-DOPA) will improve depressive symptoms in older adults.

This IRB protocol pertains to the R33 Phase of this grant proposal (R61 Phase was approved under IRB #7270). In the R33 Phase 90 adults aged > 60 years with (1) a DSM 5 depressive disorder, (2) significant depressive symptoms, and (3) decreased thinking or walking speed will receive 8 weeks of treatment with

L-DOPA up to 450mg. We will test whether L-DOPA increases brain dopamine release using neuroimaging and whether it speeds up thinking and walking speed. Data collected in the proposed studies may help identify a new treatment for LLD, which could have large public health ramifications given the prevalence, frequent treatment resistance, and chronicity characteristic
of LLD. This project also will elucidate the neurobiology of slowing at molecular, structural, and functional levels of analysis, increasing our understanding of the interplay between these aging-associated processes and the pathophysiologic changes underlying late life neuropsychiatric disorders. Exploring patient characteristics that predict response to L-DOPA may provide useful information to guide differential therapeutics and develop personalized medicine for LLD.

Background, Significance and Rationale

Background, Significance and Rationale
LLD affects 3% of community-dwelling adults over 60 years old (1), and 15% of older adults have clinically significant depressive symptoms (2). LLD increases an older adult's risk of disability by 67-73% over 6 year follow up (26), causes twice the functional impairment compared to those without LLD (27), increases mortality in patients with heart disease, and is associated with high rates of completed suicide in individuals over 65 (28-29). LLD is highly recurrent, can become chronic (30), and is often difficult to treat (31).

Executive Dysfunction (ED) is common in patients with LLD, predicts poorer acute response to antidepressants, and is associated with higher relapse rates during the continuation phase (5,32-33). Among the executive functions disturbed in LLD, decreased processing speed has been called "the core cognitive deficit (8,34)." Processing speed mediates performance on measures of verbal reasoning, fluency, and knowledge (35), and measures of working memory primarily depend upon speed of processing (36). Decreased processing speed has been repeatedly found in patients with LLD relative to healthy controls (8) and mediates the effects of depression and ED on daily functioning (7). The development of decreased processing speed places older individuals on a trajectory of poor outcomes, including increased risk of dementia (37), dependence in activities of daily living (ADL) (38), and driving cessation (39).

Less well recognized is the fact that depressed older adults also experience motor performance deficits, including problems with coordination (14), slowed movement (15), and difficulties with balance and gait (16). Depressive symptoms lead to the development of decreased gait speed, and slowed gait speed leads to incident depression in older adults (12-13). Decreased gait speed has been associated with a greater risk of falls (40-42), disability (14), admission to the hospital (16,43), and all-cause as well as cardiovascular mortality (44-45). While LLD and decreased gait speed are each independent risk factors for adverse health outcomes, their comorbidity synergistically increases mortality risk in older adults (46). For these reasons gait speed has become a fifth "vital sign" to be monitored in older adults, and it merits increased attention by mental health specialists treating LLD.

Post-mortem experiments and in vivo neuroimaging studies have shown that aging is associated with reduced dopamine levels, decreased D1/D2 receptor density, and loss of dopamine transporters (DAT) (17-21). Mesolimbic dopaminergic tone modulates processing speed in both humans and animal models (47), and decreased striatal dopamine transmission has been associated with decreased motor speed (48), deterioration in frontal functioning (23), and impaired balance (49). Cham et al (2008) examined gait speed and dopamine metabolism in healthy adults aged 21-85 years, finding that lower striatal DAT activity was associated with decreased gait speed and explained 23% of the variance in gait after controlling for other factors (50). These age-associated declines in dopaminergic functioning are topographically distinct from the denervation pattern typical of Parkinson's disease (PD), being observed diffusely across the striatum rather than predominantly posterior putaminal in location (51-3). While subtle Parkinsonian-like phenomena may be observed with normal aging, the non-specific slowing associated with aging is clinically distinct from the signs and symptoms of PD. Thus, the hypodopaminergic state associated with aging and LLD has a distinct neurobiology from PD and appears to represent a parallel pathway to developing cognitive and motor deficits.

Pharmacologic augmentation of dopaminergic neurotransmission may ameliorate slowing and treat LLD. Studies in non-human primates as well as older adults with and without PD suggest that dopamine receptor agonism improves working memory (54), verbal fluency (55), problem-solving (56), and motor performance related to ADLs (57). Since slowed processing speed and gait predict the development of LLD and mediate a large portion of the disability associated with LLD, it is reasonable to hypothesize that improving slowing will positively impact LLD. Multiple case series from the 1960s onward report improved depressive symptoms (particularly psychomotor retardation) with levodopa (hereafter referred to as L-DOPA) monotherapy or augmentation (58-61). L-DOPA is the immediate precursor of dopamine, is converted to dopamine in presynaptic dopaminergic nerve terminals, and enhances dopaminergic transmission in multiple brain regions. L-DOPA has been reported to relieve depressive symptoms in new onset PD, improving symptoms in 90.3% of patients (N=31) and resulting in a mean Hamilton Rating Scale for Depression (HRSD) decrease of 11.7 points in one study (62). Relatedly, augmentation with methylphenidate, which also increases synaptic dopamine levels, was recently shown to accelerate and enhance antidepressant response in depressed older adults (63).

Despite these promising results, negative studies of L-DOPA, stimulants, and dopamine agonists as monotherapies and augmentation agents for depression also have been reported (64). One reason for these heterogeneous results is the different diagnostic criteria and experimental methodology used in older studies, which makes their results difficult to interpret. More importantly, no study examining dopamine augmentation as a treatment for depression selected subjects based upon the presence of decreased processing and gait speed. If the mechanism by which enhancing synaptic dopamine relieves depressive symptoms is by improving slowing, then including patients without slowing may contribute to negative results. By focusing on the subgroup of patients with LLD and slowing, we believe it will be possible to more clearly demonstrate the efficacy of dopaminergic agents and contribute to the development of personalized medicine for LLD.

Three types of interventions may be considered to enhance dopaminergic function and ameliorate slowing: dopamine receptor agonists (e.g., piribedil, pramipexole, ropinirole), stimulants (methylphenidate and amphetamine derivatives), and dopamine precursors such as L-DOPA. Among these options, L-DOPA enhances dopaminergic neurotransmission globally, including increasing vesicular storage, enhancing release, and stimulating post-synaptic receptors. In contrast, stimulants may not increase synaptic dopamine in individuals with diminished vesicular storage, and dopamine agonists may have reduced effects in older patients having fewer post-synaptic receptors. Moreover, a large literature shows beneficial effects of LDOPA on cognitive performance and gait in patients with PD (65-67), whereas the few available studies in elderly patients show minimal effects of dopamine agonists (68-70) or stimulants (71) on cognition. LDOPA, especially at lower doses, is a safe and well-tolerated medication that is difficult to differentiate from placebo in terms of side effects (72). In contrast, a black box warning for adverse cardiac effects exists for stimulants, and even modest elevations in heart rate and blood pressure may significantly increase cardiac work in older patients. Similarly, dopamine agonists are associated with sleep attacks and increased impulsive behavior. For these reasons, this proposal focuses on L-DOPA as the safest, most promising pharmacologic agent for the treatment of slowing and LLD.

This study will elucidate the neurobiology of slowing and LLD, identify a novel therapeutic target for depression, and contribute to the development of personalized treatment regimens for LLD. The multimodal neuroimaging methods detailed in this application will provide information about the neurobiology of aging-associated slowing and LLD at molecular, structural, and functional levels of analysis. These data will fill a crucial gap in our knowledge regarding what are the physiologic and functional consequences of dopamine depletion occurring across the lifespan in individuals without PD. Results from this project also will allow us to evaluate a novel therapeutic approach to LLD, which could have large public health ramifications given the prevalence, frequent treatment resistance, and chronicity characteristic of LLD. Even apart from patients with LLD, cognitive and motor slowing exact a large public health burden in terms of impaired functioning and increased morbidity and mortality, and this burden will only grow as the population ages. It is critical to develop treatments capable of altering the negative health trajectories associated with slowing in order to help older adults maintain independent functioning and live longer with an increased quality of life. Finally, while PET and MRI may prove critical to understand the neurobiology of slowing and LLD, their invasiveness and expense limit their roles in informing treatment decisions in clinical practice settings. For this reason we are also assessing the influence of genetic moderators such as interleukin-6 (IL-6) and catechol-O-methyl-transferase (COMT) genotype on baseline dopamine functioning and response to L-DOPA. This may facilitate the identification of both high-risk individuals and those most likely to benefit from treatment interventions.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
We hypothesize that treatment with levodopa (L-DOPA) will improve depressive symptoms in LLD by enhancing striatal dopamine release and improving cognitive/motor slowing. In the R33 Phase, 90 adults aged > 60 years with (1) a DSM 5 depressive disorder, (2) significant depressive symptoms (CES-D > 10), and (3) decreased processing speed (0.5 SD below age-adjusted norms on the Digit Symbol Test or Trails A) or decreased gait speed (average walking speed over 15’ course < 1m/s) will be receive 8 weeks of treatment with LDOPA 450mg. Subjects will be tested for engagement of molecular target by determining whether subacute (8 week) treatment with L-DOPA displaces [11C]-raclopride on positron emission tomography (PET).

R33 Phase.

Aim 1: To determine whether L-DOPA improves depressive symptoms in older adults.

Hypothesis 1: Compared to placebo, L-DOPA administration will result in greater improvements in depressive symptoms (as measured by HRSD scores).

Hypothesis 2: Greater post-L-DOPA decreases in [11C]-raclopride BP and increases in processing/gait speed will be associated with greater depressive symptom improvement.

Exploratory aims: To explore the role of inflammatory markers and Catechol-O-methyl-transferase (COMT) genotype in moderating L-DOPA induced changes in slowing and depressive symptoms.

Description of Subject Population

Sample #1

Specify subject population
adults aged >59 years with a depressive disorder, decreased processing speed, or decreased gait speed
Number of completers required to accomplish study aims
68
Projected number of subjects who will be enrolled to obtain required number of completers
90
Age range of subject population
60 years or older

Gender, Racial and Ethnic Breakdown
On the basis of previous depression studies conducted in the Adult and Late Life Depression Research Clinic, it is anticipated that the sample will be composed of 60% women and 40% men as well as approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects.

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Description of subject population
This phase will enroll 90 outpatients who (1) are aged ≥ 60 years, (2) diagnosed with Diagnostic and Statistical Manual (DSM) 5 (107) MDD, Dysthymia, or Depression Not Otherwise Specified (NOS), (3) have Center for Epidemiologic Studies-Depression Rating scale (CES-D) (108) score ≥ 10, (4) have decreased gait speed (defined as average walking speed over 15' course < 1m/s) or decreased processing speed (defined as 1 SD below age-adjusted norms on the Digit Symbol Test), and (5) are willing to and capable of providing informed consent and complying with study procedures.

Exclusion criteria are (1) diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) within the past 12 months, (2) history of psychosis, psychotic disorder, mania, or bipolar disorder, (3) diagnosis of probable Alzheimer's Disease, Vascular Dementia, or PD, (4) Mini Mental Status Examination (MMSE) ≤ 24 (109), (5) HRSD suicide item > 2 or Clinical Global Impressions (CGI)-Severity (110) score of 7 at baseline, (6) current or recent (within the past 4 weeks) treatment with antidepressants, antipsychotics, or mood stabilizers, (7) history of allergy, hypersensitivity reaction, or severe intolerance to L-DOPA, (8) any physical or intellectual disability adversely affecting ability to complete assessments, (9) acute, severe, or unstable medical or neurological illness, (10) mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, mobility limiting history of joint replacement surgery, or history of spine surgery, (11) having contraindication to MRI scanning (such as metal in body) or unable to tolerate the scanning procedures, (12) history of significant radioactivity exposure (nuclear medicine studies or occupational exposure), and (13) presence of a clinically significant brain abnormality.

Recruitment Procedures

Describe settings where recruitment will occur
We will be specifically recruiting via advertisements for patients who feel depressed as well as slowed down physically and mentally. Advertisements will include research flyers and brochures posted around CUMC, advertisements in local newspapers and on radio stations, information posted on departmental websites, and flyer mailings. For direct clinical or research referrals, a clinical staff member known to the patient will approach him/her and raise the possibility of study participation. We would also like to implement Columbia University's RecruitMe website as a recruitment method.
How and by whom will subjects be approached and/or recruited?
If the patient expresses a potential interest in participating, he/she will then be scheduled for a full evaluation with a study clinician. The nature of the study will be thoroughly reviewed with its risks, benefits, and alternatives to participation, and subjects' questions regarding the study will be answered. Subjects will be notified that they may leave the study at any time. Informed consent will be obtained in a private research office. A study clinician will review study procedures and the consent form with each potential participant. Each individual may take as much time as they like to decide if they do or do not wish to participate. The consent form specifies (and the study coordinator emphasizes) that participation is voluntary and withdrawal after signing consent will not affect future care. Subjects will be given a copy of the consent form, and the original will become part of the clinical record.
How will the study be advertised/publicized?
Advertisements will include research flyers and brochures posted around CUMC, advertisements in local newspapers and on radio stations, and information posted on departmental websites. Advertisements will also include research flyers mailed out individuals whom will primarily come from consumer marketing databases, which are compiled using public information, surveys, subscription information, home owner information, and phone directory information.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects completing IRB #6836 (Rutherford PI) who meet the selection criteria for this study will be offered participation. Additionally, subjects who are currently participating in #7289R, #7409, #7360, #7489, and/or #7379 and meet the selection criteria for this study will be offered participation. Only an investigator not directly involved with an eligible subject's care will approach the subject to describe this protocol and have an informed consent discussion.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Patients
Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Age >59 years	1. Interview
2. DSM 5 non-psychotic Major Depressive Disorder, Dysthymia, or Depression Not Otherwise Specified	2. Clinical interview and SCID
3. Center for Epidemiological Studies Depression (CES-D) Rating Scale >9	3. CES-D
4. decreased processing speed (defined as performance > 0.5SD below age-adjusted norms on Digit Symbol Substitution Test or Trail Making Test Part A) OR decreased gait speed (defined as average walking speed over 15' course < 1m/s)	4. Digit Symbol Substitution Test, Trails A, timing of walking speed
5. willing to and capable of providing informed consent and complying with study procedures	5. Clinical interview
6. Alternative standard treatments for MDD, Dysthymia, or Depression NOS (e.g., antidepressant medication or psychotherapy) have been discussed and the individual agrees to be involved in an experimental treatment.	**6. Clinical interview**

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion Method of Ascertainment

1. diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) within the past 12 months	1. Clinical interview and SCID
2. history of or current psychosis, psychotic disorder, mania, or bipolar disorder	2. Clinical interview and SCID
3. diagnosis of probable Alzheimer's Disease, Vascular Dementia, or PD	3. Clinical interview, MMSE for AD and VD. PD will be ruled out by satisfying (1) and (2) and (3 or 4) below: (1) patient gives no history of PD during clinical interview (2) patient's primary doctor gives no history of PD (3) there are no signs of PD on physical exam in the LLDC (e.g., absence of asymmetric resting tremor, decreased arm swing, soft voice, decreased facial expression, difficulty rising from chair, dystonia) (4) If a patient does have one or more signs of possible PD on exam as per (3), Dr. Nora Vanegas-Arroye (study neurologist) will come examine the patient and comment on whether PD can be ruled out or whether PD is possible and patient needs further neurologic work up.
4. Mini Mental Status Exam (MMSE) < 25	4. MMSE
5. Total HRSD ≥ 25, HRSD suicide item>2, or the presence of significant suicide risk as judged by clinician. pasting. HRSD suicide item > 2	5. Clinical interview, HRSD, CGI

or Clinical Global Impressions (CGI)-Severity score of 7 at baseline.	
6. current or recent (within the past 4 weeks) treatment with antidepressants, antipsychotics, dopaminergic agents, or mood stabilizers	6. Clinical interview
7. history of allergy, hypersensitivity reaction, or severe intolerance to L-DOPA	7. Clinical interview
8. acute, severe, or unstable medical or neurological illness	8. Clinical interview, physical exam, EKG
9. mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, mobility limiting history of joint replacement surgery, or history of spine surgery	9. Clinical interview, physical exam
FOR SUBJECTS	

RECEIVING PET/MRI SCANS ONLY:	
10. having contraindication to MRI scanning (such as metal in body) or unable to tolerate the scanning procedures	10. MRI safety screening form
11. history of significant radioactivity exposure (nuclear medicine studies or occupational exposure)	11. Clinical interview

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6395R
Describe Study Consent Procedures
Following the study screening procedures, a study clinician authorized to obtain patient consent will explain

the study procedures along with the attendant risks, benefits, and alternatives, including the anticipated outcome of doing nothing. The study clinician will then leave the room while the potential subject reads the consent form and return to answer any questions the subject has. During the consent discussion, individuals will be offered the option to take the consent home to discuss with family and/or physician prior to signing it. Subjects who wish to participate will sign the consent form, while those who do not wish to participate will receive appropriate referrals.

Indicate which of the following are employed as a part of screening or main study consent procedures

✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Broft, Allegra, MD
Roose, Steven, MD
Rutherford, Bret, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study
Evaluation

1. Every subject evaluated for this protocol will receive a clinical interview by a psychiatrist or psychologist. **A psychiatrist or other qualified physician will see participants to evaluate medical aspects of eligibility, including screening for signs or symptoms of Parkinson's Disease (PD). If there is any concern, they will be referred to a neurologist.** Additional assessments will be administered by a trained rater (BA, RN, or SW) in the LLDC, including the Center for Epidemiologic Studies Depression Scale (CES-D) and the 24-item Hamilton Rating Scale for Depression (HRSD), and have a SCID performed by a trained rater. If a subject has a diagnosis of Major Depressive Disorder (MDD) or Dysthymia, he/she will be informed of this and educated about the availability of treatments for depression. If a subject is not interested in depression treatment and/or prefers to begin with an experimental treatment for slowing and depression, he/she will be offered participation in the present study provided their HRSD < 25 and there is no suicidal ideation present. Severe MDD (i.e., HRSD ≥ 25) and/or the presence of significant suicide risk (e.g., HRSD suicide item > 2, clinician judgement that there is significant risk of suicide) are exclusions for this study. Patients with Depression NOS will be educated that as yet, there are no FDA-approved treatments for their condition. Based on the extant data supporting the efficacy of antidepressants for MDD and Dysthymia, they will be informed that antidepressant treatment would be a very reasonable option for their condition. These potential subjects will be offered the option of being referred out for depression treatment, and it will be clarified that L-DOPA is not as yet a treatment for MDD. Thus, all potential participants in this study must state their preference not to be treated with a standard treatment for depression.

2. Next, trained raters (BA, RN, or SW) in the LLDC will assess processing speed using Digit Symbol test from the WAIS-III, the Trail Making Test Part A, the Pattern Comparison Test, and the Letter Comparison Test. Previous research established that these tests were all reliable and valid (moderate to high loadings on the latent speed factor). Digit Symbol or Trails A will be used as a selection criterion, with patients included in this study if they scored 0.5 SD below the age-adjusted norms on Digit Symbol or Trails A. A latent factor (and subsequent factor score) will be extracted from the 3-test battery pre- and post-treatment and used as the main outcome in this pilot study. By extracting a latent factor and factor loadings we will utilize a more pure measure of processing speed for pre- post-testing than if we used the raw scores from an individual test or a sum total score from the three raw scores combined.

3. Patients' gait will be assessed by trained raters as walking speed in m/s on a Gaitrite walkway system. Patients are instructed to walk at their usual or normal speed starting and ending at a point 6 feet prior to and after the walkway course to eliminate acceleration and deceleration effects. Two trials will be completed, and gait speed will be based on the average of 2 trials. Gait speed will be used as a selection criterion, with patients included in this study if they have a gait speed < 1 m/s.

4. If subjects are eligible for the study after review of their processing speed and gait speed and decide to participate by signing informed consent, then they will complete the remainder of the baseline assessment. This includes recording of each subject's chief complaint, referral source, age of onset of mood and/or cognitive decline, number prior depressive episodes, age, sex, marital status, race and ethnicity, years of education, employment status and income, years of education, family history. We also will document medical history, physical exam, urine drug screen, CBC, chemistries and electrolytes, thyroid profile, vitamin B12 and folate levels, urine analysis, and ECG. Vital signs will be measured at baseline and monitored weekly throughout the study. The Cumulative Illness Rating Scale-Geriatric (CIRS-G) (112) will be filled out at baseline to measure chronic medical illness burden. Subjects' current physical pain will be assessed weekly using a 100mm Pain Visual Analog Scale (VAS) and used as a covariate in analyses of gait speed (113).

5. Baseline markers of inflammatory status will be added to the serum assessments detailed above, including C-reactive protein (CRP), IL-6, and Tumor Necrosis Factor α (TNFα). The rationale for inflammatory marker measurement is evidence that dopaminergic dysfunction in older adults may be caused by the chronic, low-grade inflammatory process concomitant with aging ("inflammaging") (151). Pro-inflammatory cytokines such as IL-6 may reduce dopaminergic transmission in multiple ways, including decreasing dopamine synthesis by limiting tetrahydrobiopterin (BH4) availability, impairing vesicular release of dopamine in presynaptic neurons by decreasing expression of vesicular monoamine transporter 2 (VMAT2), increasing DAT reuptake of synaptic neurotransmitter, and decreasing glutamate-dependent dopamine signaling (152).

6. Other neuropsychological measures completed at baseline include trained study rater (BA, RN, SW) assessment of episodic memory functioning using the Wechsler Memory Scale Logical Memory Test I & II (153). Inclusion of this test will allow us to identify deficits in episodic memory functioning consistent with a classification of amnestic mild cognitive impairment (aMCI) (7). Executive function will be assessed via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently (154-155). This battery examines working memory, inhibition, set shifting, fluency, insight, planning, social cognition and behavior. Confirmatory factor analysis supports both a one-factor model and

a three- factor model, and these models formed the basis for an Executive Composite score and subscales scores for Working Memory, Cognitive Control, and Fluency.

7. Domains of function assessed by trained study raters (BA, RN, SW) at baseline include: the Short Physical Performance Battery (SPPB) (156), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change. The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability and 7 domain-specific scores based on the conceptual framework of the International Classification of Functioning, Disability, and Health (ICF) (157). The self-report 38-item Measure of Everyday Cognition (ECog) is adapted from an informant-report version and measures impairment and change in domains of everyday/real-world functioning relevant to 7 specific neuropsychological domains (158). The Falls Efficacy Scale-International will assess subjects' fear of falling weekly using a 16-item scale rating respondents' confidence (1 not at all concerned—4 very concerned) in doing daily tasks without falling (159-160).

8. Finally, aliquots of peripheral blood will be frozen for subsequent DNA isolation and determination of interleukin-6 (IL-6) and catechol-O-methyl-transferase (COMT) genotype. These genotypes will be analyzed in exploratory analyses to determine their effects on baseline dopamine functioning and response to L-DOPA.

<u>MRI Scanning</u>

9. N=30 subjects of the total N=90 sample will undergo neuroimaging. The first 30 subjects who are eligible/safe for PET/MRI procedures and are willing to be scanned will be offered participation in these procedures. Subjects who are not willing or able to participate in the PET studies will be offered participation in the MRI studies. These subjects will undergo a pretreatment MRI and PET scan and a post-treatment MRI and PET scan (i.e., 2 total MRIs, 2 total PET scans, separated by the 8 week clinical trial). Subjects who do not meet imaging selection criteria or who do not wish to undergo scanning will be allowed to participate in the clinical trial portion of the study only. MRI and PET scanning may occur on the same day if this can be scheduled (MRI occurring first, followed by PET scan). However, due to the tightness of scheduling for these scanners, it is more likely that the MRI and PET scans will occur on different days--one day for MRI scan and one day for the PET scan. Typically the MRI scanning day will come before the PET scanning day.

10. MRI of the brain will be acquired using a GE Premier 3.0T System. At the start of the session, a 3-Plane localizer (scout) will be acquired to determine patient position. Subjects will then receive T1-weighted 3D SPGR (Spoiled Gradient Echo), T2 FLAIR, and EPI scans. Acquisition parameters for the EPI scans will be: TE/TR (ms) 20/2000; Flip Angle (deg) 72o; in-plane resolution (voxels) 112x112; slice thickness/gap (mm) 3/0; slices 41.

11. For the MRI procedures, participants are instructed to lie as still as possible within the magnet. The MRI scan is completed in one session, and lasts for a total of 60 minutes. All precautions and protections are given to the participant to ensure that they are as safe and as comfortable as possible. For participants' comfort within the scanner, they lie on a padded table with a pillow to rest their heads on. A blanket is also provided to keep participants warm during the procedure. If the participant appears nervous or anxious, a trained member of the research staff remains with them inside the scanning

suite for the duration of the scan. The participant is given a squeeze ball to terminate the scan at any time. If he/she squeezes the ball, he/she will be removed from the scanner immediately. Participants may decline the MRI scans at any time. If the participant chooses not to be scanned, his/her participation in the study will not be affected. Of course, a structural MRI scan would be required to participate in the PET scans. Any subject who cannot have at least a structural MRI scan would not be able to participate in this protocol. All of the MRI procedures are conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. Conducting these procedures will be an accredited Magnetic Resonance Technologist and one member of the research staff (Bachelor's Level or Higher), or Dr Rutherford or Broft, present.

<u>PET Scanning</u>

12. The neuroimaging subset of depressed subjects will have 2 [11C]-raclopride PET scans: (1) pre-treatment and (2) post-treatment (at the end of the 8 week duration trial).

13. PET experiments will be conducted with the mCT scanner in the PET Suite on the R1 level of the Public Health Building. Subjects participating in the study will be escorted on PET scan day by a research staff member to the R1 level of the Public Health Building where the PET scanner is located. A research staff person will stay with the subject throughout the procedure. The preparation of the subject will include the placement of a venous catheter.

14. The radiochemistry laboratory and PET suite staff will be in frequent communication regarding the status of preparation of the research subject (such as placement of venous line) and the progress of the radiotracer synthesis. As scan time approaches, the subject will be placed in a supine position on the camera table and will have vital signs (blood pressure and heart rate) obtained. Head will be positioned and a headholder will be used to decrease head movement during the scan.

15. Baseline scan: A low dose CT transmission scan is then obtained prior [11C] raclopride administration. At the end of the transmission scan, a maximum of 14 mCi of [11C] raclopride will be injected intravenously. The dose of [11C] raclopride, diluted in a 10 cc syringe, will be given as a single bolus over a period of 30 seconds. [11C] raclopride will be prepared by the central radio-ligand staff of the PET Center and will be administered by an approved Nuclear Medicine physician (Drs. Arif Sheikh, Esther Coronel, or Randy Yeh). Study physicians will be present for all radiotracer injections. All study physicians have New York State Medical license and have had extensive training and experience with these types of PET studies. [11C] raclopride will be synthesized and tested for purity and sterility according to our standard procedure. The injected dose of [11C]-raclopride for each scan will not
exceed 14 mCi, and lower amounts will be permitted. The study physician or Nuclear Medicine physician will evaluate the reconstructed PET image in order to ensure tracer uptake in the brain and will inform the radiochemist if there is a lack of expected uptake in the brain. All subjects will be monitored by the study physician at the time of injection and a study physician or nurse will be present in the PET suite.

16. Post-treatment scan: As close to the end of the 8 week study as possible (based on PET scheduling), subjects will undergo their post treatment scan. We will follow standard procedures for measuring LDOPA-induced changes in synaptic dopamine levels set forth in PET studies of PD patients. Subjects will be given 75mg carbidopa/300mg L-DOPA approximately 1.5 hours before scanning. Subjects in week 8 of the

protocol are taking 450mg LDOPA per day (150mg three times daily), so the 300mg administered prior to the post-treatment PET scan will constitute 300mg of their usual 450mg daily dose on the scan day. A low dose CT transmission scan is obtained prior to intravenous administration of 14mCi [11C] raclopride (or less). The start of tracer injection will be timed to coincide with the time of onset of L-DOPA effects (approximately 60-90 minutes following oral dose). Thus, the 60 minute PET scanning session will occur from 90 minutes to 150 minutes following L-DOPA dosing in all subjects. At the completion of the scan the IV catheter will be removed, and the subject will be evaluated (including mental status and vital signs) by a study physician. Vital signs, and physical exam will be performed prior to discharge from the PET suite.

17. Since nausea is a known side effect of L-DOPA, we will be particularly vigilant about monitoring for it. When nausea occurs patients generally feel warm and sick to their stomachs. It will likely occur after PET scanning, but if vomiting were necessary, the MD would remove the subject from the scanner so that vomiting does not occur while supine. Removal from the scanner can occur immediately.

18. PET data will be reconstructed into images using the appropriate reconstruction protocols and filters. PET images will be coregistered to the MRI and regional time activity curves will be measured. Data will be fitted to pharmacokinetic models, and relevant pharmacokinetic parameters, including the percent of receptors engaged by dopamine, will be estimated based on the model fitting procedures.

16. Drs. Abi-Dargham and Slifstein continue to be Co-Investigators responsible for neuroimaging as part of a subcontract executed between RFMH and SUNY-Stony Brook. They will lead analyses of neuroimaging data. In terms of on-site execution of PET and MRI scans, these are supervised by the study PI (Bret Rutherford) and/or Dr. Allegra Broft, who works with the PI as a study clinician and has a research background in PET neuroimaging.

<u>Clinical treatment</u>

19. **At each weekly visit, subjects will meet with a psychiatrist of study physician.** At Week 0, subjects will be randomized to L-DOPA vs. placebo according to a blocked randomization schedule developed by the study statisticians and supplied to the NYSPI pharmacy. Raters, clinicians, and participants will be blinded to treatment assignment, though clinicians will be able to break the blind in case of clinical emergency. Treatment allocation will be concealed by over-encapsulation of 25/100 sinemet tablets or placebo tablets, such that all study pills will appear identical. All subjects will take 1 pill three times daily regardless of their treatment assignment. Those assigned to L-DOPA will begin taking 37.5mg carbidopa/150 mg levodopa once daily (with placebo twice daily) for one week, then increase to 75mg carbidopa/300mg levodopa (37.5 mg carbidopa/150mg levodopa twice daily and placebo once daily) for one week, and finally increase to 112.5mg carbidopa/450mg levodopa (37.5 mg carbidopa/150mg levodopa three times daily and no placebo) for the final six weeks. Subjects assigned to placebo will take placebo three times daily throughout the study. The 1.5 25/100 sinemet pills that are needed to make up a dose of 150mg levodopa will be installed a single, overencapsulated pill by the pharmacy.

20. Each subject assigned to the L-DOPA arm will be titrated to 450mg L-DOPA unless they cannot tolerate higher doses, in which case subjects will have their dosage reduced to the maximum tolerable dose. We chose 450mg as the target dose based on its being the dose that met the target progression criteria in the R61

Phase of this project (increased dopamine release in the striatum and increased processing/gait speed) and was highly tolerable to subjects. Both in our Pilot study and the literature overall, L-DOPA is an extremely well tolerated medication at doses < 600mg, which is substantially less than the doses often reached in the treatment of Parkinson's disease (900-1200mg). L-DOPA has been administered to healthy subjects in single dose studies and found to be well-tolerated. In Parkinson's disease, a recent clinical trial published in the New England Journal of Medicine randomized patients to receive 150mg, 300mg, or 600mg L-DOPA for 40 weeks. No dyskinesias or other neuropsychiatric effects were observed that were greater than the placebo group.

<u>Assessments</u>

21. Subjects are expected to have a screening/evaluation visit, pre-treatment PET/MRI scanning day(s) (for those receiving imaging), and weekly visits from Week 0-8.

22. The following measures will be collected weekly throughout the study: 24-item HRSD, CGI Severity and Improvement, Structured Pill Count Interview, Unified Parkinson's Disease Rating Scale (UPDRS) (questions 32 and 33 will be used in this study to assess the duration and disability of dyskinesias caused by L-DOPA), Treatment Emergent Side Effect Scale, and Inventory of Depressive Symptoms—Self Report (IDS-SR).

23. In addition, baseline processing and gait speed assessments will be repeated after **Weeks 1, 2, 5, and 8** at 1pm to control for time of day effects and the duration since the last morning L-DOPA dose (anticipated to be 4 hours). Processing speed will be assessed using the Digit Symbol test from the Wechsler Adult Intelligence Scale-III (WAISIII) (119) and the Pattern and Letter Comparison tests (120). These tests are all reliable and valid, with moderate to high loadings on the latent speed factor. A latent factor (and subsequent factor score) will be extracted from the 3-test battery pre- and post-treatment and used as the main outcome in the R61. By extracting a latent factor and factor loadings we will utilize a more pure measure of processing speed than if we used the raw scores from an individual test or a sum total score from the three raw scores combined (121-124).

24. Gait will be assessed as both a single and dual task (ST, DT) on a Gaitrite walkway system in the LLDC. For the ST, patients are instructed to walk at their usual or normal speed over the walking course. For the DT, patients are instructed to walk at their usual pace while simultaneously verbally listing as many animals as possible (fluency DT). In addition, a counting DT will be used in which patients are instructed to walk at their usual pace while simultaneously performing serial subtractions by threes starting at 100 (125). Patients will start and end at a point 2 meters from beginning of the course to eliminate acceleration and deceleration effects. Each ST and DT will be assessed two times with the average used in the analyses.

25. Activity levels will be monitored in real time throughout the 8 week duration study using the GT3X+ Activity Monitors from Actigraph and the ActiLife Enterprise Software. We will analyze the average energy expenditure level (total counts in kcal per day assessed over 8 days with partial first day and last day assessments discarded) recorded in the week prior to baseline and the week prior to the Week 8 visit. A 60-second epoch will be used, and the percentage of time spent as sedentary vs. moderately active will also be explored. The combination of the Work-Energy Theorem and the Freedson Equation to adjust for lower

caloric expenditures if necessary. We will purchase 10 GT3X+ Activity Monitors for repeated use by all of the R33 Phase subjects.

<u>End of study procedures</u>

26. Following the 8 week duration treatment study, endpoint assessments of depressive symptoms, processing speed, and gait speed will be made. Subjects will undergo endpoint neuropsychological testing and post-L-DOPA MRI and PET scanning.

27. Once post-treatment research procedures are completed, patients will enter 3 month open treatment period provided free of charge as described below.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
The risk of non-response or adverse events to L-DOPA during the study period is addressed by having close clinical follow up of study subjects and stringent withdrawal criteria. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening as defined by a slowing assessment rating using the CGI-Improvement scale of 6 (worse) or 7 (much worse) for 2 consecutive visits; or (3) development of significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated clinically. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. No treatment is currently available for slowing, so there is not a standard of care treatment to offer patients withdrawn from the study. Thus, withdrawn patients will be followed in the open treatment period, offered appropriate psychiatric treatments if they have any conditions requiring treatment (e.g., depression), and be referred to their internist for close medical follow up.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
A 20cc blood sample will be drawn at baseline. General medical tests will be performed, such as CBC, Chem 7, LFTs, TSH, cholesterol, B12, and folate. Also, tubes of whole blood will be aliquoted and frozen for subsequent measurement of (1) serum inflammatory markers and (2) IL-6 and COMT genotypes.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Structured Clinical Interview Diagnostic for DSM 5 (SCID) (114): this semi-structured diagnostic interview will allow determination of whether subjects meet selection criteria.

Cumulative Illness Rating Scale-Geriatric (CIRS-G) (112) will be filled out at baseline to measure chronic medical illness burden.

Subjects' current physical pain will be assessed weekly using a 100mm Pain Visual Analog Scale (VAS) and used as a covariate in analyses of gait speed (113).

Center for Epidemiologic Studies—Depression Scale (CES-D): depression screening measure chosen given its ease of administration and wide use in epidemiological studies.

MMSE: standard means of assessing global cognition. The SCID, CES-D, and MMSE will be measured at baseline for the purpose of subject selection, while the following measures will be collected weekly throughout the study.

24-item HRSD (115): standard measure of depression severity that measures changes in depressive symptoms, though L-DOPA effects on depression are not the focus of the R61 Phase.

CGI Severity and Improvement: scales measuring the clinician's view of subjects' global functioning that will provide a clinical assessment of subjects at each visit and help maintain safety by identifying clinical worsening.

Structured Pill Count Interview: assessment of study medication compliance accounting for each dose of prescribed study medication during the study period.

Blind Assessments rate clinician's and patient's guesses as to study drug assignment.

Unified Parkinson's Disease Rating Scale (UPDRS) (116): standardized, reliable, and valid instrument for assessing the severity of the clinical features of PD; questions 32 and 33 will be used in this study to assess the duration and disability of dyskinesias caused by L-DOPA. While we include this measure, we are not expecting to observe dyskinesias in healthy subjects or at the L-DOPA doses being used in this study. Typically, such L-DOPA side effects emerge only in patients who have had Parkinson's disease for a number of years and then only if the LDOPA dose is raised to 600 mg or more.

Treatment Emergent Side Effect Scale: standardized general checklist used in our clinic for monitoring side effects associated with medication treatment.

Inventory of Depressive Symptoms—Self Report (IDS-SR) (117): rating scale for depressive symptoms based on DSM criteria that has been increasingly used in antidepressant studies due to its equivalent weightings for each item, understandable anchor points, and inclusion of all DSM criteria (118).

Processing speed will be assessed using the Digit Symbol test from the Wechsler Adult Intelligence Scale-III (WAIS-III) (119) and the Pattern and Letter Comparison tests (120). These tests are all reliable and valid, with moderate to high loadings on the latent speed factor.

Episodic memory functioning will be assessed using the Wechsler Memory Scale Logical Memory Test I & II (153). Inclusion of this test will allow us to identify deficits in episodic memory functioning consistent with a classification of amnestic mild cognitive impairment (aMCI) (7).

Executive function will be assessed via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently (154-155). This battery examines working memory, inhibition, set shifting, fluency, insight, planning, social cognition and behavior.

The Short Physical Performance Battery (SPPB) (156), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change.

The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability and 7 domain-specific scores based on the conceptual framework of the International Classification of Functioning, Disability, and Health (ICF) (157).

The self-report 38-item Measure of Everyday Cognition (ECog) is adapted from an informant-report version and measures impairment and change in domains of everyday/real-world functioning relevant to 7 specific neuropsychological domains (158).

The Falls Efficacy Scale-International will assess subjects' fear of falling weekly using a 16-item scale rating respondents' confidence (1 not at all concerned—4 very concerned) in doing daily tasks without falling (159-160).

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
✓ Radiolabeled drug/compound
Select the number of drugs used in this study
1

Drug #1

Name of the drug
carbidopa/levodopa (Sinemet)
Manufacturer and other information
We will be using generic sinemet 25/100 tablets in this study. We will purchase them through the pharmacy, using whichever generic manufacturer is recommended by the NYSPI pharmacy.
L-DOPA is currently approved by the Food and Drug Administration (FDA) for the treatment of the symptoms of idiopathic Parkinson's disease, post-encephalitic parkinsonism, and symptomatic

parkinsonism. This project proposes off-label use of L-DOPA in individuals with significant cognitive/motor slowing. When we submitted an NIMH grant application Oct 2014 for this study, we contacted the Division of Neurology Products at the FDA to inquire whether an IND was required for LDOPA use in this project. We had a phone conversation with Cathleen Michaloski (Sr. Regulatory Project Manager, Division of Neurology Products), during which she listened to our description of the study methods and stated that an IND was not required. She later sent us an email after discussion with Dr. David Podskalny (Team Leader, Division of Neurology Products) confirming that in their assessment an IND was not needed for a project such as this.

Text of email follows:

Dear Dr. Brown [Co-Investigator on submission],

Thank you for your time by phone. As we discussed by phone and after consulting with our Team Leader, Dr. Dave Podskalny, believes an IND is not required (unless your IRB stipulates otherwise). The information provided in your email suggests that the indication is covered in labeling. Also, as you may know we do not regulate off label, “practice of medicine” usage.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager
Division of Neurology Products
FDA / CDER / OND / ODEI /DNP
White Oak Building 22 room 4342
301-796-1123
Cathleen.michaloski@fda.hhs.gov
Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Off label and investigational use of radiolabeled drugs/compounds

Radiolabeled Drug/Compound #1

Name of the radiolabeled drug/compound
[11C] raclopride
Manufacturer and other information
[11C]raclopride or
[C-11]-(S)-3,5-dichloro-N-(1-ethyl-pyrrolidin-2-yl-methyl)-2-hydroxy-6-methoxy-benzamide)
[11C]raclopride is manufactured onsite in the Radioligand lab
Approval Status

IND is approved
IND#
141742
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Rutherford, Bret, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
None.
Maximum duration of delay to standard care or treatment of known efficacy
Since patients may be assigned to placebo and the effects of L-DOPA on depression in this population are currently unknown, there will be an 8-week duration delay to receiving an agent of known efficacy to treat depression posed by subjects' participation in this study.
Treatment to be provided at the end of the study
We will provide 3 months of additional free clinic visits following the end of this project. At the conclusion of the 3 week study, a non-study clinician in our research clinic will be given the data on the subject's response to L-DOPA. This clinician will discuss with each subject on a case-by-case basis the risks and benefits of continuing L-DOPA treatment as well as other treatment options if warranted. Those who have benefited from the treatment and have not had significant side effects may elect to continue receiving LDOPA after receiving an explanation of the potential risks of chronic administration. If they do not want to continue L-DOPA, it will be discontinued after a 3 day step-down withdrawal of the drug. Transferring after-study care to a non-study clinician protects against the development of bias in the study clinicians and offers optimal clinical care to the subjects at the study conclusion.

Clinical Treatment Alternatives

Clinical treatment alternatives
The alternative to participating in this study is to seek treatment outside the research project. Patients who would rather receive treatment elsewhere will be given referrals to appropriate and affordable care.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
1. Interview, emergencies, and possible suicidal ideation. Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms and current life events. The study coordinators are experienced and skilled in interviewing depressed subjects. Half-way through the initial assessment, the coordinator will ask the subject if they would like to take a break, and this will be provided

if desired. A study clinician will be available during all aspects of the assessment if there are any questions or problems. In addition, should the subject express suicidal ideation at any time during the interview, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver, referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

2. L-DOPA Side Effects: Side effects will be assessed at each planned visit and if needed through additional or unscheduled contacts. We will attempt to minimize side effects by slow dosage titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of carbidopa/levodopa (L-DOPA) 37.5mg/150mg daily. L-DOPA is a well-tolerated medication at the doses we will be using in this study. Older (i.e., 1960s-70s era) case studies report administering L-DOPA doses of 400-1200mg and in some cases much higher to depressed, non-PD patients over subacute time periods (4-12 weeks). Variable clinical results were observed, but few side effects were reported and no dyskinesias. More recently, a double-blind study (conducted by Co-Investigator Yaakov Stern and colleagues) of a single dose of L-DOPA 200mg vs. placebo investigated the role of dopamine in the impaired interval timing abilities observed in older adults. Thirty two healthy aged participants aged 71.2 ± 7.6 years were trained to produce two target time intervals
(6 and 17 seconds in duration) in separate blocks corresponding to drug/placebo administration. Of the 16 elderly subjects who took 200mg L-DOPA, no severe side effects were noted, and no individuals discontinued participation in the study. Forty-four percent reported mild nausea at some point during the experiment, which was the only side effect noted. There are sporadic other reports in the literature examining the effects of single-dose 200mg L-DOPA on cognitive outcomes in healthy controls (e.g., Rihet et al, Psychopharmacology 2002; Hasbroucq et al, Psychopharmacology 2003), but no other recent (i.e., post 2000) studies have been performed of subacute L-DOPA dosing in healthy controls.
There are many studies of chronic L-DOPA administration for the treatment of PD, since this drug has been used since the 1960s. Perhaps the most relevant recent study was a clinical trial published in the New England Journal of Medicine in 2004 (72). In this study 361 patients with PD were randomized to receive 150mg, 300mg, or 600mg L-DOPA for 40 weeks. No dyskinesias or other neuropsychiatric effects were observed that were greater than the placebo group, and this study lasted 40 weeks as opposed to 8 weeks in the R33 Phase of this study. Despite these reassuring data, and recognizing that we include a different patient population, we will carefully assess subjects with new complaints to determine if they may be related to study drug and if there is a need for closer monitoring or change in study drug dosing.

a. L-DOPA common side effects: In patients taking L-DOPA for the management of bradykinesia and freezing associated with PD, the most common side effects are dyskinesias (i.e., choreiform, dystonic, and other involuntary movements) and nausea.

b. Other L-DOPA side effects: blood pressure changes, orthostasis, anorexia, dyspepsia, constipation, psychotic episodes (e.g., delusions, hallucinations), vivid dreams, and nightmares.

c. Discontinuation Syndrome: Case studies of a neuroleptic malignant-like syndrome (fever, akinetic crisis, rigidity, autonomic disturbances) have been reported following withdrawal of levodopa in patients with PD. Retrospective analyses suggest NMS syndromes appear to occur in approximately 2% of PD patients, and levodopa discontinuation may be a risk factor in approximately half of these instances (1% of PD patients) (Hashimoto et al, Parkinsonism and Related Disorders, 2003). Controlled studies measuring NMS incidence following levodopa withdrawal have not been performed.

d. Sensitization to L-DOPA: It is not fully known how the normal slowing down that occurs during aging relates to the type of slowing that occurs in patients with Parkinson's disease. Some individuals who experience slowing with age may be at increased risk for Parkinson's disease. L-DOPA is a treatment for Parkinson's disease, but in patients with the illness it can be associated with increased risk for developing abnormal movements over time. It is difficult to estimate the risk of sensitizing healthy participants to L-DOPA in this study as there are no studies in which participants without PD were given L-DOPA, then followed for many years to see whether they developed PD and whether, if so, they had increased rates of motor complications. However, even if subjects later on develop PD, the likelihood of developing dyskinesias is reliant on well described factors such as disease duration and high doses of L-DOPA. Thus a short exposure to L-DOPA before disease diagnosis appears less likely to have play a role in the development of motor complications with L-DOPA treatments in non PD patients. If we were to conservatively estimate that <10% of individuals treated with 450mg L-DOPA for 40 weeks (much longer than the duration in this study) will develop a dyskinesia and <5% of individuals with significant age-related slowing in our study will go on to develop PD and require future L-DOPA treatment, then the risk of sensitizing patients in our study such that their later PD treatment would be compromised should be 0.5%.

3. PET imaging—Radiation Exposure: The dose of radiation will be submitted for approval to the Columbia University Medical Center Joint Radiation Safety Committee (JRSC). All scans will be done in the presence of medical supervision and trained nursing staff in an institution specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to, or consultation with, specialized medical units at the Columbia University Medical Center (CUMC). Preparation of radiopharmaceuticals and performance of PET scans will be by radiochemists, physicians, and technologists of the Department of Radiology, Columbia University Medical Center. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The study doctor will be informed regarding subjects' previous radiation exposure. Dose estimates indicate that the maximum, permissible single study dosage of [11C]-raclopride in human subjects, to remain below the CFR 361.1 dose limits for research subjects, is 42.8 mCi (i.e., calculation based upon gallbladder as the critical organ; 5 rads per single study limit and 0.117 rads per mCi to the gallbladder). Thus, a dose of max 14 mCi per injection, and the dose associated with participation to this study (2 injections: 28 mCi) will be within this limit. Subjects will be instructed not to participate in any other research studies that include radiation exposure during the year starting on the day of the first study. Subjects exposed to radiation in the work place are excluded, as well as subjects exposed to nuclear medicine procedures during the previous year, including research protocols.

4. PET imaging—The dose of raclopride used in this study is negligible (equal or below 6.94 µg per administration) and is expected to induce less than 5% occupancy of D2 receptors. [11C]raclopride is a radiotracer that has been extensively used to measure striatal D2 receptors both in the US and in Europe. Side effects have never been reported at the tracer doses used in PET studies. In

addition, unlabeled raclopride has been tested at pharmacological doses in humans, as a potential antipsychotic drug. Its safety and tolerability have been well characterized (Farde et al., 1989; Farde et al., 1988; Cookson et al., 1989; The British Isles Raclopride Study Group, 1992) Therefore, we do not anticipate any pharmacological effects from the radiotracer used in the proposed studies. As with any drug, the possibility of idiosyncratic reaction exists and is mentioned in the consent forms. A physician is present at each experiment.

5. Magnetic Resonance Imaging: Although this procedure is generally low-risk, there are particular concerns. Individuals will be screened for the presence of implanted metal (including but not limited to medical devices, shrapnel, tattoos or permanent makeup). Those who screen positive will be excluded from the study. Claustrophobia is also an issue for many potential subjects. During the MRI, subjects will have voice contact with a radiology technician, and they may request the scan be stopped at any time.

6. Incidental Findings: Magnetic Resonance Imaging: Another risk is the occurrence of incidental findings on MRI. All scans are reviewed at time of acquisition and concerning findings are discussed with an attending neuroradiologist. Should any concerning findings be seen, the site PI will convey these findings to the subject along with recommendations for further evaluation, and facilitate referrals for such evaluation and treatment.

7. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical, genetic, and laboratory information. Dr. Rutherford has extensive experience as a clinical investigator in dealing with sensitive information and assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file.

8. a. Risks of placing an intra-venous catheter. Drawing blood from and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture. The volume of blood collected during this study, include screening laboratories, will be approximately 2-3 tablespoons. These are not expected to have any serious negative effects on the study participants.

b. Risks of blood draw: In the obtaining a 20 cc blood sample, patients can experience side effects that include pain, fainting, bruising, light-headedness, and, on rare occasions, infection. The staff will take every precaution to avoid these difficulties. The staff members are all certified at the hospital to be drawing blood from patients, and are instructed to keep the comfort and welfare of our patients as their primary priority.

9. Gait speed assessment: During the gait speed assessment, patients may feel unsteady and as such their risk of falls may increase. To mitigate these risks, patients are accompanied by research coordinators and/or doctors during each of the performance-based assessments. Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

10. Patients assigned to placebo may experience continued symptoms or clinical worsening. As noted above, this risk is mitigated by the fact that there are currently no treatments available for psychomotor slowing. Slowing also is a negative prognostic factor for antidepressant response in patients who are both slowed and depressed, and there are currently no evidence based treatments specifically aimed at this subgroup. The risk of harm to subjects in this study will be minimized by restricting the study to moderately depressed, nonsuicidal patients, following them closely, and dropping them from the study for signs of clinical deterioration.

Describe procedures for minimizing risks
1. The study coordinators are experienced and skilled in interviewing subjects with a variety of mental health issues. Half-way through the initial assessment, the coordinator will ask the subject if they would like to take a break, and this will be provided if desired. A study clinician will be available during all aspects of the assessment if there are any questions or problems. In addition, should the subject express suicidal ideation at any time during the interview, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver, referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

2. Side effects will be assessed at each planned visit and if needed through additional or unscheduled contacts. We will attempt to minimize side effects by slow dosage titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of carbidopa/levodopa (L-DOPA) 37.5mg/150mg daily.

3. The dose of radiation was approved by the JRSC for the R61 Phase of this project (IRB 7270), and we will resubmit an additional application to cover this R33 Phase. No changes have been made to the PET scanning procedures for this R33 Phase. All scans will be done in the presence of medical supervision and trained nursing staff in an imaging center specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to a consultation with specialized medical units at New York Presbyterian Hospital. Preparation of radiopharmaceuticals and performance of PET scans will be by radiochemists, physicians, and technologists of the Department of Radiology at Columbia. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The information on the previous radiation exposure of study subjects will be notified to the study doctor.

4. In terms of raclopride pharmacologic effects, we do not anticipate any pharmacological effects from the radiotracer used in the proposed studies. As with any drug, the possibility of idiosyncratic reaction exists and is mentioned in the consent forms. A physician is present at each experiment.

5. To minimize MRI risks, each subject will fill out the MRI Safety Questionnaire before the study. Only subjects who fulfill the criteria by this questionnaire will be eligible for the study. In addition, subjects will remove all metal (watch, hair pins, jewelry) before entering the MRI room. If the

subject has any metallic prostheses/implants they will be excluded from the study. If a subject becomes anxious during the scan they can request that the MRI scan be stopped. 6. Dr. Rutherford has extensive experience as a clinical investigator in dealing with sensitive information
and assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file.

7. Risks of bruising, clotting, and infection during IV placement and blood draw will be minimized by having venipuncture performed by trained and experienced personnel under sterile conditions. To avoid injury due to fainting, the antecubital vein catheter will be inserted when the subjects are recumbent.

8. The staff will take every precaution to avoid difficulties with gait speed assessments. Patients are accompanied by research coordinators and/or doctors during the test of gait speed. Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
All records of the participating subjects will be kept in a locked room with access provided only to staff members. Patients' names will be linked with code numbers in a password protected file to which only the research assistant has access. Only these code numbers will appear on all pill bottles and paper measures collected during study. All data collected will be kept confidential and used for professional purposes only. Publications using these data will be done in a manner that protects the subjects' anonymity. All electronically stored data will be accessible by password known only to the principal investigator and research assistants for the study.

Data shared with the National Institute of Mental Health Data Archive (NDA) will maintain patient confidentiality by ensuring exclusion of all 18 identifiers (outlined by HIPAA) prior to data sharing.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
There is no direct benefit to subjects. If L-DOPA treatment is effective in ameliorating slowing, subjects may experience improved quality of life and decreased of falls and other sequelae of slowing.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Subjects will receive reasonable reimbursement for transportation related costs associated with study involvement as long as they provide receipts.

Subjects will receive $15 for each weekly study visit (Weeks 0-8) attended. This money will be paid by cash at the conclusion of each of these visits for a total of $135 if all study visits are attended.

Subjects will receive $50 for each MRI scan ($100 total for the MRI) and $150 for completing each PET scan ($300 total for PET). Of note, subjects will be compensated for scheduled scans if they are brought to the MRI or PET suites and the scans are not completed that day due to chemistry failure or other similar issues.

Thus, subjects undergoing neuroimaging may earn $400 in this study, which will be a lump sum payment mailed in the form of a check at the conclusion of the study, plus an additional $135 cash ($15 cash at the end of each weekly visit) if all weekly study visits are also completed. If a subject does not complete the study, payment is pro-rated to portions completed. Subjects are advised to allow 1-3 weeks for receipt of payment for neuroimaging.

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