Study Title: Antidepressant Response in the Treatment of Depressive Symptoms and Frailty Characteristics in Older Adults

Document Date: 4/6/2020

NCT: 01973283

Protocol Title:
Antidepressant Response in the Treatment of Depressive Symptoms and Frailty Characteristics in Older Adults (formerly #6470)

Version Date:
04/06/2020

Protocol Number:
7289R

Clinic:
Clinic for Aging, Anxiety, and Mood Disorders

First Approval:
05/13/2016

Expiration Date:
05/01/2021

Contact Principal Investigator:
Patrick Brown, PHD
Email: Patrick.Brown@nyspi.columbia.edu
Telephone: 6467748666

Research Chief:
Davangere Devanand, MD

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

Division & Personnel

Division

What Division/Department does the PI belong to?
Geriatric Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Adult and Late Life Depression Research Clinic

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.
There are no personnel participating in the clinical research outlined in this protocol that are not affiliated

with NYSPI/CU.

Amendment

Describe the change(s) being made
We would like permission to send plasma samples to our colleague Dr. Jennifer Felger at Emory University to conduct testing on these samples. Dr. Felger's laboratory will only be used as a service, and no identifiable data will be shared with her laboratory.
Provide the rationale for the change(s)
Given problems with the reliability of the laboratory where we have previously sent plasma samples for inflammatory marker measurement, we would like to change the laboratory performing these measurements to Dr. Jennifer Felger's lab at Emory University.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
N/A
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
N/A

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.
The study has progressed well to date. Potential subjects found the study interesting and agreed to participate at high rates. Ninety-three participants signed consent for this protocol. Enrollment has closed and all study visits have been completed. There have been no other policy or procedure issues in the study.

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
60
Total number of participants enrolled to date
93
Number of participants who have completed the study to date
72
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
We have more participants enrolled (93) than originally anticipated (60). After the May 2018 ACAR we increased expected enrollment to 85 subjects, anticipating that 60 would complete the 12-month protocol. At this time 72 participants have completed the study. A protocol violation was submitted in April 2019 to address the over-enrollment and no new patients have enrolled in the study since.
Comments / additional information
N/A

Sample Demographics

Specify population
Depressed adults
Total number of participants enrolled from this population to date
93
Gender, Racial and Ethnic Breakdown
Gender:
Female: 59
Male: 33
Not specified/missing: 1

Ethnicity:

Hispanic/Latino: 13
Not Hispanic/Latino: 79
Not specified/missing: 1

Race:
American Indian/Alaska Native: 1
Asian: 1
Black/African-American: 15
Native Hawaiian/Pacific Islander: 0
White: 65
More than one: 4
Don't know: 4
Not specified/missing: 3

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
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
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Off-label Use of Drug or Device

Population

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

✓ Adults over 50

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name
The Phenomenology and Antidepressant Treatment of Depressed, Frail Older Adults
Grant Number
1 K23 MH099097-01A1
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

Lay Summary of Proposed Research

The goal of this open-administration treatment study of escitalopram (or duloxetine) is to evaluate the effect of antidepressant medication on treating the syndrome of "frailty" in older adults with depressive symptoms. Patients with significant depressive symptoms (DSM-IV diagnosis of

dysthymia or Major Depression with a Hamilton Rating Scale for Depression (HRSD) ≥ 16) and 1 or more symptoms of the frailty syndrome (exhaustion, decreased energy, weight loss, decreased grip strength, and slow/unsteady gait) will be evaluated and treated with escitalopram (or duloxetine) for 8 weeks to test whether antidepressant medication improves both the syndrome of frailty and depressive symptoms. Because these patients have a diagnosis of major depression or dysthymia, there is a responsibility to first and foremost ensure that patients achieve measurable improvement in depressive symptoms. For this reason, remission of symptoms (8-Week HRSD<10) is the clinical goal. All patients will continue in the protocol for a total of 12-months (Follow-up Phase). Patients who remit to the Acute Phase trial will be maintained on their treatment regimen and followed monthly. Patients who do not remit to the Acute Phase trial will be treated as clinically indicated (i.e. augmentation strategies) in the Adult and Late Life Depression Clinic (ALLDC) during the Follow-up Phase.

Patients who had a DSM-IV diagnosis of Major Depression with a HRSD≥ 16 and 1 or more frailty characteristics at their initial evaluation who entered study 6836 and completed an 8-week placebo control trial will have the option to enter this study following the completion of 6836. If the patient remitted to treatment in 6836, they will remain on that treatment and monitored as part of protocol 7289R (formerly #6470). If the patient did not remit to treatment in 6836, patients can discuss alternative treatment strategies with the study psychiatrists and will be treated openly as part of this protocol. Patients who respond to placebo as part of 6836 will be given the option of remaining off medication and being monitored through this protocol's follow-up phase, or starting treatment as clinically indicated as part of this protocol.

Patients evaluated at the Adult and Late Life Depression Clinic and eligible to participate in the study will be treated with an antidepressant medication and assessed on the primary outcome variables (characteristics of frailty, depressive symptoms) as well as on secondary variables which include cognition (global cognition, episodic memory, executive function), and function (physical mobility/activity, instrumental activities of daily living, and social functioning) prior to treatment initiation and at the end of an Acute Phase trial (Week 8); during the Follow-up Phase, patients will have monthly assessments in the ALLDC, and full assessment batteries at 6- and 12-months post treatment initiation.

Background, Significance and Rationale

Background, Significance and Rationale

Frailty, “a syndrome of decreased resiliency and reserves”, is defined by five characteristics: 1)“shrinking” (definition: unintentional weight loss of ≥ 10 lbs in prior year, or ≥ 5% loss of body weight in prior year at follow-up), 2) weakness (definition: grip strength in lowest 20% at baseline, adjusted for gender and BMI), 3) poor endurance/energy (definition: self-report of exhaustion on 2 items on the Center for Epidemiologic Studies Depression Scale (CES-D), 4) slowness (definition: slowest 20% on timed 4 meter or 15 foot walk, adjusted for gender and standing height), and 5) low physical activity (definition: weighted score of kilocalories expended per week as calculated from the Minnesota Leisure Time Activity questionnaire). Frailty is associated with poor prognosis including hospitalization, falls, worsening disability and mobility, and death.

There is a relationship between frailty and depression, as the five defining characteristics of frailty (exhaustion, decreased energy, weight loss, decreased grip strength, and slow/unsteady gait) overlap

significantly with symptoms of geriatric depression (decreased energy and motivation, psychomotor slowing, weight loss, decreased participation in leisure activities). Despite the strong association between depression and the syndrome of frailty, there are currently no clinical studies being funded by the NIMH or NIA on the association between depression and frailty in late life (NIH's RePORTER system). In fact, the clinical studies of frail older adults that have been funded (primarily exercise trials for frail older adults) have excluded depression (Brown et al., 2000, Binder et al., 2005). The proposed study is innovative in that it is focused on a group of older adults who have been unrepresented (via exclusion criteria) in previous clinical studies (frail older adults with comorbid depressive illness), and it treats the depressive symptoms and targets characteristics of the frailty syndrome in the hopes of altering the prognostic trajectory of this clinical sample. This protocol serves two purposes: 1. It tests the feasibility of recruiting and retaining frail older adults with a depressive illness in a treatment trial, and 2. It provides pilot data for the effectiveness of an antidepressant medication on treating the characteristics of frailty and the comorbid depressive symptoms.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Specific Aims and Hypotheses

The hypotheses for this protocol predict that we will discover a significant improvement on both frailty characteristics and depressive symptoms in this clinical population when treated with antidepressant medication (escitalopram or duloxetine).

Specific Aim: Evaluate the effect of antidepressant medication on treating the syndrome of frailty and depressive symptoms in an older adult sample.

Hypothesis 1: Patients on antidepressant medication will show improvements in frailty characteristics 8-weeks after treatment implementation.

Hypothesis 2: Patients on antidepressant medication will show improvements in depressive symptomatology (Week 8 Hamilton Rating Scale – Depression, HRSD $\leq$ 10) 8-weeks after treatment implementation.

Hypothesis 3: Patients on antidepressant medication will show improvements in secondary outcomes including physical activity/mobility and instrumental activities of daily living 6 months and 12-months after treatment implementation.

Description of Subject Population

Sample #1

Specify subject population
Older adults with characteristics of frailty and depressive illness
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
85
Age range of subject population
60-95 years

Gender, Racial and Ethnic Breakdown

Based on previous depression studies conducted in the Adult and Late Life Depression Clinic, we expect a gender distribution of approximately 60% female and 40% male. We expect an ethnic breakdown of approximately 75% Caucasian, 15% African American, and 10% Hispanic.

No patients who meet study criteria will be excluded from study participation on the basis of gender or ethnicity.

Description of subject population

N = 60
- frailty characteristics $\geq$ 1

AND

- DSM diagnosis of MDD or dysthymia with a HRSD$\geq$16, Age range 60-95 years

Recruitment Procedures

Describe settings where recruitment will occur
Patients will be recruited from the Adult and Late Life Depression Clinic (ALLDC)
at the New York State Psychiatric Institute (NYSPI).
How and by whom will subjects be approached and/or recruited?
Patients will be evaluated via the ALLDC evaluation (protocol #7284R) as well as for the frailty characteristics and, if eligible and interested in participating, enrolled into this protocol. If eligible the person doing the initial evaluation (including Patrick J. Brown, Ph.D., Bret Rutherford, M.D., Steven Roose, M.D., and Allegra Broft, M.D.) will briefly describe the current protocol to the patient. If the patient expresses interest in participating, Dr. Brown will speak with the patient about the current protocol. If patient is willing to participate, informed consent will be obtained.

For patients who are enrolled in Dr. Rutherford's study (6836): During the Week 5 visit of the 8-week acute trial that Dr. Rutherford is conducting, the treating physician will mention that there is currently a study ongoing that patients can enroll in at the end of the 8-week trial that will allow for continued follow-up care and antidepressant treatment for 10 more months (10-months in 7289R (formerly #6470) plus 3-months of open treatment as compared to 3-months of open treatment following the completion of Dr. Rutherford's study). If the patient is interested, a non-study physician will speak with the patient in detail about study 7289R (formerly #6470) at the end of their Week 5 visit.
How will the study be advertised/publicized?
Letters will be sent to geriatricians and senior citizen centers, ads will be placed in local publications and fliers at local businesses and senior centers. Additionally, we will post our study on RecruitMe, CUMC's new tool for listing clinical trials and other human subjects 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
NCT01973283

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Because treatment strategy in this current protocol mirrors the treatment strategies used in other protocols conducted in the ALLDC, subjects who meet criteria for this and other protocols in the ALLDC can participate in both protocols concurrently. These protocols are listed below:

- MECHANISMS OF ANTIDEPRESSANT NONRESPONSE IN LATE LIFE DEPRESSION (PI Rutherford) - IRB #6836
- PHYSICAL AND MENTAL FATIGABILITY IN LATE LIFE CLINICAL POPULATIONS (PI Brown) - IRB #7360
- FLAVANOL AUGMENTATION FOR ANTIDEPRESSANT NON-RESPONSIVE LATE LIFE DEPRESSION (PI Rutherford) - IRB #7368
- A STUDY OF L-DOPA FOR DEPRESSION AND SLOWING IN OLDER ADULTS (PI Rutherford) - IRB #7270
- MITOCHONDRIAL FUNCTION, FATIGUE, AND DEPRESSION IN LATER LIFE (PI Brown) - IRB #7379
- OPTIMIZING OUTCOMES OF TREATMENT-RESISTANT DEPRSESION IN OLDER ADULTS (OPTIMUM) STUDY (PI Roose) - IRB #7409
- TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS(PI Rutherford) - IRB #7540
- L-DOPA VS. PLACEBO FOR DEPRESSION AND PSYCHOMOTOR SLOWING IN OLDER ADULTS (PI Rutherford) - IRB #7733

Subjects may also participate in the following protocols outside of the ALLDC if eligible:
- OLFACTORY DEFICITS AND DONEPEZIL TREATMENT IN COGNITIVELY IMPAIRED ELDERLY (PI Devanand) - IRB #6655

The consent form for this study is separate from those from 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
Older adults with frailty characteristics and depressive symptoms
Create or insert table to describe the inclusion criteria and methods to ascertain them

At the time of initial clinic evaluation*:

- Anyone with 1 or more characteristics of frailty (frailty evaluation)
- A HRSD≥16 and a DSM-IV depressive disorder (e.g., MDD, Dysthymia) (HRSD, SCID)
- Capable of providing informed consent (clinical interview)
- Currently followed by a PCP (had an eval in last 6-months) (patient report)
    - Patient required to provide release of information to facilitate communication with PCP

* Patients who enroll in Dr. Rutherford's 8-week placebo control antidepressant trial (6836) are eligible for enrollment following the completion of that trial regardless of treatment outcome if they met the above criteria during their initial clinic evaluation. Patients who responded to treatment in study 6836 and may no longer meet the severity criteria (HRSD ≥ 16) at the time they provide informed consent for 7289R (formerly #6470) are still eligible to enroll in 7289R (formerly #6470) as long as they met the above criteria at their initial clinic evaluation prior to their enrollment in 6836.

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

- Acute cancer treatment (clinical interview)
- Acute, severe or unstable medical illness (clinical interview)
- End stage medical illness (e.g. liver, kidney, pulmonary) (clinical interview)
- Mini Mental Exam < 24 or a diagnosis of dementia (clinical interview, MMSE)
- Individuals who do not have capacity to consent (clinical interview)
- Diagnosis of substance abuse or dependence (last 12 months) (clinical interview, SCID)
    - Excluding Nicotine dependence
- History of psychosis or bipolar disorder (clinical interview, SCID)
- Patient is considered a significant risk of suicide (clinical judgment, HRSD)

- Subject is considered based on history to be unlikely to respond to the single agent escitalopram or duloxetine (i.e., subjects with treatment resistant depression, including subjects with previous treatment with ECT) (clinical interview, SCID)
- History of allergic or adverse reaction to escitalopram or duloxetine, or non-response to adequate trial of escitalorpam (at least 4 weeks at dose of 20 mg) or duloxetine (at least 4 weeks at dose of 90 mg) (clinical interview)

Waiver of Consent/Authorization

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

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
7284R
Describe Study Consent Procedures
Step 1. Patients will undergo a medical, psychosocial, and psychiatric evaluation by a clinic physician as part of the evaluation procedures for the ALLDC (protocol # 7284R). As per #7284R, the five frailty characteristics will be assessed during this initial evaluation.

Step 2*. If the patient meets inclusion/exclusion criteria for this current study, the evaluating physician will briefly describe the study. If patient expresses interest in participating, Dr. Brown will speak with the patient about the current protocol. If patient is willing to participate in this protocol, informed consent will be obtained. At this time, a signed release of information form will also be obtained so that the study physician can communicate with the patient's internist or Primary Care Physician prior to treatment initiation and during the study. We respect that this clinical population may have multiple medical issues that contribute to their clinical presentation of frailty and to their comorbid depressive symptoms. As such, an ongoing communication with their primary physician is necessary. If patient is unwilling to participate in this protocol, this will not affect his/her standing in ongoing research protocols within the clinic.

* For patients who are enrolled in study 6836: During the Week 5 visit of the 8-week acute trial that Dr. Rutherford is conducting, the treating physician will mention that there is currently a study ongoing that patients can enroll in at the end of the 8-week trial that will allow for continued followup care and antidepressant treatment for 10 more months (10-months in 7289R (formerly #6470) plus 3-months of open treatment as compared to 3-months of open treatment following the completion of Dr. Rutherford's study). If the patient is interested, a non-study physician will speak with the patient in detail about study 7289R (formerly #6470) at the end of their Week 5 visit. If patient is willing to participate in this protocol, informed consent will be obtained.

Step 3. Patients will return for a baseline assessment (See Study Procedures for details).

Capacity to consent:
Patients who would have capacity issues (e.g. dementia, psychotic depression) are excluded from this study.

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

Drug Washout:
If patients are currently on antidepressant medication, have been for at least 6 weeks, and are not responding (defined as depressive symptoms as measured at baseline by the Hamilton Rating Scale for Depression, HRSD, are > 14), they may be eligible to enter this study. Those who decide to participate will be asked to stop taking the antidepressant medication they are currently on before beginning the study medication (washout period). The study psychiatrist or nurse practitioner will speak with the patient about the length of the washout period, which differs depending on which drug they are taking. Weekly visits are required for washout periods lasting more than one week to evaluate the patient's health and to check for increased symptoms during the washout period. The patient's health will be

monitored using a clinical interview and the Treatment Emergent Signs and Symptoms (TESS) scale both conducted by the study physician or nurse practitioner, and the patient's symptoms will be monitored by the HRSD which will be conducted by either the study physician, nurse practitioner or a trained rater. Follow-up by the study physician or nurse practitioner will occur weekly during the washout period, and, while follow-up can be conducted via telephone, patients will not go more than 2 weeks during the washout period without an in-person clinic follow-up evaluation. Patients will be instructed to contact the study doctor or nurse practitioner for any concern.

Psychotherapy:

During the 8-week Acute Phase of the study, patients will not be allowed to begin new psychotherapy. If they are currently in stable psychotherapy and have been for 3 months or more, they will be eligible to participate in this study and may continue psychotherapy during the study. Following the Acute Phase of treatment, however, patients may start new psychotherapy as it is not reasonable to prohibit potential treatments from patients for a full 12-months. If patients start psychotherapy during the Follow-up phase, it will be noted in the patient's chart and in the database.

Prior to Baseline:

Patients physical activity levels will be measured prior to treatment initiation via the use of actigraphy watches. Patients who meet study criteria at initial evaluation and provide informed consent to participate in the study protocol will be taught how to use the actigraphy watches for the week in between initial evaluation and baseline visits. The watches will record total daily activity levels via expended kcal and the data will be uploaded into the database when the watches are returned at the Baseline visit.

* Patients who enter protocol this study via the completion of protocol 6836 will not participate in the actigraphy assessment procedures throughout the study.

Baseline:

Patients who meet study criteria at initial evaluation and provide informed consent to participate in the study protocol will complete a baseline assessment prior to treatment initiation. This 90-minute assessment includes: Recording the patient's height and weight, vital signs (including blood pressure, heart rate, and postural changes), blood work (including inflammatory markers [C-reactive protein, CRP, and Interleukin 6, IL 6] and albumin levels), a depression evaluation (HRSD), a function evaluation (World Health Organization Disability Assessment Scale 2, WHODAS2, the Measure of Everyday Cognition, ECog, and the Short Physical Performance Battery, SPPB), and a brief cognitive evaluation (Logical Memory Wechsler Memory Scale (WMS) III, Stroop Color-Word test, Trailmaking Test A & B, and Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol Test). A study psychiatrist or nurse practitioner will assess patients' side effect profiles using the modified Treatment Emergent Signs and Symptoms (TESS) scale, and overall severity using Clinical Global Impression – Improvement (CGI-I) ratings. Given the fact that the patients in this protocol by definition may experience exhaustion, deceased energy and/or motivation the patient will be told that they can request a rest at any time and will be asked if they need a break every 15 minutes. If necessary the evaluation session can be divided into 2 separate 45-minute sessions.

* Patients who enter this study via the completion of protocol 6836 will have completed baseline testing as part of protocol 6836.

Dosing Schedule for Acute Phase:
Escitalopram: 10 mg of escitalopram daily for first 4 weeks, and, if patients do not meet remission criteria (HRSD ≤ 10) or patients continue to report depressive symptoms, are tolerating the medication well, and wish to try a higher dose, 20 mg daily for final 4 weeks.

Duloxetine: If patients have previously failed a trial of escitalopram, they will be treated with duloxetine: 30 mg daily for the first week, then 60 mg for the next four weeks, and, if patients do not meet remission criteria or patients continue to report depressive symptoms, are tolerating the medication well, and wish to try a higher dose, the dose is increased to 90 mg for the final three weeks.

* Patients who enter this study via the completion of protocol 6836 who were treated with placebo and did not respond and who have no history of unsuccessful treatment with escitalopram will be treated with escitalopram via the above dosing schedule.
* Patients who remitted to escitalopram or duloxetine as part of 6836 will be maintained on their treatment upon entering this protocol and monitored via the study protocol.
* Patients who remitted to placebo treatment will have the option of being monitored without treatment or starting antidepressant treatment as part of this protocol; those who choose to be monitored without treatment will have the option of starting antidepressant treatment should symptoms worsen.
* The study physician or nurse practitioner will discuss alternative treatment strategies with patients who did not remit to escitalopram or duloxetine as part of study 6836.
*If patients require medications for sleep disturbance during the course of their participation, they will be prescribed lorazepam (up to 2 mg daily) or its equivalent, zolpidem (up to 10 mg), or trazodone (up to 150 mg). These medications have been used to successfully treat sleep disturbances.

It is possible that patients may experience side effects from these medications. The side effects most commonly associated with lorazepam include sedation, somnolence, and falls. The side effects most commonly associated with zolpidem include fatigue and drowsiness, along with headache or muscle aches. The side effects most commonly associated with trazodone include dizziness, drowsiness, headache, and nausea.

Follow-up during Acute Phase:
Following the baseline assessment, patients will be followed up weekly in clinic for the duration of the Acute Phase of treatment (8-weeks). Patients will receive clinical management and complete follow-up HRSD, CGI-I, and TESS by trained raters to monitor weekly depression levels, improvement, and side effect profiles. During follow-up clinic visits, vital signs (blood pressure, heart rate, and postural changes) will be collected.

WEEK 7: In addition to the standard weekly clinic follow-up procedures, patients will again be provided actigraphy watches to record their physical activity levels at the end of the acute medication trial. Patients will wear actigraphy watches throughout the period between Week 7 and Week 8 and return the watches when they arrive for their full assessment procedures at Week 8.

WEEK 8: At Week 8 of an Acute Trial, patients will undergo the same 90-minute assessment that

was conducted at baseline with an additional reassessment of the frailty characteristics: Recording the patient's height and weight, blood work (including inflammatory markers [C-reactive protein, CRP, and Interleukin 6, IL 6] and albumin levels), a depression evaluation (HRSD), a function evaluation (World Health Organization Disability Assessment Scale 2, WHODAS2, the Measure of Everyday Cognition, ECog, and the Short Physical Performance Battery, SPPB), and a brief cognitive evaluation (Logical Memory WMS III, Stroop Color-Word test, Trailmaking Test A & B, and Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol Test) along with a Week 8 TESS and final CGI-I. The Week 8 assessment will take 2 hours total and as at baseline may require frequent breaks or be divided into two sessions if necessary. Week 8 assessments for those patients who enter this protocol via study 6836 will be conducted as part of study 6836.

Follow-up Phase:

At the end of the acute treatment trial, all patients will continue into the Follow-up Phase. Patients who remit to the Acute Phase trial will be maintained on their treatment regimen and followed monthly. Patients who do not remit to the Acute Phase trial will be treated and followed as clinically indicated (i.e. augmentation strategies, etc.) in the ALLDC. During the Follow-up Phase, patients will have monthly assessments in the ALLDC with procedures that mirror the weekly assessment procedures from the Acute Phase Trial. If more frequent follow-up visits are clinically indicated by the treatment strategy during the Follow-up Phase, more frequent follow-up visits will be conducted. Full assessment batteries (as described in the Baseline and Week 8 subsections above) will be repeated at 6- and 12-months following patients' initial baseline visit. Physical activity levels via actigraphy will be assessed over the course of the week leading up to the 6-month and 12-month full assessment visits.

Psychological assessments performed on study participants by a psychiatrist or nurse practitioner, 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).

Study assessments and prescribing of drugs to study participants may also be done by a Psychiatric Nurse practitioner, Galit Sharon Marcus, who has completed NYSPI-specific CITI training for human subjects research (specifically the biomed or social/behavioral course and Good Clinical Practice.

The NP is licensed and board certified as a Psychiatric and Mental Health NP. She has considerable experience in working with a late-life population but no prior research experience in this population. That is why she will have an extended period of time where all her work is directly in-person supervised. The NP will have a lengthy orientation
where she will be observing evaluations done by Drs. Roose, Rutherford, Brown and Broft. She will then do evaluations under the observation of the same MDs. Even when she is doing evaluations and follow-ups by herself, all cases are reviewed weekly at a clinic meeting. Even after orientation is over, it is the practice of the clinic that the doctors consult with and present cases to each other so all patients are essentially treated by the entire clinic team.

Following the completion of the 12-month study, patients will be treated in the clinic at no cost to them

for at least three months or, if they prefer, the clinic staff will refer them elsewhere for continued treatment.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Criteria for Early Discontinuation

If the study doctor feels that during the course of escitalopram or duloxetine treatment the patient's condition worsens significantly, or intolerable side effects occur, the study medication will be discontinued and the patient will be treated in the clinic as clinically indicated with other medications.

The study doctor may stop patient participation in the study at any time for reasons such as, for example, staying in the study would be harmful to patients, patients need treatment not allowed in the study, or patients do not follow study procedures. During the follow-up period, patients will be discontinued from the acute treatment phase if there is a rating of 6 (much worse) or 7 (very much worse) on the CGI-I for 2 consecutive weeks. No further research measures will be performed on patient dropped from the study. These patients will be evaluated weekly in the clinic following discontinuation. If patients are removed from the study, they will be treated in the clinic at no cost to them for at least three months or, if they prefer, the clinic staff will refer them elsewhere for continued treatment.

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 followed in the clinic for 3 months. 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 discontinues study participation. If a patient discontinues treatment but is willing to continue participation in study assessments, the patient will continue to be followed and monitored as per the assessment schedule outlined in this PSF.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Evaluation/Baseline: CBC, blood chemistries, and electrolytes as well as inflammatory markers (C-reactive protein, Interleukin 6), Serum 25-hydroxyvitamin D level, and Albumin levels.

Week 8: CBC, blood chemistries, and electrolytes as well as inflammatory markers (C-reactive

protein, Interleukin 6), Serum 25-hydroxyvitamin D level, and Albumin levels

6-Months: CBC, blood chemistries, and electrolytes as well as inflammatory markers (C-reactive protein, Interleukin 6), Serum 25-hydroxyvitamin D level, and Albumin levels

12-Months: CBC, blood chemistries, and electrolytes as well as inflammatory markers (C-reactive protein, Interleukin 6), Serum 25-hydroxyvitamin D level, and Albumin levels

The total amount of blood drawn per visit should be no greater than 20 cc. The total amount of blood for the entire study should not exceed 100 cc.

Plasma samples will be sent to Dr. Jennifer Felger at Emory University to conduct testing. Dr. Felger's laboratory will be used only as a service, with no identifiable data being shared.

Assessment Instruments

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

- Frailty criteria assessment at Clinic Evaluation, Week 8, Month 6, and Month 12: *20 minutes*
  - Exhaustion (CES-D items "I felt that everything I did was an effort" and "I could not get going"),
  - Weight loss (patient report of 10 lb loss unintentionally in last year)
  - Weak grip strength (via hand dynamometer; stratified by gender and body mass index)
  - Slow walking speed, (15 feet speed stratified by gender and height)
  - Low energy expenditure (Short version of the Minnesota Leisure Time Activity questionnaire. Kcals per week expended are calculated using standardized algorithm and stratified by gender).
- Hamilton Rating Scale for Depression: *15 minutes*
  - Conducted at each follow-up visit
- UCLA Revised Loneliness Scale: *1 minute*
  - Self report form
- 90 minute assessment at the Baseline, Week 8, Month 6, and Month 12 Visits consists of:
  - Height and Weight and blood work
    10 *minutes*
    - Includes:
      - C-reactive protein, CRP, Interleukin 6,
      - Serum 25-hydroxyvitamin D level, and
      - Albumin levels
  - Depression evaluation
    20 *minutes*
    - Includes:
      - Hamilton Rating Scale for Depression

- Conducted at each follow-up visit as well
- Clinical Global Impression – Improvement
  - Conducted at each follow-up visit as well

- Function evaluation *25 minutes*
  - *Includes:*
    - *World Health Organization Disability Assessment Schedule 2.0*
    - *(WHODAS2)*
    - *Short Physical Performance Battery (SPPB)*
    - *Measure of Everyday Cognition (ECog)*
    - *Self-report fatigability measures (Borg Rating Scales, Pittsburgh Fatigability scale, Multidimensional Fatigue Inventory)*
- *Cognitive evaluation* *30 minutes*
  - *Includes:*
    - *Logical Memory (WMS III)*
    - *Stroop Color-Word Test*
    - *Trailmaking Test A & B*
    - *Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol test*
- *Side Effect evaluation* *5 minutes*
  - *Includes:*
    - *Treatment Emergent Signs and Symptoms scale*
      - *Conducted at each follow-up visit as well*

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
2

Drug #1

Name of the drug
Escitalopram
Manufacturer and other information
Manufactured by Forest Laboratories and sold under the brand name Lexapro, escitalopram is an SSRI medication approved by the US Food and Drug Administration for the treatment of major depression.
Approval Status
No IND is required

Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
Although the FDA has not ruled as such, we believe an IND is not required for this project as no patients will be treated in this study without significant depressive symptomatology (i.e. Patients with frailty but without dysthymia or MDD will not be included in this study).

Drug #2

Name of the drug
Duloxetine
Manufacturer and other information
Manufactured by Eli Lilly and sold under the brand name Cymbalta, duloxetine is an SNRI medication approved by the US Food and Drug Administration for the treatment of major depression.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
Although the FDA has not ruled as such, we believe an IND is not required for this project as no patients will be treated in this study without significant depressive symptomatology (i.e. Patients with frailty but without dysthymia or MDD will not be included in this study).

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
Patients will be followed for one year in this study, and provided 3 months of subsequent treatment at no cost to them, or if patients prefer, patients will be provided referral information for further psychiatric follow up elsewhere.

Clinical Treatment Alternatives

Clinical treatment alternatives
Patients do not have to participate in this study to receive treatment for their depressive symptoms. Many other available antidepressant medications have also been shown to be effective in the treatment of depressive symptoms. In addition, some patients with similar symptoms may respond to psychotherapy.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

The main risks in this study are the side effects of the medication. Commonly observed side effects associated with escitalopram and duloxetine are diaphoresis, diarrhea, nausea, insomnia, somnolence, disorder of ejaculation, impotence, and fatigue. Long-term use of duloxetine is associated with the risk of worsening osteoporosis/osteopenia. The FDA black box warning in the package insert for all SSRIs warning of increased suicidal ideation and behavior does not apply to the age of patients included in this study.

If patients require medications for sleep disturbance during the course of their participation, they will be prescribed lorazepam (up to 2 mg daily) or its equivalent, zolpidem (up to 10 mg), or trazodone (up to 150 mg). These medications have been used to successfully treat sleep disturbances. It is possible that patients may experience side effects from these medications. The side effects most commonly associated with lorazepam include sedation, somnolence, and falls. The side effects most commonly associated with zolpidem include fatigue and drowsiness, along with headache or muscle aches. The side effects most commonly associated with trazodone include dizziness, drowsiness, headache, and nausea.

Other potential risks that could be encountered include (1), during the assessment procedures, some patients may find some questions upsetting, and (2), in the obtaining a 20 cc blood sample, patients can experience side effects that include pain, fainting, bruising, lightheadedness, and, on rare occasions, infection.
Describe procedures for minimizing risks

Side effects of the medications will be assessed at each follow-up assessment, with emphasis on the assessment of mobility-related changes. If the side effects represent an intolerable burden in the assessment of the patient or the treating clinician, the medication will be discontinued.

Regarding the risks during the assessment procedures, if patients become upset during the assessment of their cognition or functioning, they are not obliged to answer the questions; if they wish to discontinue participation in the treatment protocol, they can withdraw their participation at anytime without effecting their participation in any other study protocol. Regarding the risk associated with blood draw, 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.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
The information obtained from this protocol will be kept strictly confidential and used for professional purposes only. Each person participating in the study receives a coded number and

only the researchers have access to the master list identifying names and numbers. All electronically stored and transmitted data will use these code numbers only, and not names or other identifying information. Only research staff and institutional personnel will review the records. Publications using this data will be done in a manner that fully protects the subject's anonymity.
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 effective for improving their depressive symptoms. Therefore, the major benefit is that patients may achieve treatment response from their depressive symptomatology 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.
Participants will not be compensated, however, they will be reimbursed for travel expenses up to $10 per visit. They will not have to pay for any of the study medications, medical examinations, or laboratory tests that are required for this study.

References

References
Binder EF, Yarasheski KE, Steger-May K, et al. Effects of progressive resistance training on body composition in frail oder adults: Results of a randomized, controlled trial. J Gerontol Med Sci. 2005; 60A: 1425-1431.

Brown M, Sinacore DR, Binder EF, Kohrt WM. Physical and performance measures for the identification of mild to moderate frailty. J Gerontol Med Sci. 2000; 55A: 350–355.

Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56(3): 146-156.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload copy(ies) of the HIPAA form
Frailty_HIPAA_4-18 unstamped unchanged.pdf
Upload any additional documents that may be related to this study
7289R Data Request for Use of De-Identified Data.pdf