Protocol Title:
Combination Treatment with L-DOPA and Exercise for Mood and Mobility Problems in Later Life

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8065

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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 an annual continuation with modifications

Department & Unaffiliated Personnel

Department

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

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.

Michael Treadway, PhD
Emory University School of Medicine

Amendment

Describe the change(s) being made
Galit Sharon Marcus, NP is being removed as an individual designated to discuss and document consent, as she no longer works in our clinic. Denise McClellan, NP is being added as an individual designated to discuss and document consent, as she is joining our team.
Provide the rationale for the change(s)
Changes to our staff necessitate an update to the protocol's persons designated to discuss and document consent.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
None - no alterations to risks/benefits to subjects.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
No - changes to the CF are not necessary.

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Although recruitment has been slower than expected (no subjects enrolled so far), CAAM has continued to conduct evaluations assessing eligibility for enrollment. All study set-up procedures have been completed, and the research staff are prepared for the first enrollment once a potential subject is identified.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
80
Total number of participants enrolled to date
0
Number of participants who have completed the study to date
0
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Adults 60 years or older with a depressive disorder and decreased processing speed or decreased gait speed
Total number of participants enrolled from this population to date
0
Gender, Racial and Ethnic Breakdown

Gender:
Male: 0
Female: 0

Race:
American Indian/Alaska Native: 0
Asian: 0
Black/African-American: 0
Native Hawaiian/Pacific Islander: 0
White: 0

More than one: 0
Unknown: 0

Ethnicity:
Not Hispanic/Latino: 0
Hipanic/Latino: 0
Missing: 0

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

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

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ 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 application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name
Mentoring to Develop Aging-Informed Patient Oriented Research in Neuropsychiatry
Grant Number
K24 MH122514
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

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In this new research study, 80 adults aged > 60 years with a significant depressive disorder and slowed processing and/or gait speed will be randomized to receive levodopa (L-DOPA; which the Candidate has previously shown to increase psychomotor speed and decrease depressive symptoms in older adults), aerobic exercise (itself an effective antidepressant treatment as monotherapy), or their combination in a 2x2 design incorporating placebo and a stretching/toning control. Participants will be evaluated before and after this 12-week duration study across cognitive domains, psychiatric symptoms, gait kinematics and mobility, and task-based magnetic resonance imaging (MRI) focused on effort-based decision making and reward

processing. Data from this study will contribute toward the development of improved treatment and prevention strategies to maximize the functioning and active healthspan of older adults with neuropsychiatric disorders.

Background, Significance and Rationale

Background, Significance and Rationale

Late Life Depression [LLD]), is prevalent (83-84), disabling (85-86), and associated with high rates of completed suicide (87). Among the LLD patients at highest risk of these adverse outcomes are those who manifest decreased processing speed and/or decreased gait speed. To develop urgently needed novel therapeutics for LLD, a reasonable approach is to target systems underlying the development and persistence of psychomotor slowing. One such approach has been to augment dopaminergic signaling, since post-mortem experiments and in vivo neuroimaging studies have implicated age-related dopaminergic decline in the development of slowing. 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. As opposed to other dopaminergic interventions (i.e., dopamine receptor agonists and stimulants), a large literature shows beneficial effects of L-DOPA on cognitive performance and gait in patients with Parkinson's disease (88-89), all while being a safe and well-tolerated medication that is difficult to differentiate from placebo in terms of side effects (90).

A second therapeutic strategy that has been tested for LLD and is relevant to psychomotor slowing is aerobic exercise training. A number of reports and meta-analytic reviews suggest that exercise is an effective non-pharmacologic treatment for depression, including depression in older adults (91). The largest recent study found that progressive aerobic exercise conducted three times weekly for 30min over 24 weeks was effective for depression and was tolerated extremely well (14.3% drop-out rate, 70% intervention adherence) (55,92). Exercise training may be effective for LLD by counteracting deleterious age-related changes related to its development and maintenance, such as by reducing pro-inflammatory cytokines (93), normalizing hypothalamic-pituitary-adrenal axis hyperactivity (94), and decreasing physical disability and social isolation (95). Exercise also appears to facilitate adaptive neuroplastic changes in the hippocampus, prefrontal cortex (PFC), and anterior cingulate cortex (ACC) as well as increased white matter connectivity (96-97).

While both dopaminergic augmentation and exercise are promising interventions, neither treatment alone may be sufficient to address the serious adverse medical and psychiatric outcomes associated with LLD and psychomotor slowing (34-35). In our preliminary study (NYSPI IRB# 7270), L-DOPA was associated with significant improvements in gait speed, but the effect size of this improvement was only moderate (d=0.4) (1). L-DOPA failed to increase average gait speed in this study above the 1m/s threshold associated with functional disability and increased mortality risk in epidemiologic samples (98). While exercise has not been studied specifically in this patient population, meta-analyses of exercise interventions in older adults suggest overall effects on gait speed are modest (d=0.3) and perhaps not clinically significant (99). Thus, one goal of this study is to combine these interventions having complementary mechanisms of action to realize a greater therapeutic benefit.

This study includes task-based functional MRI that will allow us to probe the differential therapeutic mechanisms of L-DOPA and exercise and further elucidate the nature of effort-based decision making and reward deficits in LLD. Decision making about voluntary behavior requires weighing the benefit of potential rewards against the effort cost required to achieve them (100-102). This calculation is performed by separable populations of dopaminergic midbrain neurons whose signals for value and effort are integrated in the ventral striatum (VS) (103). Anterior VS (aVS) consistently has been shown to encode subjective value, increasing with the probability of reward and decreasing with effort discounting (32), while recent work suggests dorsomedial VS (dmVS) activates during the initiation of effortful action (33). We hypothesize that older adults are biased toward inactivity (and thereby at risk for depression) on the basis of dopaminergic decline that diminishes subjective value estimates and increases the effort cost of action (i.e., by the development of slowing). Among PD patients, L-DOPA increases willingness to work independent of facilitating movement by increasing subjective value estimates (104). By increasing fitness and helping individuals learn about their increasing capacities, exercise may facilitate effort initiation. Below, we evaluate whether complementary effects on effortful behavior may be achievable via L-DOPA increasing subjective value and Exercise reducing effort cost

Specific Aims and Hypotheses

Specific Aims and Hypotheses
AIM 1: To measure individual and combined effects of L-DOPA and Exercise (Ex) on cognitive, psychiatric, and physical performance measures in depressed older adults with psychomotor slowing.

Hyp 1: L-DOPA and Ex individually will be associated with significant main effects on processing speed, gait speed, and depressive symptoms.

Hyp 2: An L-DOPA x Ex interaction will be observed on these outcomes, such that the greatest improvements will occur among participants randomized to L-DOPA + Ex.

AIM 2: To investigate responsivity of reward-related dopamine circuits to L-DOPA and Ex.

Hyp 3: In an effort-based decision making (EBDM) task, L-DOPA and Ex each will be associated with increased willingness to work (right-shift in subjective value discounting curve) and changes in associated neural activations (ventromedial prefrontal cortex [vmPFC] and dorsal anterior cingulate [dACC]).

Hyp 4: In a virtual reality maze-navigation (VRMN) task, L-DOPA will be associated with increased neural responses to subjective value (anterior VS [aVS]), while Ex will be associated with increased dorsomedial ventral striatum (dmVS) activation during effort initiation.

Exploratory aims: We will explore correlations between real-world physical functioning metrics (i.e., gait speed, fatigability, physical activity) and behavioral/neural responses on the EBDM and VRMN tasks in the scanner. Differences in L-DOPA and Ex acceptability, side effects, and attrition will be compared.

Description of Subject Population

Sample #1

Specify subject population
Older depressed subjects
Number of completers required to accomplish study aims
72
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
>= 60 years old

Gender, Racial and Ethnic Breakdown

We will recruit participants of all races and ethnic groups, to the extent possible within the local population demographics. We will make efforts to ensure a representative sample by working to boost minority enrollment to maintain sample consistency with population averages.

On the basis of previous studies conducted at Columbia/NYSPI's Clinic for Aging, Anxiety, and Mood Disorders (CAAM), it is anticipated that the sample at this site will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects. We will make every effort to recruit minority individuals in order to ensure the generalizability of the study's findings to the overall population of individuals with Late-Life Depression (LLD). Given the increased prevalence of depression in women, we do not anticipate difficulty in women representing 60% of our sample. Previous samples in studies conducted in CAAM have been approximately 60% women and 40% men.

Description of subject population
The N=80 Depressed sample will enroll subjects who are 1) aged 60 years old or greater, 2) have DSM5 diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder, 3) Montgomery-Asberg Depression Rating Scale (MADRS) >= 15, 4) 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 of **0.5 SD below age-adjusted norms**), and are 5) capable of providing informed consent and adhering to study procedures. Subjects will be excluded for 1) diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) in the past 12 months, 2) history of psychosis, psychotic disorder, mania, or bipolar disorder, 3) primary neurological disorder, including dementia, stroke, Parkinson's disease, epilepsy, etc., 4) MMSE < 24, 5) MADRS suicide item > 4 or other indication of acute suicidality, 6) current or recent (within the past 2 weeks) treatment with antidepressants, antipsychotics, or mood stabilizers, 7) history of hypersensitivity, allergy, or intolerance to L-DOPA, 8) any physical or intellectual disability adversely affecting ability to complete assessments, 9) acute, severe, or unstable medical illness, 10) mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, or history of joint replacement / spine surgery that limits mobility, or 11) contraindication to MRI scanning.

Recruitment Procedures

Describe settings where recruitment will occur
Patients will be recruited from around the general New York City/New York area and will present to the Clinic for Aging, Anxiety, and Mood Disorders.

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, NAMI website, Facebook advertisements, advertisements in local newspapers and on radio stations, information posted on departmental websites, flyer mailings, pharmacies, Craigslist, ResearchMatch.com, senior community centers, college campuses, and public talks and events. 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?

Recruitment in the Clinic for Aging, Anxiety, and Mood Disorders (CAAM) comes from clinician referrals, response to advertisements (radio, flyer, newspaper, online participant matching websites, Facebook), patients who have finished or are currently enrolled in other protocols in the CAAM, or word of mouth.

How will the study be advertised/publicized?
The study will be advertised/publicized through clinician referrals and advertisements, Columbia's RecruitMe website, Research Match website, Facebook, Clinical Connection website, Craigslist website, newspapers, recruitment flyers/brochures and mass mailers at community and senior centers, radio, the National Alliance on Mental Illness NYC Metro Research Studies Website, mass email campaigns from consumer marketing databases, which are compiled using public information, surveys, subscription information, home owner information, and phone directory information, pharmacies, senior community centers, college campuses, and public talks and events.

All web based recruitment procedures have been previously approved by Chris Stanley for all of our approved studies.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT04650217

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects who are currently participating in or have recently completed IRBs #7540, #7289R, #7409, #7360, #7489, #7976, #7733, and/or #7379 and meet the selection criteria for this study may 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
Depressed older adults
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion criterion	Method of ascertainment
1. Age >= 60 years old	1. Clinical interview
2. DSM5 diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder	2. SCID, clinical interview
3. Montgomery-Asberg Depression Rating Scale (MADRS) >= 15	3. MADRS
4. Decreased processing speed (**0.5** SD below age-adjusted norms on the Digit Symbol Test or **Trails A**) OR decreased gait speed (**0.5 SD below age-adjusted norms**)	4. **0.5** SD below age-adjusted norms on Digit Symbol Test **or Trails A** (processing speed) or average walking speed on 15 feet course **0.5 SD below age-adjusted norms** (gait speed)
5. Capable of providing informed consent and adhering to study procedures	5. Clinical interview

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

Exclusion criterion	Method of ascertainment
1. Diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) in the past 12 months	1. SCID, clinical interview

2. History of psychosis, psychotic disorder, mania, or bipolar disorder	2. SCID, clinical interview
3. Primary neurological disorder, including dementia, stroke, Parkinson's disease, epilepsy, etc.	3. Medical history, MMSE. Parkinson's disease (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 CAAM (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), then Dr. Kimberly Kwei (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 work up
4. MMSE < 24	4. MMSE
5. MADRS suicide item > 4 or other indication of acute suicidality	5. MADRS, clinical judgement, CGI
6. Current or recent (within the past 2 weeks) treatment with antidepressants, antipsychotics, or mood stabilizers	6. Clinical interview
7. History of hypersensitivity, allergy, or intolerance to L-DOPA; exposure to LDOPA in the past 30 days	7. Clinical interview
8. Any physical or intellectual disability adversely affecting ability to complete	8. Clinical interview, physical exam, Falls Efficacy Scale, Short Physical Performance Battery

assessments or exercise training, including significant risk of falling or fear of falling during home exercise as measured by Falls Efficacy Scale >27 or SPPB < 7	
9. Acute, severe, or unstable medical illness or in the opinion of primary medical doctor (PMD) not safe to participate in exercise program	9. Clinical interview, physical exam, history from PMD
10. Mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, or history of joint replacement / spine surgery that limits mobility	10. Clinical interview, physical exam, medical history
11. Has a medical condition managed with medication and/or device and the managing physician considers the condition and/or its management a contraindication to the research use of L-DOPA in	11. Clinical interview, medical history, discussion with participant's clinician

this participant	
For participants undergoing MRI scanning procedures only (N=40; participants may participate in clinical portion of study-only if they are ineligible for MRI scanning):	12. Clinical interview, MRI Safety Screening Form
12. Contraindication to MRI scanning	

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 clinical evaluation and 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
Brewster, Katharine
Broft, Allegra, MD
McClellan, Denise
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

Study Overview

Briefly, following baseline screening and eligibility determination, subjects who decide to participate by signing informed consent will undergo testing of baseline aerobic capacity in Mentor Dr. Richard Sloan's laboratory in the Division of Behavioral Medicine at Columbia/New York State Psychiatric Institute (NYSPI). Half of all subjects (N=10 per group, N=40 total) will undergo baseline magnetic resonance imaging (MRI) including structural scanning and functional imaging with an effort-based decision making (EBDM) and virtual reality maze navigation (VRMN) tasks. All subjects will have comprehensive cognitive assessment, including specific tests focused on processing speed and executive function, and a motor evaluation (including gait speed and kinematics using the GaitRite walkway) will be performed. Next, participants will be randomized in double-blind fashion to receive carbidopa/levodopa (L-DOPA) or placebo tablets three times daily (9am, 1pm, 5pm). Also at Week 0, participants will be randomized to exercise training 4 times weekly (Exercise) or a stretching and toning control (Control). This will result in four treatment groups: L-DOPA + Exercise (N=20), L-DOPA + Control (N=20), Placebo + Exercise (N=20), and Placebo + Control (N=20). Subjects assigned to Exercise training will exercise individually at their home on a program set each week by Dr. Sloan and the research assistant (RA) coach, who will work with the patient to ensure they train according to the program at the appropriate level of intensity. Participants assigned to the Control condition will engage in a series of stretches and toning exercises designed to promote flexibility and improve core strength. All subjects will have follow up clinic visits for 12 weeks in order to monitor their depressive symptoms as well as assess compliance and tolerability of L-DOPA/Placebo and Exercise/Control interventions. Baseline assessments, including structural and task-based MRI scanning, will be repeated at Week 12 to measure the effects of the interventions. Please see Fig. 1 for a graphic depiction of the design.

Evaluation

1. Every subject evaluated for this protocol will receive a clinical interview by a psychiatrist, psychologist, or nurse practitioner. 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 the study neurologist (Dr. Kimberly Kwei at Columbia). Additional assessments will be administered by a trained rater (BA, RN, or SW) in CAAM, including the Montgomery Asberg Depression Rating Scale (MADRS) and a SCID performed by a trained rater. Raters in CAAM receive their initial training from Nancy Turret, SW who has been administering these tools in CAAM for many years. The training involves a combination of in person didactics, videotaped interview viewing, shadowing an experienced rater, and conducting a number of supervised interviews. Supervision occurs by Ms. Turret as well as study clinicians (MDs and NP) in weekly CAAM meetings and on an ongoing basis as needed.

2. If a subject has a diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder (PDD), 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 during the 12 weeks of study participation and/or prefers to begin with an experimental treatment for slowing and depression, he/she will be offered participation in the present study provided there is no suicidal ideation present. Based on the extant data supporting the efficacy of antidepressants for MDD and PDD, 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.

3. Next, trained raters (BA, RN, or SW) in CAAM will assess processing speed using the Digit Symbol test from the WAIS-III and the Trail-Making Test Part A. Digit Symbol or Trails A will be used as a selection criterion, with patients included in this study if they score **0.5 SD** below the age-adjusted norms on Digit Symbol or Trails A. 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 **of 0.5 standard deviations below age-adjusted norms.**

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) 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.

5. In the situation where a potential participant is taking medication and/or has a device to stabilize or manage a medical condition, the research physician will, without exception, contact the physician managing the condition to describe the possible research use of L-DOPA, to discuss any possible risks, and to obtain the managing physician's opinion as to whether the participant's condition and/or it's management is a contraindication to the research use of L-DOPA in this participant. This discussion and its outcome will be documented in the research chart.

6. Otherwise eligible subjects who are currently taking an ineffective antidepressant medication (i.e., the individual is symptomatic at a level meeting inclusion criteria) will be offered participation as above after a discussion of the risks, benefits, and alternatives. No patients will be taken off of effective antidepressant medications solely for the purpose of research. Should an individual taking an ineffective antidepressant medication wish to participate and sign consent, their psychiatric care will be taken over by a CAAM study clinician after a discussion with their prescribing physician. Such participants will be tapered off of the ineffective medication as per standard clinical practice (depending on the medication) and be followed closely in CAAM, likely through weekly visits. Should a participant be unable to tolerate the medication taper due to increasing depressive symptoms, they will be withdrawn from the study and entered into the 3 month open treatment period directly. Once participants are washed off of the medication they will proceed with the study assessment described in points 7-9 immediately below. Subjects must be off medication for 2 weeks prior to neuroimaging procedures and beginning the L-DOPA study medication.

7. We will assess episodic memory using the Wechsler Memory Scale Logical Memory Test I & II (119). Inclusion of this test will allow us to identify deficits in episodic memory functioning consistent with amnestic mild cognitive impairment (aMCI). Executive function will be assessed via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently (120-121). Domains of physical function assessed at baseline and Week 12 include the Short Physical Performance Battery (SPPB) (122), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change and the Pittsburgh Fatigability Scale (PFS) (123). The Falls Efficacy Scale-International will assess subjects' fear of falling (124-125), and weekly physical activity will be measured with the 7-Day Physical Activity Recall questionnaire (126). The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability, and the self-report Measure of Everyday Cognition (ECog) will measure change in functioning relevant to 7 specific cognitive domains (127). These measures will be repeated at study endpoint.

8. Baseline aerobic capacity of all subjects will be assessed prior to randomization in the Behavioral Medicine Division at CUMC (Co-Inv Sloan) using a sub-maximal stress that correlated highly with the results of a full-maximal stress test (128). The tests will be conducted by Vincenzo Lauriola, who has a master's degree in exercise physiology and is a PhD candidate in the exercise physiology program at Teachers College. The RA coaches are all college graduates who have been trained by Vincenzo. This is the arrangement used for many of the Behavioral Medicine Division's IRB approved exercise studies. This test comprises walking on a treadmill at progressively increasing rates. If the participant's heart rate (HR) at the end of a stage, measured by telemetry (Model RS400, Polar Electro OY, Finland) is less than 85% of that

predicted by the maximal heart rate equation (220-age), the participant will complete the next stage. Each participant's V̇O2max is estimated from the exercise HR at the end of the test according to established equations, and the results are used to establish target HR for the 12-week training period. Following the 12-week treatment program, these procedures will be repeated to determine change in aerobic capacity.

9. To minimize any risks of COVID transmission during assessments in Dr. Sloan's Laboratory, all NYSPI and Columbia safety procedures will be followed, including the pre-screening of participants for COVID symptoms prior to their appointments and screening on the day of appointments. All participants will be required to wear a face covering when they come on site. The minimum number of staff necessary to conduct the testing in the Sloan Lab will be present, and these staff will be wearing N95 masks and face shields during the entire time the participant is onsite. Participants will not wear face coverings during the submaximal exercise tests at baseline and endpoint. We will minimize the risk of COVID transmission in three ways. First, no more than one subject per day will be assessed in the Sloan Lab, which will allow time for sufficient air turnover in the space. Second, we have consulted with Dr. Rochelle Goldsmith, Director of the Exercise Physiology Laboratory at Columbia, who has researched the best methods to disinfect the air in exercise laboratories. Following her recommendation (which mirrors procedures currently being used at the Mayo Clinics), will purchase a Model SS-400 portable air cleaner from Sentry Air Systems (please see specs for this device in attachments). This industrial grade fume extractor will run during the time participants are in the Sloan Lab and for 3 hours afterward. Third, we will follow relevant procedures for wiping down surfaces and minimizing infection risk as implemented in the dentistry department at Columbia (please see summary of procedures that we have obtained from the Dentistry Dept. attached).

10. Finally, additional clinical measures include the Antidepressant History Form (ATHF) and the Inventory of Depressive Symptoms--Self Report (IDS-SR).

MRI Scanning

10. All of the N=80 Depressed subjects will undergo MRI scanning on NYSPI's 3T GE Premier system before and after 12 weeks of treatment with L-DOPA and/or Exercise. For structural imaging, we will acquire a high resolution 3D T1 weighed image using a MPRAGE sequence with TI=1060ms, flip angle=8º, voxel size=1x1x1mm, and 208 contiguous slices (6 min). For task-based fMRI, we will use a multi-band (or Simultaneous Multi-Slice) EPI sequence with multiband acceleration factor 6, TE/TR=30/800ms, flip angle=52°, matrix=90x90, 60 slices, and voxel size=2.4x2.4x2.4 mm (EBDM 2 runs at 9 min/run; VRMN 2 runs at 11 min/run). Thus, total scan time will be approximately 1 hour. All scanning RAs have undergone MRI safety training and are experienced with the preparation of research subjects in the MRI scanner. RAs have been trained in the performance of fMRI tasks via didactics with the Principal Investigator and ongoing supervision provided in biweekly scientific meetings of the larger Columbia/Vanderbilt neuroimaging team.

11. As previously implemented in Dr. Michael Treadway's Lab (Mentor and collaborator on this K24 project), the Effort-based Decision Making (EBDM) task requires participants to make binary choices given information about the dollar amount of a reward and the required amount of physical effort to obtain that reward. Individuals opt to receive $1.00 for no work or to complete an effortful task (button pressing) for a larger reward of varying amounts (32). In the Virtual Reality Maze Navigation (VRMN) task, participants undertake first-person navigation through a single-path virtual maze in pursuit of monetary rewards. Trial

types include a High-Effort condition requiring repeated button presses to advance through the maze, a Low-Effort condition allowing participants to advance through the maze by simply holding down buttons, a Passive-Motion condition in which participants view moving through the maze without making any action, and a No-Motion condition where participants wait for the approximate duration of the maze and are then teleported to the goal (33). Each trial is associated with one of 4 reward magnitudes from which an amount is randomly selected.

12. For all of 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 approximately 60 minutes, including time for positioning subjects in the scanner. 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. 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, Brewster, Roose, or Broft, present.

Clinical treatment

13. Participants will be randomized to receive either active L-DOPA or matching placebo as well as Exercise or a stretching/toning control based on a block design using R Statistical Software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Participants, physicians and research staff will be blinded to L-DOPA vs. placebo group assignment but given the nature of the intervention will be aware of assignment to Exercise or stretching/toning control. The NYSPI Pharmacy will maintain the randomization key for each site and can unblind individual subjects in emergencies. The medication blind will not be broken until study completion. Following the 12 week duration trial participants will have repeat MRI scanning and cognitive/behavioral testing.

14. Subjects will take active or placebo tablets three times daily (9am, 1pm, 5pm). Those assigned to L-DOPA will begin with a Week 1 L-DOPA daily dosage of 150mg, or 1.5 25mg carbidopa/100mg levodopa tablets at 9am and placebo tablets at 1pm and 5pm. In Week 2 the L-DOPA daily dose will increase to 300mg (1.5 25mg carbidopa/100mg levodopa tablets at 9am and 5pm, with placebo at 1pm), followed by a Week 3 L-DOPA daily dose of 450mg (1.5 25mg carbidopa/100mg levodopa tablets three times daily). This dose will then be continued for the remainder of the 12 week duration study. Subjects assigned to placebo will take 1.5 placebo tablets three times daily for three weeks. Individuals will be instructed to maintain the same timing of doses throughout the study. Individuals unable to tolerate an increased dose will have their dosage reduced to the maximum previously tolerated dose.

15. At each weekly visit, subjects will meet with a psychiatrist or study physician. 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).

LDOPA 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.

16. After a training visit in Dr. Sloan's laboratory, during which subjects are taught the proper use of the equipment, how to monitor HR, and maintain training logs, subjects assigned to Exercise will complete 4 training sessions per week at their homes on the equipment of their choosing (either an Exerpeutic 900XL Extended Capacity Recumbent Bike with Pulse or Sunny Folding Climbing Stepper). Exercise equipment will be provided to participants at no cost to them by the study. Proper home assembly and initial working of the exercise equipment will be verified with the participant, including visually through the use of teleconferencing, prior to the initiation of the treatment portion of the study. Subjects will exercise individually at their home on a program set each week by Dr. Sloan and the research assistant (RA) coach assigned to him/him, who will work with the patient to ensure they train according to the program at the appropriate level of intensity. Additionally, we will gather information on support people available at home for each participant and invite them, if the participant so desires and grants permission, to be involved with the exercise regimen and help ensure that the participant is following the proper regimen. Adherence to the training programs is documented by weekly logs and data from HR monitors used during each training session. Subjects are contacted on a weekly basis by their coaches to monitor their progress. If the performance of participants in the aerobic training condition falls out of range, they will be contacted more frequently until they return to prescribed training levels. All training sessions will comprise 10-15 minutes of warm-up and cool down and 30-40 minutes of workout. Subjects will select from a series of aerobic activities and for Weeks 1-2 will train at 55-65 percent of maximum HR as established during their qualifying CPET. In Weeks 3-4, they will increase exercise intensity to 65-75 percent of maximum HR, and in Weeks 5-12 they will train at 75 percent of maximum HR. To exercise at their target HR, participants will wear a Polar Electro model s610i heart rate monitor during each training session, which provides a digital display of HR and recorded HR throughout the training session. At the end of each session, participants upload their training data so that coaches may verify their compliance with exercise program.

17. Subjects assigned to the Exercise control condition will participate in a prescribed stretching and toning regimen. Under the guidance of their trainers and coaches, participants in this condition will engage in a series of stretches and toning exercises designed to promote flexibility and improve core strength. All upper body and lower body major muscle groups will be included. Core strengthening exercises will include abdominal, back, and pelvic muscles. Like subjects in the exercise condition, they will wear Polar HR monitors to assure that they will not improve in aerobic capacity.

Assessments

18. Subjects are expected to have a screening/evaluation visit, Week 0/pre-treatment MRI scanning day, and monitoring visits at Weeks 2, 4, 8, and 12. Participants will have telephone contacts with study physician and research staff at Weeks 6 and 10 and will be offered more frequent in-person visits if indicated. At each contact, depression severity is measured using the MADRS and adverse events are assessed. The presence of any suicidal thoughts will be assessed at every contact. Vital signs (weight, heart rate, blood pressure) will also be measured.

19. Cognitive assessments will be performed at baseline and Week 12. Gait will be assessed at baseline and Week 12 with both single and dual tasks (ST, DT) using the GaitRite system (Sparta, NJ), which assesses gait parameters in real time (gait speed, cadence, stride length). For the ST (primary gait outcome), participants are instructed to walk at their usual or normal speed over the 15' walking course. For the DT (secondary outcome), participants 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 participants are instructed to walk at their usual pace while simultaneously performing serial subtractions by threes starting at 100.

20. Other clinical assessments collected each visit include the CGI Severity and Improvement (provide a clinical assessment of subjects at each visit and help maintain safety by identifying clinical worsening), Inventory of Depressive Symptoms—Self Report (IDS-SR) (provide a self-report measure for depressive symptoms), Structured Pill Count Interview (to assess study medication compliance), and the Treatment Emergent Side Effect Scale (TESS) to monitor side effects associated with medication treatment. We will utilize the Unified Parkinson's Disease Rating Scale (UPDRS) to identify any dyskinesias caused by LDOPA, although based on our previous studies we are not expecting to observe motor side effects with the L-DOPA doses and duration being used in this study.

End of study procedures

21. Following the 12 week duration study, endpoint assessments of psychiatric symptoms, cognition, and motor functioning will be made and post-treatment MRI will be conducted. Once post-treatment research procedures are completed, patients will enter 3 month open treatment period provided free of charge as described below.

Attestations

As both Area Leader and Principal Ivestigator of this study, I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

•Infection Control/PPE – Guidelines
•Research participants will only come on-site if absolutely necessary (e.g., for procedures).
•No volunteers/externs on-site.
•Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building. •COVID/COVID-like symptoms in participants will be reported to IRB via PRISM.

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 and/or Exercise 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 (in any aspect, including motoric function or depressive symptoms) as defined by a 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 from all depressed subjects at baseline. General medical tests will be performed as safety screens for Depressed subjects, such as CBC, Chem 7, LFTs, TSH, cholesterol, B12, and folate.

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): this semi-structured diagnostic interview will allow determination of whether subjects meet selection criteria.

Cumulative Illness Rating Scale-Geriatric (CIRS-G) 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.

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.

Montgomery Asberg Depression Rating Scale: standard measure of depression severity that measures changes in depressive symptoms.

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): 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): 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.

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

We will assess episodic memory using the Wechsler Memory Scale Logical Memory Test I & II. Inclusion of this test will allow us to identify deficits in episodic memory functioning consistent with amnestic mild cognitive impairment (aMCI).

Executive function will be assessed via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently.

Domains of physical function assessed at baseline and Week 12 include the Short Physical Performance Battery (SPPB), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change and the Pittsburgh Fatigability Scale (PFS).

The Falls Efficacy Scale-International will assess subjects' fear of falling, and weekly physical activity will be measured with the 7-Day Physical Activity Recall questionnaire.

The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability, and the self-report Measure of Everyday Cognition (ECog) will measure change in functioning relevant to 7 specific cognitive domains.
Gait will be assessed as both a single and dual task (ST, DT) using the GaitRite system (Sparta, NJ), which assesses gait parameters in real time (gait speed, cadence, stride length). For the ST, patients are instructed to walk at their usual or normal speed over the 15' 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. Patients will start and end at a point 2 meters from the GaitRite mat to eliminate acceleration and deceleration effects. Each ST and DT will be assessed two times with the average used in the analyses. The ST assessment of walking speed in m/s will be the primary gait outcome measure for this study.

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
Select the number of drugs used in this study
1

Drug #1

Name of the drug
carbidopa/levodopa
Manufacturer and other information
We will be using generic carbidopa/levodopa (L-DOPA) 25/100 tablets in this study. We will purchase them through the New York State Psychiatric Institute (NYSPI) pharmacy, using the generic manufacturer recommended. 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.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
The proposed use of L-DOPA is below or within the usual range, and we are not seeking an FDA indication for its use in this condition. Our prior communications with Frank Lutterodt (Senior Regulatory Health Project Manager) in connection with IRBs 7270, 7733, and 7976 have confirmed this.

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 not proven, there will be a 12-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 12 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 L-DOPA 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. L-DOPA Side Effects: Side effects will be assessed at each planned visit and as 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. In healthy controls, the only available studies are single-dose experiments, in which the sole reported side effect has been nausea. No serious adverse events or side effects due to an effect on the nigrostriatal dopamine system have been observed in these studies. There are many studies of chronic L-DOPA administration for the treatment of Parkinson's disease (PD), since this drug has been used since the 1960s. Perhaps the most relevant study was a clinical trial published in the New England Journal of Medicine in 2004. In this study 361 patients with PD were randomized to receive 150mg, 300mg, or 600mg L-DOPA for 40 weeks. In the 150mg and 300mg L-DOPA treatment groups, the only side effects observed that were different from placebo were headache and nausea. No dyskinesias or other neuropsychiatric effects were observed that were greater than the placebo group, and this study lasted 40 weeks as opposed to 4 weeks (3 week dose titration, with 1 week taper) in this study.

In our preliminary work at NYSPI (IRB 7270), a series of depressed older adult outpatients (N=36 subjects aged 75.3 ± 7.5 years, 44.4% male) were treated with open L-DOPA for three weeks (one week each of 150mg, 300mg, and 450mg). The overall drop-out rate was 8.3%, with 5.6% subjects dropping out due to adverse effects of L-DOPA. Thirty of the total N=36 analyzed subjects reached the final L-DOPA dose of 450mg. Nausea was the most frequently reported treatment-emergent side effect, and the frequency of subjects reporting nausea decreased over the course of the trial, from 19.4% of subjects reported for 150mg

LDOPA, to 17.1% for 300mg L-DOPA, and 9.1% for 450mg L-DOPA. The only other side effects reported by more than one subject were insomnia and headache. The emergence of dyskinesias during L-DOPA treatment was evaluated using items 32 and 33 of the UPDRS, and no significant change from baseline was observed on either these items. Mean scores were 0.0 at Week 3 for both items. No significant adverse events (SAEs) attributable to study medication were noted during the project. Since we found the greatest effects on processing/gait speed at 450mg without no decrease in tolerability relative to 150mg and 300mg doses, we selected 450mg as the target dose for the mechanistic probe in the present study. In our pilot work, L-DOPA 450mg was associated with increased dopaminergic availability in the sensorimotor and associative striatum.

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: A neuroleptic malignant-like syndrome (fever, akinetic crisis, rigidity, autonomic disturbances) has been reported following withdrawal of levodopa in patients with PD.

2. Exercise Intervention: Another potential risk is associated with the exercise trial in older patients, and specifically in adults with LLD and psychomotor slowing. Individuals can experience physical injury, muscle soreness, and fatigue due to assessments of balance and gait and increased physical activity due to exercise. Most will be self-limiting, though it is possible for more serious injuries to occur including broken bones or joint dysfunction. Although an exercise-induced cardiovascular event is a potential risk, risk is minimized by excluding patients with acute and unstable medical illnesses (e.g., severe aortic stenosis, or severe congestive heart failure) and receiving verbal approval from the patient's PMD prior to randomization. All baseline and endpoint assessment sessions will be conducted in the Behavioral Medicine Division here at Columbia University Medical Center. Center staff is trained in CPR and the facility is equipped with an automated external defibrillator. In the event of a medical emergency, a team from the hospital responds immediately. While we respect these risks associated with exercise, steps have been taken to mitigate these risks:

a) Evaluation: Patients will undergo a medical and psychiatric assessment during their initial evaluation at CAAM.

b) Pre-enrollment: Communication between the patients' PMD and the study psychiatrist prior to study enrollment and throughout the study will allow for any safety concerns from the PMD or from the research staff to be discussed and addressed in a timely manner.

c) Exercise Protocol: The design of the intervention itself minimizes risk of physical injury. It is a progressive, sequential design with built-in parameters to assess the progress each patient is making prior to graduating to the next component of the exercise intervention. The exercise sessions are carefully designed each week by the study team and communicated to the patient at the start of each week. These designs will include warm-up, stretching, and cool-down components utilized to minimize injuries. Stretching exercises

will consist of arm circles, neck rotations, toe reach, gluteal stretches, lateral leg swings, Achilles stretch and ankle rolls. If a patient develops a significant illness requiring mobility restriction, surgery or hospitalization, the PI, Dr. Sloan (who is experienced in the conduction of exercise protocols), and the study psychiatrist will be informed and will contact the participant's PMD to gauge as a team the preferred time for his/her return to the exercise program. If adverse events develop during participation in the exercise intervention, the adverse event will be reported and a one-week hiatus will be enforced. During this time the patient will perform gentle, static stretching exercises and communicate his/her condition with the PI, Dr. Sloan, study psychiatrist, and/or PMD, and, in accordance with this conference, will be slowly reintroduced to the exercise program following the hiatus. Every precaution will be taken to ensure each patient's comfort, safety and security including the provision of fluids and rest as needed. For those individuals who are extremely deconditioned, frequent rest periods and exercise in a seated position (stationary bike) will be offered.

3. Exercise training—Risk of Dropout: Virtually all exercise-training programs suffer from substantial attrition. Based on experience in several training programs and on the exercise literature, we have devised a series of activities that maximize participant retention. The activities that are included to improve adherence and monitor the safety of the patients throughout the 12-week protocol include:

a) Baseline Assessment and Training: Subjects will come to the Behavioral Medicine Division at the Columbia University Irving Medical Center (CUIMC) for baseline assessment. They will undergo an aerobic capacity assessment to determine the progressive nature of the exercise protocol they will undertake. During this period, subjects will be trained on the general safety issues in exercising, instruction and practice in the use of the heart rate monitor system and the exercise apparatus that they choose for their program.

b) Home-based exercise program: Given that both exercise interventions and research studies in depressed samples are met with issues of adherence, we determined that a home based exercise program with built-in monitoring would be ideal for this patient population and geographic location (given weather issues in the northeast in particular during the winter season, a home based program would allow for continued adherence without the risk of falls due to icy or snowy conditions). Currently, this model is being implemented for the treatment of individuals with social anxiety disorder at CUIMC on which Dr. Sloan is a Co-I.

c) Exercise Logs: Subjects will complete detailed logs of their activity during each exercise session. These logs will contain information on the date and duration of exercise training and the activities of each training session. These logs will be collected at CAAM during their weekly visits in the antidepressant medication portion of the trial and reviewed regularly to inform coaching phone calls.

d) HR Monitoring during all exercise sessions: Subjects will wear heart rate monitors that record HR throughout the session and upload the data into a cloud-based system. These data provide rigorous documentation of training intensity levels and determine the progressive nature of the subsequent exercise routines. These data are monitored by Dr. Sloan's lab, and the study research assistant and both the coaching phone calls and the following week's activities are devised based on these data and input from the patient.

e) Coach: An essential component of our training program is the research assistant coach assigned to each

participant after consent has been obtained. The research assistant coach is trained in several behavioral techniques. These include: phone contact two x per week (or more as needed), with email contact to acknowledge good attendance and HR compliance, or encourage improvement if needed; answer exercisers' reasons for noncompliance using positive suggestions and reframing to help the exerciser see feasible solutions for overcoming compliance obstacles, and setting obtainable goals that aim for improvement over time (e.g. exercise 2 times this week then aim for 3 times next week). The research assistant-coach is not responsible for teaching exercise techniques; Dr. Sloan and the staff at the Behavioral Medicine Division at CUIMC is responsible for communicating training and ongoing oversight of participants if needed for the study. Coaches will follow all subjects, letting them know when it is time to schedule testing sessions and begin training. The coaches also make motivation/reminder calls at a minimum two x per week. These calls are intended to "cheerlead" subjects through their exercise programs. They also are intended to inform subjects of any adherence issues (e.g., not exercising in their target heart rate range, not exercising frequently enough). Coaches will review exercise logs collected during the patients' visits to CAAM for antidepressant medication management and enter these data into the study database. We have found that the addition of coaches to our training programs substantially improves adherence.

f) Incentive: We offer an incentive for substantial adherence to the training: patients may keep both the exercise apparatus that they chose to use during the exercise training and the HR monitor. In past studies, virtually all of our subjects who completed the training sessions took advantage of this incentive.

g) Exercise Supervision: The entire program is monitored, with HR data and exercise logs monitored throughout the 12-week intervention and patients' physical health monitored during weekly visits to CAAM as part of the medication management component of the trial. This monitoring will help mitigate risk of injury. During the patient's weekly visit to CAAM, clinicians will be instructed to be vigilant for the emergence of "red flag" symptoms such as angina, shortness of breath, or hypotension. Participants will be instructed to discontinue exercise if they experience significant pain, weakness, or joint swelling during or after exercise.

4. Delay in Antidepressant Treatment Initiation: As specified in the above selection criteria, participants in this study will have a DSM 5 depressive disorder and MADRS $\geq$ 15, but current treatment with antidepressant medication is an exclusion criterion. Otherwise eligible subjects who are currently taking an ineffective antidepressant medication (i.e., the individual is symptomatic at a level meeting inclusion criteria) will be offered participation after a discussion of the risks, benefits, and alternatives. Those wishing to participate will undergo a medication washout following standard clinical practice and be closely followed by study clinicians until they are eligible to begin the study. The maximum duration of delay of treatment for depression with an agent of known efficacy will be 12 weeks. No patients will be taken off of effective antidepressant medications solely for the purpose of research, and patients will be withdrawn from the study and treated if clinically indicated and desired by the patient.

A number of precautions have been taken to safely maintain participants antidepressant-free for the duration of the proposed study. First, our selection criteria exclude individuals who are judged to be at high risk of suicide (MADRS suicide item > 4). Second, we have stringent criteria for early discontinuation and initiation of appropriate open clinical treatment. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening in the judgment of the study clinician; (3) a CGI-Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits, or (4) development of

significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated as clinically indicated. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. Finally, following the study, subjects are offered state-of-the-art clinical visits at no cost to them or their insurer for 3 months, although they will be responsible for the cost of any antidepressant medications.

5. 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.

6. L-DOPA treatment—End of Study Procedures: We will provide up to 3 months of additional free clinic visits following the end of this project to facilitate the return to clinical care. A non-study clinician in our research clinic will be given the data on each 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 options for the treatment of depression. Those who have benefited from the treatment and have not had significant side effects may elect to continue receiving L-DOPA 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.

7. Gait speed assessment: During the gait speed assessment and other physical performance measures, patients may feel unsteady and 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 (including the gait assessment, balance test, and chair stand, the latter two components of the Short Physical Performance Battery). Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

8. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical and laboratory information. PI 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.

9. MR scanner environments. The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although in our extensive past experience, subjects

generally have tolerated the procedures well. To protect against this risk, subjects will be acclimated to the MRI and its noise with training sessions in a mock scanner on the morning of the scan. Relaxation training will be used to help calm anxious subjects and to reduce motion. Frequent praise and reminders to remain still, along with an inflation pillow and taping of the subject's forehead, will help to acquire motion-free images. In the past dozen years, our group at Columbia/NYSPI has acquired superb, motion-free structural and functional scans in 100s of adults affected by a variety of neuropsychiatric illnesses. All subjects will be able to communicate directly with technologists and study staff to report any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately, and the subject will be removed from the scanner.

10. 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.

11. 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.

12. Risks of blood draw: When 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.

Describe procedures for minimizing risks

Most procedures for minimizing risks are discussed in the context of the risks themselves above. Additional procedures follow below:

1. 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.

2. 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.

3. 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.

4. 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.

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

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?
Yes, we have already received a Certificate of Confidentiality

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. Subjects may also experience physical functioning benefits from the aerobic exercise treatment or the stretching and toning control condition.

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.
All subjects who complete a screening visit will be reimbursed $35.

Each subject will be compensated for the time spent conducting the cognitive, psychiatric, and aerobic capacity assessments at both baseline and Week 12 ($100 each, totaling $200 per subject).

In addition, the subset of subjects undergoing neuroimaging procedures will receive an additional $50 per scan ($100 total).

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