NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

November 06, 2020

TO: Bret R. Rutherford, MD

FROM: Dr. Edward Nunes, Co-Chair, IRB

Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: EXPEDITED APPROVAL OF PROTOCOL AMENDMENT

The amendment to your protocol #7540 entitled: TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS **(to revise the compensation schedule for baseline and end point MRI scans from $50 to $125 each, noting updated PSF and CF version date 11/4/20; to update recruitment materials by adding QR codes that lead to a previously approved by Chris Stanley Qualtrics survey to collect contact information, as per the 11/4/2020 memorandum)** has been approved by the Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board.

Please note that this does not change the IRB's cycle of review. A progress report and an application for continuing review will be required 2 months before the study's approval is due to expire: (8/6/2021).

Signed copy on file at IRB.
EN/AW/whiteda

Protocol Title:
Treating Hearing Loss to Improve Mood and Cognition in Older Adults

Version Date:
11/06/2020

Protocol Number:
7540

First Approval:
08/15/2017

Clinic:
Clinic for Aging, Anxiety, and Mood Disorders

Expiration Date:
08/06/2021

Contact Principal Investigator:
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Co-Investigator(s):
Katharine Brewster

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 proposing an amendment only to an existing protocol

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Geriatric Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
program on healthy aging and late life brain disorders

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.

Ana Kim, MD--Columbia University Dept of Otolaryngology
Justin Golub, MD--Columbia University Dept of Otolaryngology
Jessica Galatioto, AuD--Columbia University Dept of Otolaryngology
Megan Kuhlmey, AuD--Columbia University Dept of Otolaryngology

Amendment

Describe the change(s) being made

We are amending our compensation schedule to increase study time point compensation for the baseline and end point MRI scans from $50 to $125. For completing each scan, participants will receive $125, totaling at $250 for the completion of both scans.

These changes are reflected in the recruitment materials attached, the PSF section 'Compensation and/or Reimbursement', and the attached CF.

We are also adding QR codes to recruitment materials. These QR codes lead to a previously approved (by Chris Stanley) Qualtrics survey where participants can enter their contact information and indicate that they agree to have research staff contact them for more information.

This protocol contains all language recommended through the institution's COVID-19 re-opening guidelines and was previously approved to restart recruitment.

Provide the rationale for the change(s)
We have received feedback from current and past participants that the compensation for the time spent completing assessments for the protocol could be improved. As a direct response to this feedback, we are increasing the compensation for the completion of MRI visits at baseline and end point. We believe that this increase will help better offset time spent completing study assessments.

We are adding QR codes to recruitment materials to potentially improve the odds of successfully reaching interested participants.

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)
The proposed changes require a modification to the CF. Please find the updated version of the CF attached. All changes are also reflected in the compensation and/reimbursement section of the PSF.

Procedures

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

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ MRI
✓ Somatic Treatment or Intervention

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
2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
National Institute on Aging
Grant Name
Sensation and Psychiatry: Linking Age-Related Hearing Loss to Late-Life Depression and Cognitive Decline
Grant Number
R21AG059130
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?

Yes
Subcontracted?
To
Name institution(s)
Columbia University

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No
Who is the PI of the grant/contract?
Ana Kim, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Industry
Sponsor
Phonak, Inc (donation of hearing aids only, no money)
Is the study investigator initiated?
Yes
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

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Age-related hearing loss (ARHL) is the third most common health condition affecting older adults after heart disease and arthritis and is the fifth leading cause of years lived with disability worldwide. Many hearing-impaired older adults avoid or withdraw from social contexts in which background noise will make

it difficult to communicate, resulting in social isolation and reduced communication with family and friends. Social isolation and loneliness have been linked to numerous adverse physical and mental health outcomes, including dementia, depression, and mortality, and they may also lead to declining physical activity and the development of the syndrome of frailty. Neuroimaging studies of ARHL have begun to elucidate the brain changes associated with degraded auditory input that provide plausible pathways by which chronic hearing loss may cause cognitive dysfunction and affective dysregulation. Specifically, compensatory activation increases in the cognitive control network (CCN) to support effortful listening may reduce the resources available for higher level tasks (14-15), while chronic deafferentiation leads to atrophy of primary auditory regions and impaired downstream cognitive and affective processing of speech (16-17). In this project we hypothesize that untreated ARHL represents a distinct route to developing Late-life Depression (LLD) and that individuals with comorbid ARHL/LLD are unlikely to respond to treatments (i.e., antidepressant medication) that do not treat the underlying hearing problem. Initial studies suggest remediation of hearing loss using hearing aids or cochlear implantation may decrease depressive symptoms acutely and over the course of 6 to 12 months follow-up. However, the clinical significance of these findings is obscured by lack of rigorous control groups, failure to objectively document hearing aid compliance, and enrollment of study populations lacking syndromal depression or even a threshold symptom score. We propose to conduct the first clinical trial possessing these design features, while also incorporating neuropsychological and neuroimaging assessments that allow us to examine predictors and mechanisms of treatment response. 40 individuals will be recruited who are aged ≥60 years, diagnosed with a clinically significant depressive disorder, and have moderate ARHL with impaired speech discrimination. Comprehensive baseline psychiatric, audiometric, and neuropsychological assessment will be performed in addition to structural MRI (white matter hyperintensity [WMH] estimation and grey matter morphometry), diffusion imaging with tractography, and functional MRI (task-based and resting state connectivity). Participants then will be randomized to receive antidepressant medication (AD) treatment plus full amplification hearing aids or antidepressant medication plus low amplification hearing aids over a 12-week prospective trial. If participants do not wish change their antidepressant medication, they will be randomized to receive only full amplification hearing aids or low amplification hearing aids over a 12-week prospective trial. The baseline evaluation, including MRI scanning, will be repeated at the study endpoint. Data from this study could suggest a novel therapeutic strategy for LLD and thereby mitigate its public health burden, while also contributing to the increased recognition and treatment of ARHL more generally.

Background, Significance and Rationale

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Age-related Hearing Loss (ARHL) contributes to the most prevalent and disabling neuropsychiatric conditions of later life: Late-Life Depression (LLD) and Cognitive Impairment (CI). ARHL is the third most common health condition affecting older adults after heart disease and arthritis (1) and is the fifth leading cause of years lived with disability worldwide (2). The prevalence of ARHL rises steeply with age, from 3% among adults 20-29 to 49% of adults ages 60-69 and >80% in those over 85 years (3-4). While historically considered a benign effect of aging or exclusively a quality of life issue, ARHL is in fact associated with significant psychological and medical morbidity, including social isolation, frailty, and falls (22). In addition, several analyses of epidemiological data sets (23-24), reviews (25) and meta-analyses (26), and a National Institute on Aging (NIA) workshop (27), have linked ARHL to cognitive decline in older adults.

Given its frequent sequelae of social isolation and withdrawal, ARHL has been linked to the development of depressive disorders in older adults (28-30). Gopinath et al (2009) found that depressive symptoms were associated with mild hearing loss (31), while Lee et al (2010) found that hearing thresholds measured with pure tone audiometry (PTA) were associated with scores on the Geriatric Depression Scale (GDS) (32). In an analysis of National Health and Nutrition Examination Survey (NHANES) data, self-reported hearing aid use was associated with significantly lower odds of LLD defined by a minimum score on the Patient Health Questionnaire (PHQ-9) (33). Finally, Contrera et al (2016) found in the Health Aging and Body Composition (HABC) Study that compared to individuals with no hearing impairment, participants with at least moderate (i.e., >40 dB) impairment had 23% lower odds of 'emotional vitality' (34).

Behavioral and neural mechanisms mediate the relationships between ARHL, LLD, and CI. Many hearing-impaired older adults avoid or withdraw from social contexts in which background noise makes communication difficult (5-6), resulting in social isolation and reduced communication with family and friends (7-8,35). Social isolation and loneliness have been linked to numerous adverse physical and mental health outcomes, including dementia (9-10), depression (11), and mortality (12), and they may also lead to declining physical activity and the development of the syndrome of frailty (13). Older adults with significant hearing loss report lower physical activity levels, perform worse on the Short Physical Performance Battery (SPPB), and have slowed gait speeds (36-38). Frailty and slowed gait speed exhibit significant, reciprocal relationships with both cognition (39) and LLD (40) and thus may represent an intermediate step in the progression from ARHL to CI and LLD.

Recent neuroimaging studies of ARHL have begun to elucidate compensatory and neuroplastic changes associated with degraded auditory input that provide plausible pathways by which chronic hearing loss may cause affective dysregulation, CI, and LLD. Deterioration of the peripheral hearing apparatus over time decreases input to primary auditory cortex, secondary association cortices, and the auditory thalamus, which is visualized in functional neuroimaging tasks as decreased neural activations to auditory stimuli (16,41). Blunted neural responses to sounds alters resting functional connectivity in the default mode network (DMN) (42) and leads to compensatory increased activations in the cognitive control network (CCN) to support effortful listening (14,43-47). This compensation may tax CCN capacity and cause manifest executive dysfunction (15), which is common in older depressed patients (48-51) and portends poor response to antidepressant medication as well as more chronic, recurrent course of illness (52-53). Chronic deafferentiation of auditory and CCN networks is associated with atrophy of primary auditory cortex, PFC, and ACC (16-17,54-55). This atrophy may magnify the deleterious effects of acute compensatory shifts, creating a vicious cycle of declining hearing capacity, worsening executive function, and increasing risk for LLD and dementia.

Treating ARHL represents a novel therapeutic strategy for LLD/CI and may help older adults avoid unhealthy aging trajectories. Initial studies suggest remediation of hearing loss may decrease depressive symptoms acutely and over the course of 6-12 months follow-up (18-21), though other studies have failed to find any significant influence of hearing loss treatment on depression (56-57). Mulrow and Aguilar (1990) randomized N=194 subjects to receive hearing aids vs. wait list control and reported significantly increased self-reported quality of life and cognitive function as well as decreased depressive symptoms at 6 weeks and 4 months post-hearing aid prescription (58). The clinical significance of these findings is obscured by small sample sizes, lack of rigorous control groups, and the fact that the patients enrolled were not selected based

on the presence of syndromal depression or even a threshold symptom score. In addition, analyses of hearing aid use and depressive symptoms are plagued by inaccurate reporting, as studies only rarely utilize objective measures of when hearing aids are in place, turned on, and actually being used (59). These limitations highlight the need for rigorously designed, prospective studies of ARHL and LLD such as detailed in the present proposal.

We target patients with comorbid ARHL and LLD, proposing that they represent an etiologically distinct subgroup of older depressed patients who are not likely to respond to antidepressants. Hearing aids and cochlear implants are both available therapies for ARHL, and initial studies suggest that improving hearing improves quality of life and decreases social isolation (18). Should hearing loss prove to be a modifiable risk factor for depression, increasing its treatment rate could be an effective strategy for risk reduction given its near-universal prevalence in the elderly and low treatment levels. ARHL and LLD, both individually and together, are responsible for tremendous public health costs, including extensive disability, morbidity, and mortality. Data from this study could suggest a novel therapeutic strategy for LLD and thereby mitigate its public health burden, while also contributing to increased recognition and treatment of ARHL more generally

Specific Aims and Hypotheses

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Aim 1: To investigate baseline relationships between ARHL, CCN circuit measures, and neuropsychiatric measures.

Hypothesis 1: More severe ARHL (higher thresholds on pure tone audiometry) will be associated with diminished connectivity and activation within the CCN, which themselves will be associated with poorer executive functioning and increased depressive symptoms.

Aim 2: To investigate whether augmentation of standard antidepressant medication treatment with hearing assistive devices is useful for the treatment of comorbid ARHL and LLD.

Hypothesis 2: AD + full amplification hearing aids will result in greater depressive symptom improvement (change on Hamilton Rating Scale for Depression [HRSD]) and higher response rates (proportion with Clinical Global Impressions—Improvement [CGI] score of 1 or 2 at endpoint), improved executive functioning, and increased pre-post CCN connectivity and activation compared to AD + low amplification hearing aids.

Exploratory aims: To explore the influence of hearing aid compliance (as measured by objective device usage logs) and change in social functioning (as measured by the Social Adjustment Scale—Self Report version [SAS-SR]) on pre-post change in depressive symptoms and executive functioning. We will also attempt to identify pre-treatment participant expectations related to hearing aids as well as participant-identified factors that influence hearing aid use and perceived effectiveness.

Description of Subject Population

Sample #1

Specify subject population
Older adults with hearing loss and depression
Number of completers required to accomplish study aims
32
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
>=60

Gender, Racial and Ethnic Breakdown
On the basis of previous studies conducted in the Clinic for Aging, Anxiety, and Mood Disorders (CAAM) (formerly the Late Life Depression Research Clinic [LLDRC]) at the New York State Psychiatric Institute (NYSPI) and Columbia University, it is anticipated that the sample at this site will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects.

On the basis of previous studies conducted in the CAAM, it is anticipated that the sample recruited will be composed of 60% women and 40% men.
Description of subject population
This study will enroll 40 outpatients who (1) are aged ≥ 60 years, (2) diagnosed with Diagnostic and Statistical Manual (DSM) 5 MDD or Persistent Depressive Disorder, (3) have duration of depression ≥6 months, (4) have 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16, (5) have moderate to severe unilateral or bilateral hearing loss (combined PTA >50dB at 2 and 3 kHz), (6) demonstrate impaired speech discrimination scores (60-100% on 25 word list testing) in one or both ears, (7) no history of hearing aid use within the past 6 months, (8) English speaking, and (9) are willing to and capable of providing informed consent and complying with study procedures. Exclusion criteria are (1) diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) within the past 12 months, (2) history of psychosis, psychotic disorder, mania, or bipolar disorder, (3) diagnosis of probable Alzheimer's Disease, Vascular Dementia, or Parkinson's Disease, (4) Mini Mental Status Examination (MMSE) ≤ 24 (66), (5) current or recent (within the past 4 weeks) treatment with antipsychotics or mood stabilizers, (6) current suicidal ideation (HRSD suicide item > 2) with risk of imminent self-harm, (7) any physical or intellectual disability adversely affecting ability to complete assessments, (8) acute, severe, or unstable medical or neurological illness, (9) contraindication to hearing aid placement, and (10) significant retrocochlear pathology or

organic brain lesion (e.g., acoustic neuroma) responsible for hearing loss.

Recruitment Procedures

Describe settings where recruitment will occur
The studies described will be conducted conjointly at (1) the Otology and Neurotology Clinical Practice at the Columbia University Medical Center (CUMC) and (2) the Clinic for Aging, Anxiety, and Mood Disorders (CAAM) at the New York State Psychiatric Institute (NYSPI).
How and by whom will subjects be approached and/or recruited?

Participants will be recruited in 3 possible ways: (1) patients presenting with hearing problems to the Columbia Otology and Neurotology Clinical practice who are found to have comorbid depressive symptoms, (2) patients presenting with depression to the Clinic for Aging, Anxiety, and Mood Disorders (CAAM) who are found to have comorbid hearing problems**,** and (3) patients that have been referred or are responding to study advertisement (through flyers, newspaper, RecruitMe advertising, Bus Shelter advertising, the MindMate online application, radio ads, and ResearchMatch.com) who endorse hearing problems and comorbid depressive symptoms.

Regarding (1), Dr. Kim or one of her staff will check the audiometric data that was already collected for clinical purposes for a patient whom she is seeing in the Columbia Otology and Neurotology Clinical Practice to check whether the patient potentially meets hearing eligibility criteria. If so and the patient also reports subjective feelings of loneliness, social isolation, or depression, a PHQ-9 can be conducted and Dr. Kim will verbally ask the patient whether he/she would be willing to speak with the research team regarding a study. If the patient says yes, then the research team will speak with the patient to schedule an evaluation in the CAAM. Re: (2), if a patient under evaluation in the CAAM appears otherwise eligible and interested, they will be scheduled for a hearing evaluation in the Columbia Otology Clinical Practice to confirm hearing eligibility. Re: (3), patients who have been referred or are responding to study advertisement will be scheduled for evaluation in the CAAM. If a patient has outside audiometric data from the past 12 months, it will be checked by Dr. Kim or one of her staff to determine whether the patient meets hearing eligibility criteria. If a patient does not have recent audiometric data, he/she will be scheduled for a hearing evaluation in the Columbia Otology Clinical Practice or will be asked to schedule a hearing evaluation with a doctor of their choice to confirm hearing eligibility.

Once an individual has been found eligible to participate, Dr.s Rutherford, Brewster, Broft, Roose, or Galit Sharon Marcus, NP, MPH will meet with the patient to discuss the risks, benefits, and alternatives to study participation and invite them to participate. Of note, the consent discussion process will include discussion of the technology HIPAA-compliant video conferencing to be used for remote visits and any concerns the participant may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi. The consent discussion process will also include any COVID-19 risks related to travel and in-person visits for research purposes, as well as ensuring patients are aware that treatment is available outside of the protocol.

How will the study be advertised/publicized?
Flyers posted around CUMC, RecruitMe, advertisements in local newspapers, referrals from CUMC

clinicians, advertisement on Facebook, advertisement in Bus Shelters, the MindMate online application, radio ads, and ResearchMatch.com.
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
NCT03321006

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

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

Characteristic	Method of Ascertainment
1. aged ≥ 60 years	1. clinical interview
2. diagnosed with Diagnostic and Statistical Manual (DSM) 5 MDD or Persistent Depressive Disorder	2. scid, clinical interview
3. have duration of depression ≥6 months	3. clinical interview
4. have 24-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16	4. HRSD
5. have moderate to severe unilateral or bilateral hearing loss (combined PTA of >50dB at 2 and 3 kHz)	5. audiometric testing
6. demonstrate impaired speech discrimination scores (60-100% on 25 word list testing) in one or both ears	6. audiometric testing
7. no history of hearing aid use within the past 6 months	7. clinical interview
8. English speaking	8. clinical interview

9. are willing to and capable of providing informed consent and complying with study procedures	9. clinical interview

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

Characteristic	Method of ascertainment
1. diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) within the past 12 months	1. scid, clinical interview
2. history of psychosis, psychotic disorder, mania, or bipolar disorder	2. scid, clinical interview
3. diagnosis of probable Alzheimer's Disease, Vascular Dementia, or Parkinson's Disease	3. clinical interview, MMSE
4. Mini Mental Status Examination (MMSE) ≤ 24	4. MMSE
5. current or recent (within the past 4 weeks) treatment with antipsychotics or mood stabilizers	5. clinical interview
6. current suicidal ideation (HRSD suicide item > 2) with risk of imminent self-harm	6. HRSD, clinical interview
7. any physical or intellectual disability adversely affecting ability to complete assessments	7. clinical interview
8. acute, severe, or unstable medical or neurological illness	8. clinical interview
9. contraindication to hearing aid placement	9. clinical interview
10. significant retrocochlear pathology or organic brain lesion (e.g., acoustic neuroma) responsible for hearing loss	10.clinical interview
11. having contraindication (e.g. metal) or unable to tolerate the scanning procedures	11. MRI safety screening form

Waiver of Consent/Authorization

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

No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6395R
Describe Study Consent Procedures

Dr. Rutherford, Dr. Brewster, Dr. Broft, Dr. Roose, or Galit Sharon Marcus, NP, MPH will explain the study procedures along with the attendant risks, benefits, and alternatives, including the anticipated outcome of doing nothing. The consenting physician will then leave the room while the potential subject reads the consent form and return to answer any questions the subject has. Subjects who wish to participate will sign the consent form, while those who do not wish to participate will simply not participate.

COVID-19 Phase 1 Re-Opening:
If an individual is deemed eligible for Protocol #7540 after completing the IRB approved virtual portion of the general evaluation (Protocol #7284R), they will be consented into the study. We are requesting to make an adjustment to the consent procedures to accommodate REDCap e-consenting for participants who have a computer and email access. Participants who cannot complete e-consent due to lack of appropriate technology access will be consented on the day of the in-person portion of the evaluation. The consenting clinician will explain the study procedures along with the attendant risks, benefits, and alternatives, including the anticipated outcome of doing nothing. They will also ensure that patients are aware that treatment is available outside the protocol. The consent process will include discussion of the HIPAA-compliant video conferencing to be used for remote visits and any concerns the participant may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi. The consent discussion process will also include any COVID-19 risks related to travel and in-person visits for research purposes.

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

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Brewster, Katharine
Broft, Allegra, MD
Marcus, Galit
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

Following baseline evaluation and MRI scanning, each subject will be counseled on the role of antidepressant medications in clinically significant depressive disorders as well as the risks and benefits of starting/changing antidepressant medication. Subjects will be randomized to receive antidepressant medication (AD) in combination with either full amplification hearing aids or low amplification hearing aids. Subjects who do not wish to change their antidepressant medication will also be offered participation in a subgroup of the study and will be randomized to receive either full amplification hearing aids or low amplification hearing aids. Subjects, treating clinicians, and depressive/cognitive outcome assessors will be blinded to hearing aid assignment. At randomization (Week 0) subjects will have devices placed and receive education by an audiologist, who will not be blinded but will conduct identical procedures for full vs. low amplification hearing aids and will maintain the blinding with participants. Subjects will have follow up audiology appointments at Weeks 2, 6, and 12 to receive further education, monitor compliance, and ensure devices are working correctly. Failure to adhere to hearing aid use requirements at Weeks 2 and/or 6 (as determined by the usage data log), or any hearing aid complications will prompt an additional audiology appointment at Week 9. At Weeks 2, 4, 6, 9, and 12 subjects will complete depression follow-up visits. However, a weekly CGI severity score of 6 or 7 will prompt a weekly session to check-in with the subject.

Study Assessments

1. At baseline, we will record each subject's chief complaint, age of onset of mood and/or cognitive decline, number prior depressive episodes, age, sex, marital status, race and ethnicity, years of education, employment status and income, years of education, and family history. Medical history will be documented, and physical exam, urine drug screen, CBC, chemistries and electrolytes, thyroid profile, vitamin B12 and folate levels, urine analysis, and ECG will be performed. Vital signs will be measured at baseline and monitored throughout the study. The Cumulative Illness Rating Scale-Geriatric (CIRS-G) (81) will be filled out at baseline to measure chronic medical illness burden. Psychiatric diagnosis and eligibility will be determined at screening using the Structured Clinical Interview Diagnostic for DSM 5 (SCID) (82), 24-item HRSD and MMSE.

2. As described below, patients will return for follow up audiology visits at the Columbia Otology and Neuro-otology Clinical Practice at Weeks 0, 2, 6, and 12. At Week 6, if the hearing aid devices are functioning well and the patient is meeting the usage requirement, the audiologist will ask if the patient would like to skip the Week 9 audiology visit and return at Week 12. However, if the patient's hearing aid use does not meet the requirement at Weeks 2 and/or 6 (as determined by the data log) or if there are any hearing aid complications, they will be scheduled for an audiology visit at Week 9. Patients will visit the Clinic for Aging, Anxiety, and Mood Disorders for psychiatric follow up visits at Weeks 0, 2, 4, 6, 9, and

12. However, a weekly CGI severity score of 6 or 7 will prompt a weekly session to check-in with the patient.

3. At psychiatric follow up visits patients will complete the 24-item HRSD, CGI Severity and Improvement, Structured Pill Count Interview (assessment of study medication compliance), Treatment Emergent Side Effect Scale (standardized general checklist used in our clinic for monitoring side effects), Inventory of Depressive Symptoms—Self Report (IDS-SR), Social Adjustment Scale, and Blind assessment—Clinician and Patient Versions (rates clinician and participant's guess as to the identity of full vs. low amplification hearing aids). Medical interns who come to our clinic for 4-week rotations and psychiatry fellows who come to our clinic for 6-month rotations during the Spring semester, may complete psychological assessments on study participants. All medical interns and fellows will have completed NYSPI-specific CITI training for humans subjects research (specifically the biomed or social/behavioral course).

4. At baseline and study endpoint, participants will undergo neuropsychological evaluation. The neuropsych battery will comprise the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (78-79), which was designed to reliably examine intelligence, attention, memory, language, and visuospatial/constructional ability (80-81). Because the RBANS requires instructions and some stimuli to be presented auditorily to each participants, Claes and colleagues (2016) adapted the battery for specific use in hearing impaired populations (82). This RBANS for Hearing Impaired Populations (RBANS-H) will be employed in the current study, and all components of the RBANS-H the instructions in are presented in written format on an external computer monitor simultaneous with the oral administration. Because the RBANS-H has relatively low coverage of executive functioning, we are supplementing it with measures from the NIH Toolbox (Dimensional Change Card Sort Test and the Flanker Inhibitory Control and Attention Test) (83).

5. At baseline and study endpoint, participants also will undergo functional evaluation. Domains of function assessed include: the Short Physical Performance Battery (SPPB) (94), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change. Patients' gait will be assessed by trained raters as walking speed in m/s on a Gaitrite walkway system. Patients are instructed to walk at their usual or normal speed starting and ending at a point 6 feet prior to and after the walkway course to eliminate acceleration and deceleration effects. Two trials will be completed, and gait speed will be based on the average of 2 trials. Physical activity is assessed via a measure of weekly kilocalories (kcal) derived from the 18-item Minnesota Leisure Time Physical Activity Questionnaire (106), with activity levels < 383 kcal considered frail. The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability and 7 domain-specific scores based on the conceptual framework of the International Classification of Functioning, Disability, and Health (ICF) (95). The self-report 38-item Measure of Everyday Cognition (ECog) is adapted from an informant-report version and measures impairment and change in domains of everyday/real-world functioning relevant to 7 specific neuropsychological domains (96).

<u>Hearing aid procedures</u>

1. For audiological assessment, the patient will be seated in a double walled soundproof booth. Pure tone testing will be performed using insert earphones and bone conducted stimuli. Frequencies tested include 250 Hz, 500 Hz, 1k Hz, 2k Hz, 3k Hz, 4k Hz, 6k Hz and 8 k Hz. Speech reception thresholds (SRT) will be

obtained in each ear using standard spondee words. Word recognition will be assessed in each ear using a recorded CNC (consonant-vowel nucleus-consonant) type word list (25 words) at 40dB SL above the patient's SRT. Screening: subjects will have testing of pure tone thresholds, SRT, and word recognition as above.

2. At Week 0, The Hearing Handicap Inventory for the Elderly (HHIE) (77) will be administered, which is a 10-item questionnaire developed to assess how an individual perceives the social and emotional effects of hearing loss. Unaided word recognition will be tested using CNC at 50dB HL and AzBio sentences (condition 1: signal 50dB HL in quiet, condition 2: signal 50dB HL with a +5 SNR using 4 talker babble), both presented at 0° azimuth.

3. Hearing aids will be the latest Audeo B-R 90 devices manufactured by Phonak. Low amplification and full amplification hearing aids will be identical in appearance, battery use, and data logging capability. Low amplification hearing aids will be programmed to prescription for a flat 30dB hearing loss, which will result in a small but noticeable volume increase without substantively improving subject's ability to discriminate speech, which we believe is important for the hearing aids' effect on depressive symptoms. Full amplification hearing aids will have their gain determined by audiometric profile as per standard clinical practice. Real ear measures will be performed to verify fitting, education and counseling will be provided regarding the use of the hearing aid, and subjects will be informed that a minimum of 8 hours/day hearing aid usage is required to stay in the study. To assess compliance with hearing aids, we will measure usage rates (hours/day) using data log technology built into the hearing aids (69-70) Subjects will also sign a hearing aid agreement which includes the provision that if the subject does not complete the 12-week study they must return both hearing aids. If the subject does not complete the 12-week study and would like to keep the hearing aids, he/she can buy the hearing aids at market cost ($5,300). If a subject does not return the hearing aid, he/she will be charged at market cost for the hearing aid ($5,300) to the CUMC/Audiology Department. Furthermore, if the subject does not wear the hearing aids for at least 8 hours a day this will disqualify him/her from the study and he/she will have to return all devices. However, if during the study period the subject breaks or loses the hearing aids, we will provide them a new device at no cost to the subject. .

4. Subjects will have follow up audiology appointments at Weeks 2, 6, and 12, during which their questions about hearing aid usage will be answered and the data log will be checked and reset. At Week 6, if the hearing aid devices are functioning well and the patient is meeting the usage requirement, the audiologist will ask if the patient would like to skip the Week 9 audiology visit and return at Week 12. However, if the patient's hearing aid use does not meet the requirement at Weeks 2 and/or 6 (as determined by the data log) or if there are any hearing aid complications, they will be scheduled for an audiology visit at Week 9. At Week 12, endpoint measures will be collected, which comprise the HHIE and repeat of audiological measurements from Week 0.

<u>Antidepressant medication</u>

1. Following baseline screening, subjects who choose to start a study medication will receive escitalopram 10mg per day or duloxetine 30mg per day. We opted to allow two potential medication choices so that study participation could be offered to individuals who had previously taken one medication and either not responded or not tolerated it. We selected escitalopram and duloxetine based on established efficacy in

MDD, favorable side effect profiles, minimal drug-drug interactions, and cost effectiveness (i.e., available as generics) (67-68).

2. If the best history-taking efforts of study staff (including patient interview, pharmacy records, or other medical records) indicate that a participant has not responded to or has not tolerated escitalopram or duloxetine, then we will offer an alternative SSRI, SNRI, or bupropion based upon our clinical assessment of the best option given the participant's other medications, medical health, and symptom profile. Similarly, if the patient either fails or is unable to tolerate both of the study medications during the study, they will be initiated on another medication that is clinically indicated. If this is the case, the subject receiving non-study AD medication will be responsible for the cost of the medication co-pay and will pick up the prescriptions from their pharmacy.

3. After 4 weeks if subjects do not meet remission criteria (HRSD≤10), the dose of study medication will be increased to escitalopram 20mg or duloxetine 60mg for the remaining 8 weeks of the study. Similarly, the dose of the non-study antidepressant medication will be increased under the guidance of the study clinician. Subjects unable to tolerate an increased dose will have their medication reduced to the previously tolerated dose. If a study subject wishes to change antidepressant medication at any point during the study period they may do so under the guidance of the study clinician.

MRI procedures

1. Participants will undergo an MRI scan at baseline and study endpoint (prior to unblinding).

2. Image Acquisition: MRI of the brain will be conducted using the following sequences: (1) Axial IR-FSPGR TE/TR=3ms/6.5ms, TI=450ms, flip angle=12º, voxel size=1x1x1mm, 180 contiguous slices, total acquisition time=4min; (2) Multi-Band (or Simultaneous Multi-Slice) EPI, TE/TR=30/800ms, flip angle=52°, matrix=90x90, voxel size=2.4x2.4x2.4mm, acquisition time=5min(rs-fMRI)/7min(task-fMRI); (3) for DWI, TE/TR=88ms/4100ms, voxel size=1.7x1.7x1.7mm, flip angle=90°, FOV=240×240 mm, matrix=140×140, diffusion directions=102, b value=1000s/m^2, acquisition time=7.5min, (4) 3D T2-weighted FLAIR, TE/TR=144/8000ms, voxel size=1x1x1mm, acquisition time=8 min. During the fMRI scanning, subjects' wakefulness will be monitored using a MR-compatible eye-tracking camera.

3. Simon Task: For the Simon Task, a series of white arrows pointing either left or right is displayed against a black background either to the left or right of a white gaze fixation cross-hair positioned at midline. Stimuli are ‘congruent’ (arrows pointing in the same direction as their position on the screen) and ‘incongruent’ (pointing in a direction opposite their position on the screen). Each experiment contains 3 runs, totaling 66 incongruent and 66 congruent stimuli. Participants are instructed to respond as quickly as possible to the direction of the arrow by pressing one of 2 buttons on a response box. Stimulus duration is 1300ms, with jittered inter-stimulus intervals ranging from 4 to 7 seconds. Behavioral outcome measures are reaction times (RT) and accuracy scores on congruent and incongruent trials, and the Simon effect (mean RT incongruent>mean RT congruent).

4. Subject Comfort: For the MRI procedures, the subject will be instructed to lie as still as possible within the magnet for approximately 30 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.

5. Anxious/Nervous Subject: 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.

6. MRI Conduction: 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, as well as in procedures for testing human subjects.

7. MRI Reading: 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. We will send the subject one of three MRI result letters reflecting findings of (1) no significant findings (2) findings to be discussed with study physician (3) significant irregularity that necessitates immediate follow-up

8. Safety Precautions: 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.

9. Image processing and analysis: FMRI scans will be preprocessed using SPM 12 (slice-timing correction, motion correction, spatial normalization, and smoothing with 8mm FWHM). Region-of-interest (ROI) and whole brain analysis will be done with False Discovery Rate control (86). Regions within the CCN will constitute our ROI, given an association of decreased connectivity with LLD (87) and antidepressant response (88) (e.g., the DLPFC, dACC, supramarginal gyrus, putamen, and anterior insula) (89). Simon-Task fMRI: Preprocessed data will be entered to a subject-level regression model with 3 regressors (convolved with the canonical hemodynamic response and time derivative) corresponding to 1) congruent correct trials, 2) incongruent correct trials, and 3) incorrect trials. T-contrast images of "incongruent-minus-congruent" in each participant will be entered into a group-level mixed effects model. Resting MRI: Seed-based intrinsic functional connectivity will be carried out in the CONN toolbox v13 (90). Mean BOLD time series of each seed region will be correlated (Pearson's correlation) with timeseries of every other voxel's. Structural MRI: Morphometric measures (volume, thickness, surface area, etc) will be estimated using Freesurfer suite (91). WMH volumes will be estimated from FLAIR image using a semi-automated method by which WMH are seeded and passed through an iterative algorithm to yield WMH volumes. DWI: DWI will be preprocessing in MRtrix3 (92) (brain extraction, PCA-based denoising (93), eddy current correction (94), distortion correction (95), tensor modeling fitting to get anisotropy and diffusivity measures). Two

analyses will be performed: probabilistic tractography within the CCN ROIs (as above, 92), and voxel-based morphometry optimized to WM tracts (Tract-Based Spatial Statistics) (96). For probabilistic tractography, structural connection strength will be indexed by number of estimated WM streamlines (NOS; validated quantification of WM projection strength) (97). Further, quantitative nature of tractography will be enhanced by filtering out non-biologically plausible (false-positive) streamlines using Spherical-deconvolution Informed Filtering of Tractograms (SIFT) (98). For voxel-based morphometry (TBSS), diffusivity (MD) and anisotropy (FA) images will be warped into a study-specific template brain and projected onto alignment-invariant tract representation.

End of study procedures

1. At the end of the 12 week study, participants will be notified the group to which they were assigned (low amplification or full amplification). Participants in the low amplification group will meet with the study audiologist to have their hearing aids set to full gain as per standard clinical practice. All participants will be allowed to keep their hearing aids and will have clinical follow up visits scheduled in the Columbia Otology clinic as per routine practice. Patients will use their insurance or otherwise cover the costs of their clinical audiologic care as they normally would outside the context of a research study. However, the study will cover one post-protocol audiology visit for participants in the low-amplification group in order to to ensure the devices are working correctly and to answer questions the patient may have about their newly working devices.

2. Patients will also receive the typical 3 months post-protocol open treatment in the CAAM. Depending on their clinical status, options to continue, augment, switch, or begin the study antidepressant medication will be discussed with patients.

COVID-19 Phase 1 Re-Opening:

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- No volunteers/externs on-site during Stage 1.
- Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Baseline/Week 0:
This visit will be completed in two components, one in-person and one virtual. When a participant comes in to complete the in-person portion of the evaluation, they will also complete the baseline neuropsychological (NIH Toolbox DCCST and Flanker, RBANS-H) and physical (SPPB, Gait Speed) measures, which must be completed in-person with a research staff member, as well as the physical examination. Participants will be asked COVID-19 screening questions before entering the building on the day of the in-person visit. Institute Safety guidelines for social distancing during visits and appropriate sanitation plans will be implemented and maintained. The audiology appointment will remain an in-person visit. The remainder of the

Baseline/Week 0 visit will be conducted virtually with both a research staff member and study clinician. If necessary, the Baseline/Week 0 virtual visit may become an in-person visit, at the discretion of the clinician.

Week 2-Week 9 Visits:
Week 2, 4, 6, and 9 psychiatric follow-up study visits will be completed virtually. If necessary, any virtual visit may become an in-person visit, at the discretion of the study clinician. Audiology appointments will remain as in-person visits.

Week 12:
This visit will be completed in two components, one in-person and one virtual. During the in-person portion, the participant will complete the endpoint neuropsychological (NIH Toolbox DCCST and Flanker, RBANS-H) and physical (SPPB, Gait Speed) measures, which must be completed in-person with a research staff member. The remainder of the Week 12 visit will be conducted virtually with both a research staff member and study clinician. If necessary, the Week 12 virtual visit may become an in-person visit, at the discretion of the clinician. The audiology appointment will remain an in-person visit.

Open Treatment:
The three-month open treatment procedures will be conducted virtually, per the protocol, with monthly check-in visits occurring virtually.

MRI Scans:
Scanning procedures will continue as usually conducted per the protocol once the NYSPI MRI suite re-opens for scanning. COVID-19 screeners will be completed as per suite guidelines. If a patient is scanning-eligible, a research staff member will schedule the Baseline MRI scan as close to the evaluation date as possible. The NYSPI MRI Suite may have limited availability due to the backlog generated by the COVID-19 pandemic. Safety procedures to ensure social distancing and minimal physical contact will be strictly followed. Compensation for these scans will be provided by sending participants an e-gift card, physical gift card, or check.

Patients will be offered paid transportation (i.e. Uber car service) to clinic for in-person visits, subject to a $50 limit each way per week.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
The risk of receiving low amplification hearing aids, no antidepressant medication, or non-response to antidepressant medication during the study period is addressed by having close clinical follow up of study subjects and stringent withdrawal criteria. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening in the judgment of the study clinician; (3) a CGI-Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits; or (4) development of significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated

clinically. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
A 20cc blood sample will be drawn at baseline. General medical tests will be performed, such as CBC, Chem 7, LFTs, TSH, cholesterol, B12, and folate.

Assessment Instruments

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

Cumulative Illness Rating Scale-Geriatric (CIRS-G) (71) will be filled out at baseline to measure chronic medical illness burden.

Psychiatric diagnosis and eligibility will be determined at screening using the Structured Clinical Interview Diagnostic for DSM 5 (SCID) (72) and MMSE.

24-item HRSD: standard measure of depression severity that measures changes in depressive symptoms.

CGI Severity and Improvement (73): scales measuring the clinician's view of subjects' global functioning that will provide a clinical assessment of subjects at each visit and help maintain safety by identifying clinical worsening.

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

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

Inventory of Depressive Symptoms—Self Report (IDS-SR) (74): rating scale based on DSM criteria that is increasingly used in antidepressant studies due to its equivalent weightings for each item and understandable anchor points.

The Social Adjustment Scale Self-Report (SAS-SR) is a self-report scale that measures instrumental and expressive role performance over the past 2 weeks in adults (75). The 54-item assessment covers six areas of functioning, including work (either as a paid worker, unpaid homemaker, or student), social and leisure activities, relationships with extended family, role as a marital partner (if applicable), parental role (if applicable), and role within the family unit (including perceptions of economic functioning).

Blind assessment—Clinician and Patient Versions: rates clinician and participant's guess as to the identity of active vs. sham hearing aids.

Physical function will be assessed at baseline and Week 12 using the Short Physical Performance Battery (SPPB) (76), a performance measure of gait, balance, and lower extremity strength.

Patients' gait will be assessed by trained raters as walking speed in m/s on a Gaitrite walkway system. The Gaitrite walkway system is a portable, 27-foot long mat which measures temporal (timing) and spatial (distance) gait parameters (temporal/spatial) via grids of embedded, pressure-sensitive sensors connected to a computer.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (78-79) was designed to reliably examine intelligence, attention, memory, language, and visuospatial/constructional ability (80-81). This RBANS for Hearing Impaired Populations (RBANS-H) will be employed in the current study, and all components of the RBANS-H the instructions in are presented in written format on an external computer monitor simultaneous with the oral administration.

Because the RBANS-H has relatively low coverage of executive functioning, we are supplementing it with measures from the NIH Toolbox (Dimensional Change Card Sort Test and the Flanker Inhibitory Control and Attention Test) (83).

Physical activity is assessed via a measure of weekly kilocalories (kcal) derived from the 18-item Minnesota Leisure Time Physical Activity Questionnaire (106), with activity levels < 383 kcal considered frail**.**

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
N=20 subjects will receive hearing aids that are not fully tuned such that they improve hearing, so there is a delay for hearing treatment. Mitigating this risk are the facts that all subjects will be offered an active treatment for depression (i.e., antidepressant medication), and all subjects will be aware that they will receive functioning hearing aids for their hearing loss at the end of the study. However it is possible that antidepressant and hearing treatment may be delayed due to scheduling study MRI scans and audiology visits, 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
See above.

Treatment to be provided at the end of the study
As per study procedures, all subjects will receive free functioning hearing aids at the end of the study as well as 3 mo open treatment in LLDC.

Clinical Treatment Alternatives

Clinical treatment alternatives

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

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
1. Interview, emergencies, and possible suicidal ideation: Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms and current life events. The study coordinators are experienced and skilled in interviewing depressed subjects. Half-way through the initial assessment, the coordinator will ask the subject if they would like to take a break, and this will be provided if desired. A study clinician will be available during all aspects of the assessment if there are any questions or problems. In addition, should the subject express suicidal ideation at any time during the interview, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver, referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

2. Antidepressant Side Effects: Side effects will be assessed at each planned visit and if needed through additional or unscheduled contacts. We will attempt to minimize side effects by slow dosage titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of escitalopram or duloxetine. Side effects of these medications include somnolence, diarrhea, nausea, impaired ejaculation, impotence, dry mouth, tremor, and sweating. Escitalopram and duloxetine have black box warnings regarding an increased risk for suicidal thinking and behavior in adolescents and young adults (less than 24 years old) given the drug. Both drugs are of unknown risk to a fetus. Since the proposed study will enroll subjects aged 60-90 years, these particular risks are not expected to be applicable. Regardless, all subjects will be asked to tell their doctors immediately if they experience suicidal thoughts, and menopausal status and date of last menstrual period will be documented in all female participants.

Subjects may be prescribed alternative medications (SSRI, SNRI, or bupropion) in the event they are judged to have failed or not tolerated escitalopram and duloxetine. As a class, SSRIs can be associated with somnolence, diarrhea, nausea, impaired ejaculation, impotence, dry mouth, tremor, and sweating, in addition to low risk of increased gastrointestinal bleeding in older adults. SNRIs as a class may be associated with these same risks, in addition to the risk of mildly elevated blood pressure at the upper dosage ranges. The most frequent (occurs in more than 25% of people) side effects of bupropion include

agitation, dry mouth, and headache. Common side effects (occurs in 1-25% of people) include excessive sweating, dizziness, tremor, constipation, nausea, decreased appetite, weight loss, rash, heart pounding, high blood pressure, unsteadiness when walking, confusion, anxiety, increased urination, and difficulty sleeping. Increased risk of seizures occurs in patients taking 400mgs or more.

3. Delay in Initiation of Hearing Treatment: A risk to subjects in this study is the potential delay in receiving effective treatment for their hearing loss. N=20 subjects will receive hearing aids that are not fully tuned such that they improve hearing. Mitigating this risk are the facts that all subjects will be offered an active treatment for depression (i.e., antidepressant medication), and all subjects will be aware that they will receive functioning hearing aids for their hearing loss at the end of the study.

4. Gait speed assessment: During the physical performance assessments, patients may feel unsteady and as such their risk of falls may increase. To mitigate these risks, patients are accompanied by research coordinators and/or doctors during each of the performance-based assessments (including the gait assessment, balance test, and chair stand, the latter two components of the Short Physical Performance Battery). Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

5. Non-study antidepressant subgroup: A risk for those in this subgroup who do not wish to change their current antidepressant medication despite ongoing depressive symptoms is that their symptoms may not be adequately treated with an antidepressant medication. However, prior to assigning them to this subgroup, each subject will be counseled on the risks and benefits of antidepressant medication, will be offered to change antidepressant medications, and if they choose to not change antidepressant medication they will be closely monitored for clinical worsening throughout the study period. Prior to consenting the subject, we will also offer alternative treatments to participating in this study including psychotherapy outside of the research project. Furthermore, if the subject wishes to change antidepressant medications at any point during the study period they will be initiated on antidepressant medication under the guidance of the study clinician. Also mitigating this risk are the facts that all subjects will receive functional hearing aids for their hearing loss by the end of the study.

6) MRI risks: While there have been no reports of any harmful long-term effects caused by 3T magnets or magnets of even higher strength, the long-term effects of being placed in a magnet of this strength are unknown. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. If the female subject is pre- or peri-menopausal, she will asked to take a pregnancy test to ensure that she is not pregnant. Some people have reported sensations during MRI scans with the 3T magnet, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some 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 subject experiences any discomfort and wish to stop the scan, they will be instructed to inform a MRI technologist, and he or she will stop the scan immediately.

7) COVID-19 Phase 1 Re-Opening: Due to the COVID-19, individuals are at increased risk for exposure to COVID-19 both in transit to NYSPI as well as during their time at NYSPI for in-person visits. Procedures

are in place to minimize this risk as well as minimize the number of in-person visits required for this protocol. Patients will be offered paid transportation (i.e. Uber car service) to clinic for in-person visits, subject to a $50 limit each way per week, to help reduce potential exposure on public transportation. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible.

Describe procedures for minimizing risks

We have included our plans to minimize risk in our discussion of the risks themselves, please see above.

COVID-19 Phase 1 Re-Opening:
For in-person visits to NYSPI, individuals are at increased risk for exposure to COVID-19 both in transit to NYSPI as well as during their time at NYSPI. Procedures are in place to minimize this risk. We plan to offer car transportation subject to a maximum of $50 each way, which minimizes exposure to public transportation for those participants. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible (exceptions exist for procedures such as blood draws and EKGs). Screen shields between patient and staff will be used during neuropsychological testing to further minimize exposure risk.

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.

COVID-19 Phase 1 Re-Opening:
Due to the implementation of virtual visits, additional measures to protect patient confidentiality will be employed. These include using only secure HIPAA-compliant video conferencing recommended by NYSPI for virtual calls (WebEx, etc.) and the use of headphones during virtual calls.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
No direct benefits to subjects are guaranteed, but individuals may benefit from receiving open

antidepressant treatment and from receiving full amplication hearing aids.

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 be provided **$125 for completion of MRI at baseline and $125 for completion of the end point MRI**, paid in the form of a gift card, e-gift card, or check. **Participants could earn up to a total of $250 for completing MRI procedures.**

All subjects will be allowed to keep their hearing aids following the completion of the study.

To help reduce patients' potential exposure to COVID-19 on public transportation, we will be offering patients paid transportation (subject to a maximum of $50 limit each way per week) for in-person study visits.

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DEPARTMENT OF PSYCHIATRY

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Treating Hearing Loss to Improve Mood and Cognition in Older Adults

The purpose of this study is to determine whether treating hearing loss is helpful for depression over and above the known effects of antidepressants. Age-related hearing loss (ARHL) is the third most common health condition affecting older adults after heart disease and arthritis and is the fifth leading cause of years lived with disability worldwide.

In this 12-week research study, participants will be fitted with hearing aids that may be fully tuned to improve hearing (full dose) or may be only partially tuned and not likely to substantially improve hearing (low dose). Participants will receive free hearing aids that will be at full dose at the end of the study. They will also receive treatment for depression with an FDA approved medication called escitalopram (Lexapro) or duloxetine (Cymbalta). Escitalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) medication, and duloxetine is a Selective Serotonin-Norepinephrine Reuptake Inhibitor (SSNRI) that both appear to help with symptoms of depression.

<u>You may be eligible if you:</u>

- Are 60 years or older
- Have moderate to severe hearing loss
- Have low mood or feelings of isolation

Eligible participants may receive up to $250 in financial compensation over the course of participation and free hearing aids.

Scan the QR code above for more information or call 646-774-8677 for a free screening to determine your eligibility.
You can also email us at CAAMlab@nyspi.columbia.edu

COLUMBIA UNIVERSITY MEDICAL CENTER

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Do you have hearing loss?
Are you feeling down or isolated?

Study looking at the relationship between **hearing loss** and **depression** seeking participants ages **60+** with:

- **Moderate** to **severe** hearing loss
- Low mood or feelings of isolation

<u>If you qualify, you may receive:</u>

- Comprehensive cognitive testing
- **Free hearing aids**
- Depression treatment
- Travel compensation
- MRI Scans
- Compensation of up to $250

Scan the QR code above for more information or call 646-774-8677 for a free screening to determine your eligibility.

This study is being conducted at NYSPI/ Columbia University Irving Medical Center

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NEW YORK STATE PSYCHIATRIC INSTITUTE
TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS

Overview

Below is a summary of the study that you are asked to participate in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form, which you will have to sign if you decide to participate in the study. The consent form contains detailed information about the study and about the risks which you will need to consider before making your decision. Read the consent form carefully and discuss it with others before deciding to take part. And remember that, even if you agree to participate, you can change your mind at any time with no negative consequences to the care you would otherwise receive at Columbia University and/or the New York State Psychiatric Institute.

Participation is Voluntary

As with all research, this is a voluntary study, and you do not have to participate if you do not want to. Also, you may stop participating at any time with no negative consequences to the care you would otherwise receive at Columbia University and/or the New York State Psychiatric Institute.

Alternatives

You do not have to participate in this study to receive treatment for your depression or hearing loss. Antidepressant medication, psychotherapy, and their combination may be helpful for depression. Hearing aids, other hearing assistive devices, and surgical procedures are available for the treatment of age-related hearing loss. These treatments are available outside of this research project. Additionally, it is not necessary to participate in this research study to have an MRI, and the MRIs done as part of this study are not the same as those done for medical purposes. Information being collected is for research purposes only and is to learn more about the treatment of age-related hearing loss and depression, not about you.

Procedures

- At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), and have your blood drawn. You will also have a hearing test and an evaluation of your attention, memory, and thinking.
- Before receiving the study treatment, you will be asked to have a magnetic resonance imaging (MRI) scan, which uses strong magnetic fields and radio waves to take pictures of your brain.
- Then you will be randomly assigned to receive treatment with an antidepressant medication plus “full dose” hearing aids or an antidepressant medication plus “low dose” hearing aids. If you are currently taking antidepressant medication and do not wish to change to one of the medications offered in this study, you will be randomly assigned to receive treatment with only "full dose" or "low dose" hearing aids.
- You will be asked to return for follow up visits to see one of the study doctors, talk about how you are feeling, and have the hearing aids adjusted.

- The research study will end after 12 weeks. Tests of your hearing as well as the psychological tests and MRI you had at the beginning of the study will be repeated.

Some of your visits may be conducted remotely using the telephone or HIPAA-compliant video teleconferencing.

Risks

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). These include the risk that your hearing loss may continue or remain unchanged if you are assigned to "low dose" hearing aids, that your depression may remain unchanged if you choose not change to one of the antidepressant medications offered in this study, side effects associated with antidepressant medication (such as nausea, trouble sleeping, and inability to have an orgasm during sexual activity), and nervousness or discomfort associated with the MRI scans and psychological tests.

During the COVID-19 pandemic, there is an increased risk for exposure to COVID-19 both in transit to NYSPI as well as during your time at NYSPI for in-person visits.

Benefits

This research study is not meant to benefit you directly. However, you may feel less depressed as a result of receiving medication for your depression. All participants in this study will receive free hearing aids, though half of people will receive "low dose" hearing aids for the 12 week duration study. These will be fully tuned and in working order at the end your study participation.

You may contact the study doctor, Dr. Bret Rutherford at 646-774-8660 with any questions.

NEW YORK STATE PSYCHIATRIC INSTITUTE
TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS

PURPOSE OF STUDY

In this research study, you will be fitted with hearing aids that may be fully tuned to improve your hearing ("full dose") or may be only partially tuned and not likely to substantially improve your hearing ("low dose"). You may also receive treatment for depression with an FDA approved medication called escitalopram (Lexapro) or duloxetine (Cymbalta). Escitalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) medication, and duloxetine is a Selective Serotonin-Norepinephrine Reuptake Inhibitor (SSNRI) that both appear to help with symptoms of depression. The purpose of this study is to determine whether treating hearing loss is helpful for depression over and above the known effects of antidepressants.

This study has pending support by an Exploratory/Developmental Grant from the National Institute on Aging.

VOLUNTARY

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Irving Medical Center.

ALTERNATIVE TREATMENT

You do not have to participate in this study to receive treatment for your depression or hearing loss. The alternative to participating in this study is to seek treatment outside of the research project so that you would be certain of receiving fully tuned hearing aids. In addition, other antidepressant medications besides escitalopram and duloxetine are available for the treatment of depression (e.g., fluoxetine (Prozac), sertraline (Zoloft), etc). Psychotherapy may also be helpful with depression, whether on its own or combined with medication. You also do not have to participate in this study to have an MRI, and the MRIs done as part of this study are not the same as those done for medical purposes.

STUDY PROCEDURES

If you are eligible and decide to participate in the study, you will be randomly assigned to one of the different treatment options. The random assignment is made similarly to flipping a coin. If you are assigned to the first option, you will receive treatment with an antidepressant medication (either escitalopram or duloxetine based on your past treatment history and preferences) and be fitted with "full dose" hearing aids to improve your hearing. If you are assigned to the second option, then you will receive escitalopram or duloxetine and be fitted with "low dose" (partially functional) hearing aids that will not fully improve your hearing. If you have previously received treatment with both medications offered in this study, you will be initiated on another clinically appropriate medication. If you would like to participate in the study but do not wish to change your current antidepressant medication, you will be assigned to

either the "full dose" or "low dose" hearing aid option, without receiving the antidepressant medication treatment. The “low dose” hearing aids look like the “full dose” hearing aids, but they will not be fully tuned to improve your hearing. You may or may not notice immediate changes in your hearing after the beginning of the study, because often hearing aids need to be adjusted over a period of several weeks in order to function properly. Neither you nor your doctors will know whether you are getting the low or full dose hearing aids until the end of the study.

At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), and have your blood drawn. The total amount of blood taken at this study visit is about two tablespoons. Results of these blood tests will be available to you, should you request them. You will have your hearing tested by an audiologist to measure the severity of your hearing loss and how well you are able to understand spoken words. You will also complete some psychological questionnaires and tests of your attention, memory, thinking, and physical functioning. These tests can be completed by telephone, videoconference, or in-person and take about one hour to complete. The results of these tests are for research purposes only and will not be shared with you.

You may also have MRI (Magnetic Resonance Imaging) scans at the beginning and end of the study. The MRI uses strong magnetic fields and radio waves to take pictures of your brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the imaging procedures, we will determine that you do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and you will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). You will be asked to lie flat on your back in the MRI scanner for about 60 minutes and to remain as still as possible. You will not feel anything, but you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong.

You will be asked to return for 6 visits over the course of 12 weeks to see one of the study doctors and talk about how you are feeling. During the COVID-19 pandemic, some of your visits may be conducted remotely using the telephone or secure, HIPAA-compliant video teleconferencing. Based on clinical evaluation, you may be required to complete more than 6 visits. On 4 of these visits, you will also see an audiologist to evaluate the hearing aids and make sure they are working as designed. Based on hearing aid compliance and/or complications, the audiologist may require you to return for an additional visit. These meetings will last about 30 minutes. If you choose to take one of the antidepressant medications offered in this study and still have depressive symptoms after four weeks on the pills you are given, the dose will be increased to two pills (either 20mg of escitalopram or 60mg duloxetine, depending on the medication you started). If you choose to take one of the antidepressant medications offered in this study, you will receive free medication for the duration of the study, and the hearing aids and hearing assessments during the study are also free.

During the 12 week long study, you may not receive outside treatment for your depression or hearing beyond what is supplied by your study doctor. If your doctor feels your condition worsens significantly, the current treatment will be stopped, and you will be offered different treatments for your depression or hearing. Your doctor may stop your participation in the study at any time without your consent if you do not comply with the study procedures (such as by not wearing the hearing aids for at least 8 hours per day). The research study will end after 12 weeks. During the week 12 visit, you will again fill out some psychological tests and have

your hearing tested. Some of these assessments will be completed remotely by telephone or HIPAA-compliant video conferencing, while others will be completed in-person.

Following the research study, you will receive 3 months of free doctor visits in the depression clinic and at least 1 month of free antidepressant medication. During the COVID-19 pandemic, these will be conducted remotely. You will be allowed to keep your hearing aids. If your hearing aids were "low dose" during the research study, an audiologist will fully tune them so that they improve your hearing and you will be scheduled for an additional audiology visit following the research study to make sure the hearing aids are working properly and to answer any questions you may have.

RISKS

The main risk of the study is that your hearing loss will not be fully treated if you are assigned to the "low dose" hearing aid group until after the 12 week study is over. The most common side effects reported for escitalopram and duloxetine are nausea, insomnia, and inability to have an orgasm. Less common side effects reported for escitalopram and duloxetine include constipation, dry mouth, dizziness, headache, insomnia, and sedation. If the study physician prescribes a different antidepressant for you, the potential risks and side effects of that particular medication will be discussed with you.

When taking the antidepressant medication offered in this study you should be careful about drinking alcohol, since it may have a greater effect on you in combination with medication. You must not take monoamine oxidase inhibitor (MAOI) drugs (tranylcypromine or Parnate, phenelzine or Nardil) during the study or within five weeks of ending the study. Serious reactions, including death, have been reported when MAOIs are coadministered with medications like escitalopram or duloxetine.

When your blood is drawn, there is a small risk of skin infection of that you may be left with a bruise that will resolve within a few days. The results of your blood tests will be shared with you, and if you would like, you will be provided with a copy of the results to discuss with your primary medical doctor. Blood taken for research purposes will remain confidential.

While there have been no reports of any harmful long-term effects caused by 3T magnets or magnets of even higher strength, the long-term effects of being placed in a magnet of this strength are unknown. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. If you are a female in your childbearing years, you will be asked to take a pregnancy test to ensure that you are not pregnant.

Some people have reported sensations during MRI scans with the 3T magnet, 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 your body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some 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 you experience any discomfort and wish to stop the scan, you can tell the MRI technologist, and he or she will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

During the COVID-19 pandemic, specifically for in person visits to NYSPI, there is an increased risk for exposure to COVID-19 both in transit to NYSPI as well as during your time at NYSPI. Procedures are in place to minimize this risk. We are offering paid car transportation for

in-person study visits, subject to a maximum of $50 each way per week to minimize exposure to public transportation. At NYSPI, personal protective equipment such as masks will be utilized at all times both by staff and participants, and social distancing will be adhered to when possible (exceptions exist for procedures such as blood draws and EKGs). Screen shields between staff and yourself will be used during neuropsychological testing to further minimize exposure risk.

RESULTS OF YOUR MRI

While MRI scans are sometimes done for clinical purposes, the kind of MRI scan you may have as part of this study is for research purposes only. This means that the scans are not designed to provide clinical information that might be helpful to you or your doctor and they may not show problems that would normally be found in an MRI ordered to evaluate a specific medical problem. It is likely that the MRI scans will not have the quality of those done for clinical purposes. However, within a month of each MRI, the scan will be read by a neuroradiologist for evidence of any obvious irregularities requiring your follow-up. You, or a physician whom you may designate, will be informed if significant abnormalities are detected. We can also inform you if there were no obvious findings. Given the nature of the scans, the absence of a finding does not mean that one is not present.

BENEFITS

You may not benefit from this study, and no benefit is in any way guaranteed as a result of your participation. However, you may feel less depressed as a result of receiving medication for your depression. You will receive free hearing aids by virtue of participating in this study, and these may improve your hearing loss.

CONFIDENTIALITY

Your records will be stored in a locked file and will be available only to the research staff and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Representatives of the state and institutional regulatory personnel may review your records to ensure compliance with study design. There are legal advocacy organizations that have the authority under State Law to access otherwise confidential records, though they cannot be redisclosed without your consent. All records will be kept confidential to the extent permitted by law. Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute. Electronically stored data will be accessible only by password known to the study investigators and research assistants. Your private information or biospecimens will not be used for future research studies or distributed to another investigator for future research studies. Biospecimens will not be used for commercial profit. Biospecimens will not include whole genome sequencing. All MRI scans and related data will be kept on the secure, password protected, MRI server at NYSPI and will be accessible only to the members of the research team. MRI scan reports will be provided to the clinic by the MRI scanner, and kept in a locked file. Your MRI will be interpreted and the results will be shared with you or a physician who you may designate. Your confidentiality will be protected during remote procedures through the use of secure, HIPAA-compliant video conferencing platforms and headphones for virtual calls.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide

them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COMPENSATION AND ECONOMIC CONSIDERATIONS

You will not be charged for any procedures that are a part of this study, including the hearing tests, hearing aids, antidepressant medication, and MRI scans. However, as described in hearing aid agreement if you do not complete the 12-week study or do not wear the hearing aid for at least 8 hours per day and are disqualified from the study, you must return all devices. If you do not return the devices you may be charged $5300 to the CUMC – Audiology Department. However, if you break or lose the device during the study period, the devices will be replaced at no cost to you.

We offer $**125 for the completion of each MRI scan ($250 for completion of both MRI scans).** Due to the COVID-19 pandemic, compensation can be received in the form of a gift card or check mailed to the address you specify after the completion of each MRI scan. During the COVID-19 pandemic, we will also offer you paid car transportation for in- person study visits, limited to a maximum of $50 each way per week.

IN CASE OF INJURY

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries.

If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator at 646-774-8660 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital will furnish that emergency medical determined to be necessary by the medical staff of this hospital. Please be aware that you will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.

No monetary compensation for wages lost as a result of injury will be paid to you by Research Foundation for Mental Hygiene, the New York State Psychiatric Institute, Columbia

University, or by New York Presbyterian Hospital. However, you should be aware that by signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

QUESTIONS

If you have further questions about the research procedures, or about your response to the procedures, research staff members are available to answer them to the best of their ability. You can reach Dr. Bret Rutherford at 646-774-8660 during general business hours. In an emergency, you may reach the on-call doctor at 917-786-6940, 24 hours per day. If you have general questions, you may contact the research coordinator at 646-774-8698. We will notify you of any significant new findings that may relate to your willingness to continue to participate.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of human subjects in research studies). You may call regular office hours.

DOCUMENTATION OF CONSENT

I voluntarily agree to participate in the research study described above.

Print name:_____

Signed:_____

Date:_____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name:_____
Person Designated to Obtain Consent

Signed:_____

Date:_____

You will be given a copy of this consent form to take with you.

NEW YORK STATE PSYCHIATRIC INSTITUTE
TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS

Overview

Below is a summary of the study that you are asked to participate in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form, which you will have to sign if you decide to participate in the study. The consent form contains detailed information about the study and about the risks which you will need to consider before making your decision. Read the consent form carefully and discuss it with others before deciding to take part. And remember that, even if you agree to participate, you can change your mind at any time with no negative consequences to the care you would otherwise receive at Columbia University and/or the New York State Psychiatric Institute.

Participation is Voluntary

As with all research, this is a voluntary study, and you do not have to participate if you do not want to. Also, you may stop participating at any time with no negative consequences to the care you would otherwise receive at Columbia University and/or the New York State Psychiatric Institute.

Alternatives

You do not have to participate in this study to receive treatment for your depression or hearing loss. Antidepressant medication, psychotherapy, and their combination may be helpful for depression. Hearing aids, other hearing assistive devices, and surgical procedures are available for the treatment of age-related hearing loss. These treatments are available outside of this research project. Additionally, it is not necessary to participate in this research study to have an MRI, and the MRIs done as part of this study are not the same as those done for medical purposes. Information being collected is for research purposes only and is to learn more about the treatment of age-related hearing loss and depression, not about you.

Procedures

- At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), and have your blood drawn. You will also have a hearing test and an evaluation of your attention, memory, and thinking.
- Before receiving the study treatment, you will be asked to have a magnetic resonance imaging (MRI) scan, which uses strong magnetic fields and radio waves to take pictures of your brain.
- Then you will be randomly assigned to receive treatment with an antidepressant medication plus “full dose” hearing aids or an antidepressant medication plus “low dose” hearing aids. If you are currently taking antidepressant medication and do not wish to change to one of the medications offered in this study, you will be randomly assigned to receive treatment with only "full dose" or "low dose" hearing aids.
- You will be asked to return for follow up visits to see one of the study doctors, talk about how you are feeling, and have the hearing aids adjusted.

- The research study will end after 12 weeks. Tests of your hearing as well as the psychological tests and MRI you had at the beginning of the study will be repeated.

Some of your visits may be conducted remotely using the telephone or HIPAA-compliant video teleconferencing.

Risks

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). These include the risk that your hearing loss may continue or remain unchanged if you are assigned to "low dose" hearing aids, that your depression may remain unchanged if you choose not change to one of the antidepressant medications offered in this study, side effects associated with antidepressant medication (such as nausea, trouble sleeping, and inability to have an orgasm during sexual activity), and nervousness or discomfort associated with the MRI scans and psychological tests.

During the COVID-19 pandemic, there is an increased risk for exposure to COVID-19 both in transit to NYSPI as well as during your time at NYSPI for in-person visits.

Benefits

This research study is not meant to benefit you directly. However, you may feel less depressed as a result of receiving medication for your depression. All participants in this study will receive free hearing aids, though half of people will receive "low dose" hearing aids for the 12 week duration study. These will be fully tuned and in working order at the end your study participation.

You may contact the study doctor, Dr. Bret Rutherford at 646-774-8660 with any questions.

NEW YORK STATE PSYCHIATRIC INSTITUTE
TREATING HEARING LOSS TO IMPROVE MOOD AND COGNITION IN OLDER ADULTS

PURPOSE OF STUDY

In this research study, you will be fitted with hearing aids that may be fully tuned to improve your hearing ("full dose") or may be only partially tuned and not likely to substantially improve your hearing ("low dose"). You may also receive treatment for depression with an FDA approved medication called escitalopram (Lexapro) or duloxetine (Cymbalta). Escitalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) medication, and duloxetine is a Selective Serotonin-Norepinephrine Reuptake Inhibitor (SSNRI) that both appear to help with symptoms of depression. The purpose of this study is to determine whether treating hearing loss is helpful for depression over and above the known effects of antidepressants.

This study has pending support by an Exploratory/Developmental Grant from the National Institute on Aging.

VOLUNTARY

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Irving Medical Center.

ALTERNATIVE TREATMENT

You do not have to participate in this study to receive treatment for your depression or hearing loss. The alternative to participating in this study is to seek treatment outside of the research project so that you would be certain of receiving fully tuned hearing aids. In addition, other antidepressant medications besides escitalopram and duloxetine are available for the treatment of depression (e.g., fluoxetine (Prozac), sertraline (Zoloft), etc). Psychotherapy may also be helpful with depression, whether on its own or combined with medication. You also do not have to participate in this study to have an MRI, and the MRIs done as part of this study are not the same as those done for medical purposes.

STUDY PROCEDURES

If you are eligible and decide to participate in the study, you will be randomly assigned to one of the different treatment options. The random assignment is made similarly to flipping a coin. If you are assigned to the first option, you will receive treatment with an antidepressant medication (either escitalopram or duloxetine based on your past treatment history and preferences) and be fitted with "full dose" hearing aids to improve your hearing. If you are assigned to the second option, then you will receive escitalopram or duloxetine and be fitted with "low dose" (partially functional) hearing aids that will not fully improve your hearing. If you have previously received treatment with both medications offered in this study, you will be initiated on another clinically appropriate medication. If you would like to participate in the study but do not wish to change your current antidepressant medication, you will be assigned to

either the "full dose" or "low dose" hearing aid option, without receiving the antidepressant medication treatment. The “low dose” hearing aids look like the “full dose” hearing aids, but they will not be fully tuned to improve your hearing. You may or may not notice immediate changes in your hearing after the beginning of the study, because often hearing aids need to be adjusted over a period of several weeks in order to function properly. Neither you nor your doctors will know whether you are getting the low or full dose hearing aids until the end of the study.

At the beginning of the study, you will be given a physical examination, an electrocardiogram (EKG), and have your blood drawn. The total amount of blood taken at this study visit is about two tablespoons. Results of these blood tests will be available to you, should you request them. You will have your hearing tested by an audiologist to measure the severity of your hearing loss and how well you are able to understand spoken words. You will also complete some psychological questionnaires and tests of your attention, memory, thinking, and physical functioning. These tests can be completed by telephone, videoconference, or in-person and take about one hour to complete. The results of these tests are for research purposes only and will not be shared with you.

You may also have MRI (Magnetic Resonance Imaging) scans at the beginning and end of the study. The MRI uses strong magnetic fields and radio waves to take pictures of your brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the imaging procedures, we will determine that you do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and you will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). You will be asked to lie flat on your back in the MRI scanner for about 60 minutes and to remain as still as possible. You will not feel anything, but you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong.

You will be asked to return for 6 visits over the course of 12 weeks to see one of the study doctors and talk about how you are feeling. During the COVID-19 pandemic, some of your visits may be conducted remotely using the telephone or secure, HIPAA-compliant video teleconferencing. Based on clinical evaluation, you may be required to complete more than 6 visits. On 4 of these visits, you will also see an audiologist to evaluate the hearing aids and make sure they are working as designed. Based on hearing aid compliance and/or complications, the audiologist may require you to return for an additional visit. These meetings will last about 30 minutes. If you choose to take one of the antidepressant medications offered in this study and still have depressive symptoms after four weeks on the pills you are given, the dose will be increased to two pills (either 20mg of escitalopram or 60mg duloxetine, depending on the medication you started). If you choose to take one of the antidepressant medications offered in this study, you will receive free medication for the duration of the study, and the hearing aids and hearing assessments during the study are also free.

During the 12 week long study, you may not receive outside treatment for your depression or hearing beyond what is supplied by your study doctor. If your doctor feels your condition worsens significantly, the current treatment will be stopped, and you will be offered different treatments for your depression or hearing. Your doctor may stop your participation in the study at any time without your consent if you do not comply with the study procedures (such as by not wearing the hearing aids for at least 8 hours per day). The research study will end after 12 weeks. During the week 12 visit, you will again fill out some psychological tests and have

your hearing tested. Some of these assessments will be completed remotely by telephone or HIPAA-compliant video conferencing, while others will be completed in-person.

Following the research study, you will receive 3 months of free doctor visits in the depression clinic and at least 1 month of free antidepressant medication. During the COVID-19 pandemic, these will be conducted remotely. You will be allowed to keep your hearing aids. If your hearing aids were "low dose" during the research study, an audiologist will fully tune them so that they improve your hearing and you will be scheduled for an additional audiology visit following the research study to make sure the hearing aids are working properly and to answer any questions you may have.

RISKS

The main risk of the study is that your hearing loss will not be fully treated if you are assigned to the "low dose" hearing aid group until after the 12 week study is over. The most common side effects reported for escitalopram and duloxetine are nausea, insomnia, and inability to have an orgasm. Less common side effects reported for escitalopram and duloxetine include constipation, dry mouth, dizziness, headache, insomnia, and sedation. If the study physician prescribes a different antidepressant for you, the potential risks and side effects of that particular medication will be discussed with you.

When taking the antidepressant medication offered in this study you should be careful about drinking alcohol, since it may have a greater effect on you in combination with medication. You must not take monoamine oxidase inhibitor (MAOI) drugs (tranylcypromine or Parnate, phenelzine or Nardil) during the study or within five weeks of ending the study. Serious reactions, including death, have been reported when MAOIs are coadministered with medications like escitalopram or duloxetine.

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Some people have reported sensations during MRI scans with the 3T magnet, 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 your body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some 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 you experience any discomfort and wish to stop the scan, you can tell the MRI technologist, and he or she will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

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RESULTS OF YOUR MRI

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DOCUMENTATION OF CONSENT

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Print name:_____

Signed:_____

Date:_____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name:_____
Person Designated to Obtain Consent

Signed:_____

Date:_____

You will be given a copy of this consent form to take with you.