Protocol Title:
Mechanisms of Antidepressant Non-Response in Late-Life Depression

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Protocol Number:
6836

Clinic:
Adult and Late Life Depression

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Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis 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.
Enrollment and research interventions have concluded. Data analysis is ongoing. Study recruitment met and exceeded expected enrollment (n=130), with one hundred thirty-eight subjects signing informed consent. The study progressed well, with neuropsychological testing, MRI scans, and other procedures tolerated well by participants. Overall, response and remission rates were consistent with antidepressant clinical trials in older adults. Many patients went on to receive follow-up treatment in CAAM and expressed appreciation for the high quality care we provide. Data has been well maintained and internally-monitored.

Overall Progress

Approved sample size

130
Total number of participants enrolled to date
138
Number of participants who have completed the study to date
99
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

130
Total number of participants enrolled to date
138
Number of participants who have completed the study to date
99
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Older adults with diagnosis of Major Depressive Disorder Total number of participants enrolled from this population:138

Gender, Racial and Ethnic Breakdown Gender
Male: 51
Female: 87

Race:
American Indian/Alaska Native: 0
Asian: 2
Black/African-American: 30
Native Hawaiian/Pacific Islander: 0
White: 85
More than one: 7
Don't Know: 11
Missing: 3

Ethnicity:
Not Hispanic/Latino: 112
Hipanic/Latino: 22
Missing: 4

Procedures

- ✓ Psychiatric Assessment
- ✓ Neuropsychological Evaluation
- ✓ Medication Trial
- ✓ Use of Placebo or Sham Treatment
- ✓ MRI
- ✓ Medication-Free Period or Treatment Washout

Population

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

- ✓ Adults
- ✓ Adults over 50
- ✓ Non-English Speaking Participants

Study Location

Indicate if the research is/will be conducted at any of the following

✓ NYSPI

Lay Summary of Proposed Research

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This project seeks to elucidate the mechanisms by which antidepressant medications have limited efficacy in

Late Life Depression (LLD) in order to develop new treatment interventions for this prevalent and disabling illness. We hypothesize that the presence of executive dysfunction (ED), which is common in depressed adults over 60, impairs the ability to form appropriate expectancies of improvement with antidepressant treatment. Greater expectancy has been shown to improve antidepressant treatment outcome and is hypothesized to be a primary mechanism of placebo effects. Moreover, white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are more prevalent in patients with LLD compared to healthy controls. It has been argued that WMH contribute to the pathogenesis of LLD with ED and decrease the efficacy of antidepressant medications by disrupting connections between prefrontal cortical (PFC) and subcortical structures. Vascular lesions to white matter tracts may also compromise the pathway by which expectancy-based placebo effects influence depressive symptoms. Expectancies reflect activation in PFC areas that may improve depressive symptoms by modulating the activity of subcortical regions subserving negative affective systems (i.e., amygdala) as well as those important in reward and hedonic capacity (nucleus accumbens and ventral striatum). Thus, LLD patients with ED and WMH may sustain a "double-hit" to their ability to experience placebo effects in antidepressant treatments: ED diminishes the ability to generate appropriate treatment expectancies, while WMH disrupt the physiologic pathways by which expectancies lead to improvement in depressive symptoms.

To determine whether decreased antidepressant medication response in LLD patients with ED and WMH is caused by a loss of expectancy effects, we will evaluate 130 outpatients with LLD at baseline to determine their degree of ED (interference score on Stroop Color-Word Test), WMH burden (severity score on Fazekas modified Coffey Rating Scale derived from anatomical MRI), and white matter tract integrity (using diffusion tensor imaging [DTI]). Building on work from my K23 Award, we will manipulate participants' expectancy of improvement in an 8-week duration antidepressant trial by randomizing them between open administration of escitalopram or duloxetine (i.e., high expectancy) and placebo-controlled administration of escitalopram or duloxetine (i.e., low expectancy). The difference in antidepressant response observed between open and placebo-controlled medication treatment is a measure of the expectancy contribution to outcome, which is substantial in younger depressed adults but we hypothesize will be diminished in LLD patients with ED and WMH.

Background, Significance and Rationale

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Major Depressive Disorder (MDD) is a leading cause of disability, morbidity, and mortality across the lifespan but poses a particularly severe public health problem in late life.19-20 MDD affects 3% of community-dwelling adults over 60 years old,2 and 15% of older adults living in the community have clinically significant depressive symptoms.3 Diagnosis with MDD increases an older adult's risk of disability by 67-73% over 6 year follow up,21 causes twice the functional impairment compared to those without MDD,22 increases the risk of mortality in patients with heart disease, and is associated with high rates of completed suicide in individuals over 65 (16.9/100,000 overall and 62/100,000 in white men).23-24 Late-life depression (LLD) is highly recurrent, can become chronic,25 and is often difficult to treat.1 Residual symptoms place patients at increased risk of suicide as well as cardiovascular morbidity and mortality.26-27

Available research on antidepressant non-response in older adults has focused on executive dysfunction

(ED) and white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI) scans as the variables prominently associated with poor treatment outcome. ED is common in older depressed patients5 and has been shown to predict poorer response to antidepressant medication and higher relapse rates during the continuation phase of treatment.28-29 Similarly, WMH are observed in the majority of older adults with MDD and are associated with a more chronic clinical course30 and poor response to antidepressants.31-32 To account for these data, the vascular depression model proposes that vascular lesions to deep white matter tracts disconnect prefrontal cortical (PFC) regions from striatal and limbic areas, disrupting reciprocal modulation between PFC and subcortical structures, and causing depressive symptoms as well as ED.9 It has been postulated that decreased observed antidepressant response in depressed patients with ED and WMH results from serotonergic medications being less efficacious in the setting of this structural brain pathology.

While proposing ED and WMH as predictors of non-response to antidepressant medication is useful prognostically, the vascular depression model does not provide a physiologic mechanism explaining non-response. The provision of such a mechanism would greatly advance our understanding of the pathogenesis of LLD as well as the biology of antidepressant response. It is not obvious why damage to frontostriatal tracts should block the effects of antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs). Their mechanisms of action appear to be related to salutary modulation of hyperactive limbic structures33 as well as stimulation of neurogenesis,34 which would not necessarily be affected by deep WMH. Additionally, SSRIs are effective for the prevention35 and acute treatment36 of post-stroke depression and improve functional recovery following stroke.37 If SSRIs are effective in these contexts, it is unclear why they should also not be effective in treating LLD with ED and WMH. As has been the case with other developments in the history of psychopharmacology (e.g., understanding reserpine-induced depression leading to drugs targeting monoaminergic neurotransmitter systems), it is to be hoped that identifying the mechanism of antidepressant non-response in LLD would yield treatments based on rational designs targeting the pathophysiology.

This project is designed to test the hypothesis that antidepressant response is lower in LLD patients with ED and WMH due to a loss of the component of medication response attributable to patient expectancy. Using a method of studying expectancy-based placebo effects emerging from my K23 Career Development Award,1,16,38 we will first assess participants at baseline using a neuropsychological test battery, anatomical MRI, and diffusion tensor imaging (DTI). Next, participants' expectancy of improvement will be manipulated by randomizing them to different probabilities of receiving the same antidepressant medication. The high expectancy condition is open escitalopram (i.e., 100% chance of receiving active medication), while the low expectancy condition is placebo-controlled administration of escitalopram (which participants believe represents 50% chance of receiving active medication). The difference in antidepressant response observed between the open and placebo-controlled medication treatments is a measure of the expectancy contribution to outcome, which is substantial in younger depressed adults but we hypothesize will be diminished in older patients with ED and/or WMH.

The finding that antidepressant non-response in LLD is caused by a disruption in expectancy effects would have several significant implications. Most importantly, understanding antidepressant non-response in LLD at the level of mechanism may permit the development of novel treatment interventions for patients with continued symptoms. For example, methods may be developed to restore the expectancy component of medication response through specific cognitive or manualized psychoeducational interventions aimed at

enhancing patients' expectation of improvement with antidepressant treatment. Pairing such interventions with inexpensive and widely available first-line antidepressant medications (i.e., SSRIs) may be a safe, feasible, and effective way to enhance treatment response. More speculatively, somatic treatments aimed at promoting prefrontal-limbic and prefrontal-striatal connectivity may be promising therapeutic avenues to explore. Such treatments might include drugs that augment neurotransmitters supporting frontostriatal circuitry (e.g., dopamine, acetylcholine) or transcranial magnetic stimulation (TMS).

Specific Aims and Hypotheses

Specific Aims and Hypotheses
This project seeks to elucidate the mechanisms by which antidepressant medications have limited efficacy in Late Life Depression (LLD)1 in order to develop new treatment interventions for this prevalent and disabling illness.2-3 We hypothesize that the presence of executive dysfunction (ED), which is common in depressed adults over 60,4 impairs the ability to form appropriate expectancies of improvement with antidepressant treatment. Greater expectancy has been shown to improve antidepressant treatment outcome and is hypothesized to be a primary mechanism of placebo effects.5-7 Moreover, white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are more prevalent in patients with LLD compared to age-matched healthy controls.8 It has been argued that WMH contribute to the pathogenesis of LLD with ED and decrease the efficacy of antidepressant medications by disrupting connections between prefrontal cortical (PFC) and subcortical structures.9-10 Vascular lesions to white matter tracts may also compromise the pathway by which expectancy-based placebo effects influence depressive symptoms. Expectancies reflect activation in PFC areas that may improve depressive symptoms by modulating the activity of subcortical regions subserving negative affective systems (i.e., amygdala)11-12 as well as those important in reward and hedonic capacity (nucleus accumbens and ventral striatum).13-14 Thus, LLD patients with ED and WMH may sustain a "double-hit" to their ability to experience placebo effects in antidepressant treatments: ED diminishes the ability to generate appropriate treatment expectancies, while WMH disrupt the physiologic pathways by which expectancies lead to improvement in depressive symptoms.

Consistent with the above model, cognitively intact patients with LLD appear to experience large expectancy effects during antidepressant treatment. We have shown that LLD patients enrolled in comparator-type studies, who are assured of receiving active medication for their condition, have medication response rates nearly double those of LLD patients enrolled in placebo-controlled studies, who are aware they may be receiving placebo.1 However, the ability to generate expectancy effects appears to be attenuated in LLD patients with significant WMH: we found in analyses of a large antidepressant trial for LLD that more severe WMH was associated with decreased response to placebo.15 In addition, a prospective study conducted preliminary to this application randomized depressed patients to receive the same antidepressant medication in "high expectancy" vs. "low expectancy" experimental conditions.16 Randomization to the high as opposed to low expectancy condition resulted in increased expectancy of improvement and greater change in depressive symptoms over 8 weeks for patients < 60 years old. This was not true for patients ≥ 60 years old, who experienced little expectancy change and no treatment benefit in the high vs. low expectancy conditions.

To determine whether decreased antidepressant medication response in LLD patients with ED and WMH is

caused by a loss of expectancy effects, we will evaluate 130 outpatients with LLD at baseline to determine their degree of ED (interference score on Stroop Color-Word Test17), WMH burden (severity score on Fazekas modified Coffey Rating Scale18 derived from anatomical MRI), and white matter tract integrity (using diffusion tensor imaging [DTI]). Building on work from my K23 Award, we will manipulate participants' expectancy of improvement in an 8-week duration antidepressant trial by randomizing them between open administration of escitalopram or duloxetine (i.e., high expectancy) and placebo-controlled administration of escitalopram or duloxetine (i.e., low expectancy). The difference in antidepressant response observed between open and placebo-controlled medication treatment is a measure of the expectancy contribution to outcome, which is substantial in younger depressed adults16 but we hypothesize will be diminished in LLD patients with ED and WMH.

Specific Aim 1: To determine whether ED and/or WMH moderate the difference in patient expectancy and antidepressant outcome between the open vs. placebo-controlled conditions. Hypothesis 1: Greater ED and WMH will be associated with smaller differences in expectancy and antidepressant outcome between conditions.

Specific Aim 2: To determine whether a loss of expectancy effects mediates the relationship between ED/WMH and poor antidepressant outcome. Hypothesis 2: ED and WMH will be associated with decreased change in depressive symptoms, and these associations will be mediated by a decreased contribution of expectancy to antidepressant outcome.

Exploratory Aim: To assess the integrity of frontostriatal and frontolimbic white matter tracts using DTI and explore whether specific damage to these pathways is associated with diminished expectancy effects in patients with LLD.

Substantiating this model would provide a mechanism explaining how ED and WMH predict non-response to antidepressant medications in LLD. Understanding the mechanisms of antidepressant non-response in LLD has the potential to yield treatments based on specific and rational designs that target the involved biological pathways. By combining inexpensive and widely available antidepressant medications with psychoeducational interventions or targeted psychotherapies to enhance expectancy, it may be possible to significantly improve antidepressant response rates in LLD patients.

Description of Subject Population

Sample #1

Specify subject population
N=130 outpatients with MDD
Number of completers required to accomplish study aims
90
Projected number of subjects who will be enrolled to obtain required number of completers
130
Age range of subject population

60-90

Gender, Racial and Ethnic Breakdown
Gender: We anticipate the sample will be composed of approximately 60% women and 40% men.

Racial/ethnic group: On the basis of previous depression studies conducted in the Adult and Late Life Depression Clinic, it is anticipated that the sample will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects.
Description of subject population
The proposed study will enroll 130 outpatients who are (1) men and women aged 60-90 years, (2) diagnosis with nonpsychotic Diagnostic and Statistical Manual (DSM) IV MDD, (3) 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16**,** (4) willing to and capable of providing informed consent and complying with study procedures. Exclusion criteria are (1) current comorbid Axis I DSM IV disorder other than Nicotine Dependence, Adjustment Disorder, or Anxiety Disorder, (2) diagnosis of substance abuse or dependence (excluding Nicotine Dependence) within the past 12 months, (3) history of psychosis, psychotic disorder, mania, or bipolar disorder, (4) diagnosis of probable Alzheimer's Disease, Vascular Dementia, or Parkinson's Disease, (5) MMSE < 24, (6) HRSD suicide item > 2 or Clinical Global Impressions (CGI)-Severity88 score of 7 at baseline, (7) history of allergic or adverse reaction to escitalopram and duloxetine, or non-response to adequate trial of escitalopram (at least 4 weeks at dose of 20mg) and duloxetine (at least 4 weeks at dose of 60mg) during the current episode, (8) current treatment with psychotherapy, antidepressants, antipsychotics, or mood stabilizers, (9) having contraindication to MRI scanning (such as metal in body) or unable to tolerate the scanning procedures (i.e., severe obesity, claustrophobia) **(**for subjects undergoing MRI scanning only**)**, and (10) acute, severe, or unstable medical or neurological illness.

Recruitment Procedures

Describe settings where recruitment will occur
Subjects will be recruited through radio and newspaper advertisements and referrals from other physicians.
How and by whom will subjects be approached and/or recruited?
Individuals presenting to the Adult and Late Life Depression Research Clinic (ALLDRC) are evaluated under IRB #7284R, "Evaluation at the Adult and Late Life Depression Center." Following this evaluation, one of the study psychiatrists authorized to obtain informed consent will discuss study participation with subjects.
How will the study be advertised/publicized?
Newspaper and radio advertisements, flyers posted around CPMC, physician referrals.
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
NCT01931202

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Subjects who meet criteria for this and other protocols in the ALLDC can participate in both protocols concurrently. These protocols are listed below:

-PHYSICAL AND MENTAL FATIGABILITY IN LATE LIFE CLINICAL POPULATIONS (PI Brown) - IRB #7360
-MITOCHONDRIAL FUNCTION, FATIGUE, AND DEPRESSION IN LATER LIFE (PI Brown) IRB #7379

The consent form for this study is separate from those for the above protocols. Participation in this study will not affect their participation in the other study. This is made explicit in the consent form for this study.

Inclusion/Exclusion Criteria

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

Inclusion criterion	**Method of ascertainment**
(1) men and women aged 60-90 years	Clinical interview
(2) diagnosis with nonpsychotic Diagnostic and Statistical Manual (DSM) IV MDD	Clinical interview, SCID
(3) 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16	HRSD by trained rater
(4) willing to and capable of providing informed consent and complying with study procedures	Clinical interview

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

Exclusion criterion	Method of ascertainment
(1) current comorbid Axis I DSM IV disorder other than Nicotine Dependence, Adjustment Disorder, or Anxiety Disorder	Clinical interview, SCID

(2) diagnosis of substance abuse or dependence (excluding Nicotine Dependence) within the past 12 months	Clinical interview, SCID
(3) history of psychosis, psychotic disorder, mania, or bipolar disorder	Clinical interview, SCID
(4) diagnosis of probable Alzheimer's Disease, Vascular Dementia, or Parkinson's Disease	Clinical interview
(5) MMSE < 24	MMSE
(6) HRSD suicide item > 2 or Clinical Global Impressions (CGI)-Severity score of 6 or greater at baseline	HRSD by trained rater, CGI by study physician
(7) history of allergic or adverse reaction to escitalopram and duloxetine, or non-response to adequate trial of escitalopram (at least 4 weeks at dose of 20mg) and duloxetine (at least 4 weeks at dose of 60mg) during the current episode	Clinical interview
(8) current treatment with psychotherapy, antidepressants, antipsychotics, or mood stabilizers	Clinical interview
(9) having contraindication to MRI scanning (such as metal in body) or unable to tolerate the scanning procedures (i.e., severe obesity, claustrophobia) (for subjects undergoing MRI scanning only)	MRI safety screening form, Clinical interview
(10) acute, severe, or unstable medical or neurological illness	Clinical interview, blood tests, physical exam

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 #
7284R
Describe Study Consent Procedures
When a patient arrives to be evaluated at the ALLDC, they must first sign the ALLDC evaluation consent form (IRB #7284R) and HIPAA consent form. The clinic coordinator or an ALLDC research assistant will then do the 30-item Mini-Mental State Exam to get a general idea of the patient's global cognitive performance (this is especially important in older patients who may be experiencing cognitive/memory difficulties in addition to depression). The patient is then seen by one of the ALLDC psychiatrists. Following the MD evaluation, the doctor may ask for a SCID (Structured Clinical Interview for the DSM), a structured diagnostic interview, and HAM-D (Hamilton Rating Scale for Depression) to be performed by a qualified rater (Nancy Turret or trained research assistant). Based on the information from the MD evaluation, HAM-D score, and SCID diagnosis(es), the MD will decide if the patient is eligible for any of the ALLDC research protocols.
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

Overview

The proposed 8-week antidepressant clinical trial design has been used to successfully manipulate patient expectancy and influence antidepressant outcome in pilot studies--the proposed design is nearly identical to that approved under IRB #6038. At baseline, subjects will be evaluated, and eligible individuals will be invited to participate in the study. Those signing informed consent will have physiologic tests conducted and will be scheduled for baseline neuropsychological testing and MRI scanning. Following baseline testing,

subjects will return for a Week 0 visit when continued symptoms will be confirmed and medication will be distributed, after which they will return for 8 weekly visits. Psychological assessments performed on study participants by a psychiatrist may also be performed by medical psychiatry interns (PGY-1) who come to our clinic for 4-week rotations. All medical interns will have completed NYSPI-specific CITI training for human subjects research (specifically the biomed or social/behavioral course). The interns will be supervised by our clinical team, which consists of Steven Roose, MD; Bret Rutherford, MD; Allegra Broft, MD; and Patrick Brown, PhD.

Evaluation and Screening

1. Patients will first undergo an initial evaluation comprising a psychiatric interview (MD), Mini Mental Status Exam (MMSE), as well as Structured Clinical Interview Diagnostic (SCID IV) and Hamilton Rating Scale for Depression (HRSD) by trained raters.
2. All potentially eligible subjects will complete a screening questionnaire that includes questions regarding the presence of ferromagnetic implants. If the subject has any metallic implants (i.e. metal heart valve, aortic clips, etc.) that are unsuitable for the scanner, that subject will not be offered MRI scanning in this study. Further screening will be done by New York State Psychiatric Institute – Dept. of Psychiatry MRI Metal Screening Questionnaire. This is a 38-item questionnaire that was developed by Dr. Peterson (as Director of the MRI Unit) will be administered to every subject before they enter the MRI scanner. This questionnaire asks specifically about metallic implants and past experiences with metal to further ascertain any possible risks the person may incur by entering the scanner. If any metallic implants are detected that are unsuitable for the scanner, the subject will not undergo MRI scanning. Subjects who are otherwise eligible for the study and wish to participate will be offered participation in the clinical trial portion of the study only and will not have an MRI scan.
3. The evaluating psychiatrist will review the consent form with eligible patients and invite them to participate.
4. Patients who sign the consent form will complete the remainder of the baseline evaluation, including further paper measures, urine tests, blood tests, physical exam, and electrocardiogram (EKG) (RN or qualified research assistant). Lab results will be available to patients, should they request them.

MRI scanning

1. Patients will be scheduled for their MRI scan and neuropsychological assessment immediately after baseline assessment and prior to the first administration of study medication. It is possible that treatment may be delayed up to 1 week total due to scheduling these assessments, though we will make every effort not to delay treatment.
2. For the MRI procedures, the subject will be instructed to lie as still as possible within the magnet for approximately 90 minutes. When we position a subject in the scanner, head movement will be minimized through: (a) instructions to the participant; and (b) packing the head inside the head coil with a system of foam padding and pillows that we have found is well-tolerated by the participants, yet limits movement. All precautions and protections will be given to the participant to ensure that they are as safe and comfortable as possible. For the participant's comfort within the scanner, they will lie on a padded table with a pillow to rest their heads on. A blanket will also be provided to keep subjects warm during the procedure.
3. If the participant appears nervous or anxious, a trained member of the clinical staff will remain with them inside the scanning suite for the duration of the scan. The participant will be given a button box to terminate

the scan at any time. If they push the button, they will be removed from the scanner immediately All of the MRI procedures will be conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. Conducting these procedures will be an accredited Magnetic Resonance Technologist (B.M.R.) and a member of the research staff (Bachelor's Level or Higher) trained in the acquisition of MR images by Dr. Peterson, as well as in procedures for testing human subjects.
4. Although our MRI Scans are for research purposes, a radiologist will perform a clinical reading on every MRI within 1 month of scanning; if anything clinically significant is found, Dr. Rutherford will be notified immediately and he will provide an appropriate clinical referral to the participant.
5. 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, Dual FSE (Fast Spin Echo), and DTI (Diffusion Tensor Image) scans. While scanning parameters may change slightly, power-monitoring software on the scanner will ensure total energy delivered to the subject will remain within FDA guidelines. Specifically, the specific absorption rate (SAR) will be not greater than: (1) 4 W/kg averaged over the whole body for any period of 15 minutes; (2) 3 W/kg averaged over the head for any period of 10 minutes; (3) 8 W/kg in any gram of tissue in the head or torso; (4) 12 W/kg in any gram of tissue in the extremities, for any period of 5 minutes. These safety precautions are built into the MRI hardware, and are standard with every system.
6. We will rate the severity of White matter hyperintensities (WMH) on axial T2 FLAIR images using the Fazekas modified Coffey Rating Scale, which has been used extensively in vascular depression research. DWMH are scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent areas); subcortical gray matter HIs (basal ganglia) are scored as 0 (absent), 1 (punctate), 2 (multipunctate), and 3 (diffuse); periventricular HIs are scored as 0 (absent), 1 (caps), 2 (smooth halo), and 3 (irregular and extending into the deep white matter). Our primary measure of WMH burden will be DWMH score, which has been used to establish the only empirically validated diagnostic criteria for vascular depression.
7. Regarding DTI, we will acquire the baseline image B0 and the diffusion weighted images (DWI) in 25 directions. To isolate brain from non-brain tissue, we will apply the DTI software in the FSL analytic package (Analysis Group, FMRIB, Oxford, UK) to the B0 image and use the isolated brain as a mask to define the brain in DWIs. The images will be corrected for eddy current distortions, and then we will fit a diffusion tensor model to the DWI data at each voxel. The tensor model yields a voxel-wise map of 1st/2nd/3rd eigenvectors and eigenvalues, fractional anisotropy (FA), and mean diffusivity across the entire brain. The DT images for all participants will be coregistered by applying affine transformation to a template brain using the B0 images, thereby permitting voxel-wise statistical analyses of the various DTI measures. In addition to the whole-brain voxel-wise statistical analyses, we will perform statistical analyses of the mean FA value within specified ROIs defined using regions of WMH in anatomical MR images for each participant. ROIs with significantly differing DTI measures will be associated with specific pathways in the brain by coregistering the template brain to a DTI atlas (LONI ICBM DTI atlas, cmrm.med.jhmi.edu), which parcellates the brain into 23 functionally meaningful anatomical regions, grouped by brainstem, projection fibers, association fibers, and commissural fibers (described in detail at cmrm.med.jhmi.edu). Finally, within the coordinate space of the template brain, we will perform diffusion tensor tractography from regions within prefrontal cortex to striatum and statistically analyze the various DTI measures at each voxel along these pathways. Statistically significant differences in the DTI measures along these pathways would indicate disruption of anatomical connectivity between regions in the prefrontal cortex and the striatum.

Neuropsychological testing

1. The baseline neuropsychological test battery assembled for this study meets five important criteria that we were striving to achieve (see Table 4): 1) it is short and well tolerated by the elderly (total administration time approximately 40 minutes), 2) it is a reasonably comprehensive assessment of executive functioning, 3) the measures are capable of tapping a range of abilities (minimizes floor and ceiling effects), 4) it comprises standard tests, and 5) it allows for reliable administration by trained technicians.
2. Neuropsychological testing will include assessment of global cognitive functioning, IQ, attention, memory, language, executive functions, reaction time, and visuospatial processing. The 30-item Mini-Mental State Examination (MMSE) will be used to measure general cognitive impairment. The Wechsler Test of Adult Reading (WTAR) will be used in conjunction with demographic variables to estimate IQ. Memory will be assessed using the Logical Memory Test (WMS III). We will use two standard measures to assess executive functioning. The Stroop Color Word Interference Test (Stroop) is a measure of attention, concentration, and behavioral inhibition under distracting conditions that is sensitive to frontal lobe dysfunction. The Mattis Dementia Rating Scale Initiation and Perseveration subtest (DRS I/P) measures a) verbal initiation and perseveration (e.g., naming supermarket items over 1 minute), b) performing alternating movements, and c) reproducing graphomotor designs (e.g., XOXO). Attention will be assessed using the wechler adult intelligence scale (WAIS-III) Digit Symbol Test.
3. NP testing is for research purposes only and the results of these tests will not be interpreted clinically or shared with the patient.

Clinical study

1. Patients will then be randomized to an Open Group or a Placebo Controlled Group (please see attached for flow chart).
a. Subjects in the Open Group will be informed: “You have been randomly assigned to the open group of the study. This means that there is a 100% chance you will receive the antidepressant medication escitalopram [or duloxetine] for the duration of the study. Escitalopram [or duloxetine] has been proven effective for the treatment of depression in patients like you. You will not be receiving any placebo pills for the duration of the study. While you are aware that you are receiving actual antidepressant medication and not placebo, some of the staff members seeing you do not know whether you are taking escitalopram [or duloxetine] or placebo. If it can be avoided, please do not reveal to anyone in the study what group you have been assigned to.” At the time of their entry into the study, patients will be started on escitalopram 10mg per day, which will be continued for four weeks. If at the end of that time patients do not meet remission criteria (HRSD < 11) or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose**,** the dose will be increased to 20mg escitalopram for the remainder of the study. Subjects who have previously not responded to or not tolerated escitalopram will be allowed to receive duloxetine. Subjects will receive duloxetine 30mg for 1 week, then if they do not meet remission criteria or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose, will increase to 60mg for 4 weeks, and then if they still do not meet remission criteria or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose, will increase to 90mg for final 3 weeks. The first choice is for subjects to receive escitalopram, and they will only receive duloxetine if they have previously failed or not tolerated escitalopram.
b. Subjects in the Placebo-controlled Group will be randomized unequally (6:1) to escitalopram [or duloxetine] vs placebo. They will be informed: “You have been randomly assigned to the placebo-controlled group of the study. This means that there is a chance you will receive the antidepressant

medication escitalopram [or duloxetine] for the duration of the study. Escitalopram [or duloxetine] has been proven effective for the treatment of depression in patients like you. There is also a chance you will receive placebo for the duration of the study. A placebo is a sugar pill that is not specifically effective for depression. Neither you, nor your doctors, will know whether you are receiving escitalopram [or duloxetine] or placebo. If it can be avoided, please do not reveal to anyone in the study what group you have been assigned to." Patients will receive 1 pill (10mg escitalopram or placebo) per day for four weeks. If at the end of that time patients do not meet remission criteria (HRSD < 11) or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose, the dose will be increased to 2 pills per day (20mg escitalopram or placebo) for the remainder of the study. Subjects who have previously not responded to or not tolerated escitalopram will be allowed to receive duloxetine. Subjects will receive 1 pill (duloxetine 30mg or placebo) for 1 week, then if they do not meet remission criteria or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose, will increase to 1 pill of 60mg duloxetine or placebo for 4 weeks. Then if they still do not meet remission criteria or the patient continues to report depressive symptoms, is tolerating the medication well, and wishes to try a higher dose, will increase to 2 pills (totaling 90mg duloxetine or placebo) for final 3 weeks. The first choice is for subjects to receive escitalopram, and they will only receive duloxetine if they have previously failed or not tolerated escitalopram.

2. Should a subject ask about the specific chances of being assigned to placebo or escitalopram [or duloxetine] in the Placebo Controlled Group, we will respond: "For the purpose of maintaining the study integrity, certain details of the study must be temporarily withheld from you. These details include your exact chances of receiving placebo or escitalopram [or duloxetine]. However, we can tell you that your chances of receiving placebo in this study are no greater than 50%. Also, following the conclusion of your participation in the study, we will provide you with the complete details of the study design if you so wish." This approach allows the patient sufficient information to judge whether they wish to continue participating in the study while ensuring that the data produced are informative. Of course, subjects may choose to withdraw informed consent and not participate in the study if they are not comfortable with this level of specificity.

3. Patients will return to the LLDRC for weekly visits, at which they will receive clinical management (MD) and complete assessment measures conducted by raters blinded to condition assignment. Weekly measures will include HRSD, Hamilton Anxiety Scale (HARS), Clinical Global Impressions (CGI)—Improvement, Credibility and Expectancy Scale (CES), and Quick Inventory for Depressive Symptomatology (QIDS) (MD, RN, or MSW).

4. If a patient discontinues medication due to tolerability problems, ineffectiveness, patient preference, or other reasons, the patient will be dropped out of the study and enter the 3 month long open treatment phase. Appropriate medication options will be discussed with the patient based on their symptoms and history. If the patient wishes, they will be provided referrals for psychotherapy or treatment options outside of our research clinic. No further research measures will be conducted once a patient enters the open treatment phase.

5. Patients in all treatment cells will be discontinued from the acute treatment phase if there is there is a rating of 6 (much worse) or 7 (very much worse) on the CGI—I for 2 consecutive weeks. Patients receiving medication may continue receiving the same medication if clinically indicated after being dropped from the study. No further research measures will be performed on patient dropped from the study.

6. The blind will be broken at the end of the 8 week study period. Remitters (HRSD < 11) will be continued on the same medication. Responders to placebo will be followed off of medication. Placebo non-responders

will be treated openly with escitalopram [or duloxetine], while escitalopram [or duloxetine] non-responders will be treated as clinically indicated with augmentation or switch in class of antidepressants.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
If a patient discontinues medication due to tolerability problems, ineffectiveness, patient preference, or other reasons, the patient will be dropped out of the study and enter the 3 month long open treatment phase. Appropriate medication options will be discussed with the patient based on their symptoms and history. If the patient wishes, they will be provided referrals for psychotherapy or treatment options outside of our research clinic. No further research measures will be conducted once a patient enters the open treatment phase.

Patients in all treatment cells will be discontinued from the acute treatment phase if there is there is a rating of 6 (much worse) or 7 (very much worse) on the CGI—I for 2 consecutive weeks. Patients may also be discontinued from the study if this is indicated in the clinical judgement of the study physician and/or principal investigator. Patients receiving escitalopram/duloxetine may continue receiving the same medication if clinically indicated after being dropped from the study. No further research measures will be performed on patient dropped from the study.

Patients will be informed that should they experience a crisis or acute symptom worsening between scheduled weekly appointments, they should call their study clinician via the clinic office/research coordinator or the 24 hr doctor on call pager for the LLDC. The study physician will evaluate the patient and make appropriate follow up arrangements, which may include activating EMS, calling the relevant mobile crisis team, or scheduling pt for immediate outpatient appointment in the LLDC. Patients in crisis will be assessed immediately and appropriate clinical action taken as above (i.e., those meeting criteria for early discontinuation will be dropped from the study and treated openly).

Blood and other Biological Samples

CBC, blood chemistries, and electrolytes will be drawn before initiating escitalopram/duloxetine or placebo. The total amount of blood drawn should be no greater than 20cc.

Assessment Instruments

Clinical measures

1. SCID IV -- 30 minutes
2. HRSD --15 minutes
3. QIDS -- SR 10 minutes
4. CES -- 5 minutes
5. CGI-I -- 1 minute
6. Blind assessment -- Patient guess -- 1 minute
7. Blind assessment -- Doctor guess -- 1 minute
8. TESS -- 3 minutes
9. ATHF -- 5 minutes
10. Credibility and Expectancy Scale -- 5 minute
11. HARS -- 15 minutes
12. UCLA Revised Loneliness Scale -- SR -- 1 minute

Neoruopsychological tests

1. Wechsler Test of Adult Reading (WTAR)--5 min
2. Mini Mental State Examination (MMSE) -- 8 min
3. Stroop Color Word Test (Stroop) -- 5 min
4. Mattis DRS- I/P subset -- 10 min
5. Digit Symbol Subtest of the WAIS III -- 2 min
6. Logical Memory Test (WMS III) -- 10min

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

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
It is possible that treatment may be delayed due to scheduling study MRI scans and neuropsychological testing, though we will make every effort not to delay treatment. If there are scheduling difficulties, treatment will not be delayed more than 1 week.
Maximum duration of delay to standard care or treatment of known efficacy
There will also be a delay of 8 weeks for 10/130 of patients (those assigned to receive placebo).
Justification: In this study 10 subjects will be randomized to placebo in place of antidepressant treatment with escitalopram/duloxetine, which is not so toxic that patients routinely refuse treatment. The use of placebo rather than escitalopram/duloxetine could result in longer exposure to depressive symptoms, so the

IRB algorithm would seem to judge the risk of placebo as high. This risk is mitigated since there are not large differences between antidepressant medications and placebos in most clinical trials. Typical antidepressant response rates in placebo controlled trials are 40-45%, while placebo response rates are 30-35%. If 10 subjects in this study are assigned to placebo rather than escitalopram/duloxetine, then based on these estimated rates only 1 subject would fail to respond to placebo who may have responded to escitalopram/duloxetine. That being said, continuing with the IRB algorithm, it is not possible to accurately predict placebo response in a single study (placebo response ranged widely between 13-52% in the Walsh et al 2002 meta-analysis). Finally, the potential benefit of understanding the cognitive and neural pathways by which placebo and expectancy effects cause improvement in depressive symptoms is substantial. Therefore, according to the algorithm provided by the IRB, the use of placebo in this study is ethical.
Treatment to be provided at the end of the study
At the end of the acute treatment protocol, appropriate treatment (medication continuation, change in medication, and/or follow-up) will be provided free for 3 months. Subjects will receive 3 months of free doctor visits in the clinic and at least 1 month of free medication. Every effort will be made to provide free medication for 3 months total, but we cannot guarantee the availability of free medication beyond 1 month. At the end of the three month period, patients will be referred out for further psychiatric follow up.

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
The main risks in this study are (1) patients may not respond to the medication treatment, (2) patients assigned to placebo may experience continued symptoms or clinical worsening, (3) side effects of the medication, (4) risks related to MRI, and (5) specific risks associated with being a participant aged over 60 years (such as having a comorbid medical condition, or being cognitively impaired). There are also minimal risks associated with the blood draws, but there is no greater risk in this protocol for this procedure than in any standard clinical setting.
Describe procedures for minimizing risks
Regarding (1), treatment with SSRIs and SSNRIs are accepted first line treatments for depression. Reliable evidence does not exist for the superiority of another medication or psychotherapy to escitalopram in depressed patients. Patients will be seen weekly to have their symptoms assessed, and patients who exhibit clinical worsening (as described in above procedures) will be dropped from the study and receive clinical treatment. Regarding (2), it is the case that patients in the Placebo Controlled Group will not receive a proven effective treatment for their condition if they are assigned to placebo. However, the risk of permanent harm to subjects will be minimized by restricting the study to depressed, nonsuicidal patients, following them closely, and dropping them from the study for signs of clinical deterioration**.** Regarding (3), commonly observed side effects associated with escitalopram and duloxetine are diaphoresis, diarrhea, nausea, insomnia, somnolence, disorder of ejaculation, impotence, and fatigue. The FDA has also placed a

black box warning in the package insert for all SSRIs warning of increased suicidal ideation and behavior. Side effects of the medication will be assessed at each visit. If the side effects represent an intolerable burden in the assessment of the patient or the treating clinician, the medication will be discontinued. Regarding (4), the Magnetic Resonance (MR) scanner uses strong magnetic fields and radio waves to take measurements in the brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). They will be asked to lie flat on the back in the MRI scanner for approximately 90 minutes and to remain as still as possible. Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. With any MRI scan, on occasion, some people experience nervousness or types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. If a patient experience any discomfort and wish to stop the scan, he/she can tell the MRI technologist who will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped. Finally, we will mitigate the risks associated with increased medical problems in older adults by doing a careful physical examination and blood tests to detect an unstable, severe, or acute medical problem. Since cognitive impairment is a condition impacting older adults, we will measure a MMSE and exclude subjects with a score lower than 24.

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. All MRI scans and
related data will be kept on the secure, password protected, MRI server. MRI scan reports will be provided to the clinic by the MRI scanner, and kept in a locked file.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
Patients who are not currently in treatment and are experiencing depressive symptoms may receive a medication proven effective for their condition. Therefore, the major benefit is that patients will achieve

remission from the depression as a result of participating in the study.

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. Reimbursement is limited to no more than $10 per week. To compensate subjects for the time required for the MRI scan, subjects will be compensated $100 for the scan.

References

References
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Alexopoulos GS. Role of executive dysfunction in late-life depression. J Clin Psychiatry 2003; 64:18-23.

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