Study Title: Flavanol Augmentation for Antidepressant Nonresponsive Late Life Depression

NCT Number: 02943096

Date of Document: 8/30/2017

New York State Psychiatric Institute

Institutional Review Board

August 30, 2017

To: Dr. Bret Rutherford

From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman

Subject: Approval Notice: CONTINUATION

Your protocol # **7368** entitled: **FLAVANOL AUGMENTATION FOR ANTIDEPRESSANT NON-RESPONSIVE LATE LIFE DEPRESSION** Protocol version date 08/30/2017 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **September 12, 2017 to September 11, 2018.** (Reviewed at the Full Board meeting on August 21, 2017.)

Consent requirements:
☐ Not applicable:
√ 45CFR46.116 (d) waiver of consent for the telephone interview
√ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes

Field Monitoring Requirements: √ Routine ☐Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Cc: CU Business Office (internal acct, Briger); CUMC IRB

Encl: CF, MRI letters, recruitment, HIPAA

EN/LG/alw

Signed copy on file at IRB

Protocol Title:
Flavanol Augmentation for Antidepressant Non-Responsive Late Life Depression

Version Date:
08/30/2017

Protocol Number:
7368

First Approval:
09/22/2016

Clinic:
Adult and Late Life Depression

Expiration Date:
09/11/2018

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Adam Brickman, PHD

Research Chief:
Davangere Devanand, MD

Cover Sheet

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

Division & Personnel

Division

What Division/Department does the PI belong to?
geriatric psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
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.

none

Amendment

Describe the change(s) being made
The IRB protocol under which the subjects for this study are evaluated is being amended from IRB# 6395R to IRB# 7284R
Provide the rationale for the change(s)
This change is being made to correct the evaluation protocol number.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
None
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
None

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Project goals are to establish the whether augmentation with flavanol supplements is beneficial for geriatric adults with depression and to examine the cognitive effects of flavanol supplementation.
The participants have been completing the protocol as planned. Patients are evaluated in the Adult Late Life and Depression Clinic under IRB#7284R. They are then scheduled for a baseline visit and an MRI. During these visits the patients complete a battery of neuropsych tests and undergo a gadolinium contrast MRI. The patients are then scheduled for follow up visits. These visits occur weekly until week 4. After week 4 biweekly visits are conducted until week 8. During these visits patients complete a short battery of depression ratings. On week 8 all measures taken at baseline are repeated along with the gadolinium contrast MRI. Patients are compensated $50 after the evaluation and after the completion of each MRI scan.

Recruitment for the study has been slow due to studies with competing populations ALLDC and other clinics in the Columbia Medical Center offering similar treatment for the geriatric population.

There are no new developments in the field that impact on the science or the risk/benefit balance of this protocol.

Funding

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

Summary

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

Overall Progress

Approved sample size
50
Total number of participants enrolled to date
6
Number of participants who have completed the study to date
5
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
Study recruitment has proved difficult due to competing studies recruiting a similar population of subjects. Therefore the target recruitment goals for this protocol have not been met.
Comments / additional information
None

Sample Demographics

Specify population
60 years and older

Total number of participants enrolled from this population to date
6
Gender, Racial and Ethnic Breakdown

Male: 4
Female: 2

Black:1
White:5

Not of Hispanic Descent: 6

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
6
Number of participants currently enrolled
1
Did the investigator withdraw participants from the study?
Yes
Circumstances of withdrawal:
The subject had no response to the augmentation and was feeling significantly worse after beginning the drug three weeks previously.
Did participants decide to discontinue study involvement?
No

Procedures

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

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ MRI

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?
Yes
Describe internal account
The project will be funded by a donation from the Briger family for this purpose. These funds are currently in a CU acct under PI's name.
Is the project externally funded or is external funding planned?
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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The goal of this proposal is to conduct the first pilot study of whether consuming flavanol supplements will augment the cognitive and mood benefits of antidepressant medication in older adults with Late Life Depression (LLD). Flavanols represent a specific group of plant derived nutrients that are found in cocoa beans, grapes, tea, berries and various other fruits and vegetables. The specific flavanols investigated in this study come from cocoa. Currently available treatments for LLD (i.e., antidepressant medication) are limited in efficacy, especially in individuals who also suffer from cognitive impairment. Recent studies performed at Columbia and elsewhere suggest that flavanols may induce beneficial brain changes that support cognitive functioning and elevate mood, but their precise clinical effects in older adults with combined depression and cognitive impairment remain to be evaluated.

For this study, we plan to recruit 50 adults aged ≥60 years who have Major Depressive Disorder, meet a minimum depressive symptom threshold despite currently receiving an adequate trial of an antidepressant, and have a significant cognitive complaints without a diagnosis of dementia. Subjects will be randomized to receive 8 weeks of augmentation treatment with flavanol capsules (in addition to continuing their antidepressant) vs. capsules not containing flavanols. Pre- and post-treatment MRI scanning of the brain will be conducted, and comprehensive pre- and post-treatment neuropsychological assessment will be

performed. Results from this project will allow us to evaluate a novel therapeutic approach to LLD, which could have large public health ramifications given the prevalence, frequent treatment resistance, and chronicity characteristic of LLD.

Background, Significance and Rationale

Background, Significance and Rationale
The goal of this proposal is to conduct the first pilot study of whether consuming a diet high in flavanols will augment the cognitive and mood benefits of antidepressant medication in older adults with Late Life Depression (LLD). LLD affects 3% of community-dwelling adults over 60 years old, and 15% of older adults living in the community have clinically significant depressive symptoms. Diagnosis with LLD increases an older adult's risk of disability by 67-73% over 6 year follow up, causes twice the functional impairment compared to those without LLD, and is associated with high rates of completed suicide in individuals over 65. Currently available treatments for LLD (i.e., antidepressant medication) are limited in efficacy, leading to high rates of recurrence and frequent development of chronicity. Cognitive impairment, which is commonly associated with LLD, predicts poor acute response to antidepressants, leads to higher relapse rates during the continuation phase of treatment, and is associated with the development of adverse age-related health outcomes, including increased risk of dementia, dependence in activities of daily living (ADL), and driving cessation.

Novel treatments addressing LLD's underlying neurobiology are critically needed, particularly therapies that may also have beneficial effects on the cognitive components of LLD. The most extensively studied brain region to be implicated in both the depressive and cognitive aspects of LLD has been the hippocampus. Decreased hippocampal volumes are found in depressed patients compared to controls, and this finding appears to be particularly pronounced in individuals with recurrent depressive illness. Among the subregions comprising the hippocampus, evidence suggests that it is decreased neurogenesis within the dentate gyrus (DG) specifically that may contribute to the development of depression, and it appears that part of the mechanism of action of antidepressants is to enhance neurogenesis in the DG. As the DG is also a critical contributor to the cognitive functions of the hippocampus, it stands out as a highly significant brain region that may be involved with both the mood and cognitive components of LLD.

These considerations suggest that targeting the DG may be a valuable therapeutic strategy to explore in the treatment of LLD. Recently, flavanols were shown in mice to result in a selective increase in dendritic spine and capillary density within the DG. A subsequent study of healthy elders performed by Scott Small and colleagues at Columbia found that following a cocoa-flavanol enhanced diet for three months resulted in improved functioning on a DG-dependent cognitive task and increased cerebral blood flow (CBV) in the DG. Since Dr. Small's group previously showed that increased CBV on high-resolution functional magnetic resonance imaging (fMRI) correlates with increased neurogenesis, these findings suggest that consuming a flavanol supplements may enhance DG-dependent cognitive functioning by selectively inducing DG neurogenesis. In terms of effects on mood symptoms, it has been speculated since the 1980s that cocoa-flavanols have antidepressant effects, and more recently multiple groups have reported antidepressant effects of plant-derived flavonoids in animal models of depression. Thus, it appears that flavanols may induce beneficial structural brain changes that support cognitive functioning and elevate mood, but their precise clinical effects in older adults with combined depression and cognitive impairment remain to be

evaluated.

We propose to conduct the first study of whether consuming flavanol supplements will augment the benefits of antidepressant medication treatment in older adults with LLD. Our guiding hypotheses are that older adults receiving antidepressant medication plus flavanol supplementation will experience greater depressive symptom improvement, greater improvements in cognitive functioning, and increased blood flow in the DG on CBV-fMRI compared to older adults receiving antidepressant medication alone. To test these hypotheses, we plan to recruit 50 adults aged ≥60 years who meet DSM 5 criteria for Major Depressive Disorder, meet a minimum depressive symptom threshold despite currently receiving an adequate trial of an antidepressant, and have a significant cognitive complaints without a diagnosis of dementia. Subjects will be randomized to receive 8 weeks of augmentation treatment with flavanols (in addition to continuing their antidepressant) or augmentation with capsules not containing flavanols. Pre- and post-treatment CBV-fMRI will be conducted, and comprehensive pre- and post-treatment neuropsychological assessment will be performed testing diverse domains of cognitive functioning (including cognitive tasks previously shown to be DG-dependent).

Results from this project will allow us to evaluate a novel therapeutic approach to LLD, which could have large public health ramifications given the prevalence, frequent treatment resistance, and chronicity characteristic of LLD. Even apart from the potential benefits for mood symptoms, cognitive impairment in older adults exacts a large public health burden in terms of impaired functioning and increased morbidity and mortality, and this burden will only grow as the population ages. Flavanols may represent a safe and effective means to help older adults maintain a healthy aging trajectory, maintain independent functioning, and live longer with an increased quality of life.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Aim 1. To determine whether augmentation with flavanol supplements is helpful for depression.

Hypothesis 1. Subjects randomized to the flavanol intervention will have greater depressive symptom improvement compared to subjects not receiving flavanols.

Aim 2. To examine the cognitive effects of flavanol supplementation.

Hypothesis 2. Subjects randomized to the flavanol group will have greater improvement on pattern separation performance (MST and ModBent) compared to subjects not receiving flavanols. Improvement in pattern separation performance will occur in the setting of general unchanged cognitive functioning in other domains (e.g., processing speed, EF).

Aim 3. To examine the relationship between cognitive improvement and depressive symptom improvement in patients receiving flavanol augmentation.

Hypothesis 3: Improvement in pattern separation performance will mediate the group difference in depressive symptom reduction.

Description of Subject Population

Sample #1

Specify subject population
Depressed older adults
Number of completers required to accomplish study aims
40
Projected number of subjects who will be enrolled to obtain required number of completers
50
Age range of subject population
60 and older

Gender, Racial and Ethnic Breakdown
On the basis of previous studies conducted in the Late Life Depression Research Clinic at the New York State Psychiatric Institute (NYSPI) and Columbia University, it is anticipated that the sample will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects. It is anticipated that the sample recruited from these sites will be composed of 60% women and 40% men.
Description of subject population
Community-ascertained outpatients with antidepressant non-responsive depressive disorders

Recruitment Procedures

Describe settings where recruitment will occur
We will recruit subjects via advertisements for patients who feel depressed, through the RecruitMe online platform, as well as clinical referrals from colleagues around CUMC. Advertisements will include research flyers and brochures posted around CUMC, advertisements in local newspapers and on radio stations, and information posted on departmental websites. For direct clinical or research referrals, a clinical staff member known to the patient will approach him/her and raise the possibility of study participation.
How and by whom will subjects be approached and/or recruited?
If the patient expresses a potential interest in participating, he/she will then be scheduled for a full evaluation with a study clinician.
How will the study be advertised/publicized?
Advertisements will include research flyers and brochures posted around CUMC, advertisements in local newspapers and on radio stations, and information posted on departmental websites and the RecruitMe web recruitment platform.
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
NCT02943096

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects completing IRB 6836 (Rutherford PI) or 6470 (Brown PI) who meet the selection criteria for this study will be offered participation.

Inclusion/Exclusion Criteria

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

Criterion	Method of Ascertainment
1. Men and women aged ≥60 years	1. Clinical interview
2. DSM 5 diagnosis of Major Depressive Disorder	2. SCID, clinical interview
3. Subjective report of memory or thinking problems	3. Clinical interview
4. 24-item Hamilton Rating Scale for Depression ≥16	4. HRSD
5. Failure of depressive symptoms to remit following an adequate trial of an antidepressant (defined as at least 8 weeks of treatment, with 4 weeks of at least half PDR maximum dose, of an FDA approved antidepressant)	5. Clinical interview
6. Capable of providing informed consent and complying with the study procedures	6. Clinical interview

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

Criterion	Method of

	Ascertainment
1. Diagnosis of Substance Use Disorder within the past 12 months (excluding Tobacco)	1. SCID, clinical interview
2. History of psychosis, psychotic disorder, mania, or bipolar disorder	2. SCID, clinical interview
3. HRSD suicide item > 2 or CGI =7 at baseline	3. HRSD, CGI
4. Diagnosis of probable or definite dementia (Alzheimer's Disease, Vascular Dementia, Parkinson's disease, etc.)	4. SCID, clinical interview, MMSE
5. MMSE ≤24	5. MMSE
6. Physical or intellectual disability adversely affecting ability to complete assessments	6. Clinical interview
7. History of allergy, hypersensitivity, or intolerance to cocoa flavanols	7. Clinical interview
8. Contraindication to MRI scanning or unable to tolerate scanning procedures	8. Clinical interview
9. Allergic or adverse reaction to gadolinium, 2 or more prior scans with gadolinium, or creatinine clearance < 50	9. Clinical interview, blood draw
10. Daily consumers of dietary or herbal supplements, including Gingko, flavonoid, and dietary herbal or plant extracts	10. clinical interview
11. Diabetes or acute, severe, or unstable medical or neurologic condition	11. clinical interview, physical exam, EKG

Waiver of Consent/Authorization

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

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
7284R
Describe Study Consent Procedures
Following the study screening procedures, a study physician (only MDs will obtain consent in this study) authorized to obtain patient consent will explain the study procedures along with the attendant risks, benefits, and alternatives, including the anticipated outcome of doing nothing. The study 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 receive appropriate referrals.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

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

Study Procedures

Describe the procedures required for this study

Evaluation

1. Every subject evaluated for this protocol will receive a clinical interview by a psychiatrist or psychologist, be administered the 24-item Hamilton Rating Scale for Depression (HRSD) and Antidepressant Treatment History Form, and have a SCID performed by a trained rater. During the consent process, subjects will be educated about the availability of appropriate treatments for depression (switch or augment antidepressant medication, evidence based psychotherapy). If a subject is not interested in these depression treatments and/or prefers to try an experimental treatment for depression, he/she will be offered participation in the present study provided there is no suicidal ideation present.

2. Those signing informed consent will have physiologic tests conducted (including EKG) and will be scheduled for baseline neuropsychological testing and MRI scanning. Other baseline tests include measures of frailty (Pittsburgh Fatigability Scale, Grip Strength, Gait speed, Minnesota Leisure Time Physical

Activity Questionnaire, Short Physical Performance Battery),the Mnemonic Similarity Task (MST), and the Trail Making Test Parts A and B, all which will be repeated at week 8

Neuropsychological testing

1. Neuropsychological testing will include assessment of global cognitive functioning, IQ, attention, memory, language, executive functions, reaction time, and visuospatial processing. The 30-item Mini Mental State Examination (MMSE) will be used to measure general cognitive impairment. The Wechsler Test of Adult Reading (WTAR) will be used in conjunction with demographic variables to estimate IQ. Memory will be assessed using the Logical Memory Test (WMS III). We will use two standard measures to assess executive functioning. The Stroop Color Word Interference Test (Stroop) is a measure of attention, concentration, and behavioral inhibition under distracting conditions that is sensitive to frontal lobe dysfunction. The Mattis Dementia Rating Scale Initiation and Perseveration subtest (DRS I/P) measures a) verbal initiation and perseveration (e.g., naming supermarket items over 1 minute), b) performing alternating movements, and c) reproducing graphomotor designs (e.g., XOXO). Attention will be assessed using the wechler adult intelligence scale (WAIS-III) Digit Symbol Test.

2. We will also use a specific cognitive task shown to be dentate gyrus-dependent in order to provide a functional assessment of DG to go along with our anatomic MRI assessments of DG and other hippocampal subregions. The Benton Visual Retention Test (BVRT) was developed to evaluate patients with severe impairment. It contains only a limited number of items that are not sufficiently challenging for healthy subjects, and therefore typically leads to a 'ceiling' effect. Accordingly, we (Dr. Brickman) developed a computerized modification of the BVRT, which is more appropriate for use among individuals without frank impairment across the lifespan. We call this task the 'Modified Benton' (ModBent). The ModBent is an object recognition task with immediate matching trials and delayed recognition trials. The stimuli used in the ModBent are intersecting sinusoidal curves designed parametrically to be similar to each other in order to evoke the pattern separation cognitive operation. During the immediate matching trials, participants view a single complex stimulus for 10 seconds; following a 1 second delay they are asked to select which one of two objects is identical to the studied stimulus. Following 41 matching trials, participants are shown serially individual complex objects and asked to indicate whether the object is identical to any of the target stimuli studied during the immediate matching trials. There are 82 recognition trials, which include 41 targets and 41 foils. The primary dependent variable for the ModBent is the mean reaction time (ms) for correct rejections of foil stimuli on the delayed recognition trials. Given our previous observation that performance on the BVRT is selectively correlated with functioning of the DG and that the putative role of DG in pattern separation, the ModBent was designed specifically to maximize the cognitive operation of pattern separation and tap DG functioning.

3. NP testing is for research purposes only and the results of these tests will not be interpreted clinically or shared with the patient.

CBV-fMRI

1. 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.

2. If the participant appears nervous or anxious, a trained member of the clinical staff will remain with them inside the scanning suite for the duration of the scan. The participant will be given a button box to terminate the scan at any time. If they push the button, they will be removed from the scanner immediately All of the MRI procedures will be conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. Conducting these procedures will be an accredited Magnetic Resonance Technologist (B.M.R.) and a member of the research staff (Bachelor's Level or Higher) trained in the acquisition of MR images, as well as in procedures for testing human subjects.

3.The CBV-fMRI procedure involves the acquisition of a T1-weighted MRI scan before and after the administration of a contrast agent, which in this case is a macrocylic called Dotarem. Evidence has shown this compound does not remain in the brains of patients in post-mortem studies. After the pre-contrast image is obtained, Dotarem (gadoterate meglumine) at a dose of 0.2mL/kg will be infused through a peripheral IV site. After a 4-minute delay, the second, post-contrast, image will be acquired. Participants are able to communicate with research staff by means of button press for any reason during the MRI procedures. The injection is conducted by a registered nurse or physician, who is on premises throughout each MRI study. This procedure results in the creation of whole brain and regional CBV maps by subtracting a T1-weighted MRI scan from a gadolinium-enhanced T1-weighted MRI image and then normalizing the values by a measure of 100% blood taken from a large sinus. The resulting image provides a measure of blood volume with the high spatial resolution of T1-weighted imaging. Either region-of-interest analysis or voxel-based analyses can be applied to interrogate functional neuroanatomy with submillimeter resolution.

4. Although our MRI Scans are for research purposes, a radiologist will perform a clinical reading on every MRI within 1 month of scanning; if anything clinically significant is found, Dr. Rutherford will be notified immediately and he will provide an appropriate clinical referral to the participant.

5. While scanning parameters may change slightly, power monitoring software on the scanner will ensure total energy delivered to the subject will remain within FDA guidelines. Specifically, the specific absorption rate (SAR) will be not greater than: (1) 4 W/kg averaged over the whole body for any period of 15 minutes; (2) 3 W/kg averaged over the head for any period of 10 minutes; (3) 8 W/kg in any gram of tissue in the head or torso; (4) 12 W/kg in any gram of tissue in the extremities, for any period of 5 minutes. These safety precautions are built into the MRI hardware, and are standard with every system.

6. Subjects will receive 2 MRI scans in this protocol: immediately before treatment begins and after 8 weeks of high vs. low flavanol diet augmentation.

Clinical trial

1. Subjects will be continued on their baseline dose of antidepressant medication for the duration of the protocol and will be randomized to augmentation with flavanol capsules (500mg per day) or placebo. Placebo is being purchased from the NYSPI pharmacy, and flavanols are being purchased commercially in

the form of CocoVia supplements. We selected the 500mg dose in collaboration with colleagues who have performed previous flavanol studies (Drs. Small and Sloan) and on the literature. A 500mg dose of cocoa flavanols has previously been associated with cognitive benefits (Mastroiacavo et al, Am J Clin Nutrition 2014).

2. Following baseline testing, subjects will return for a Week 0 visit when continued symptoms will be confirmed and medication will be distributed, after which they will return for visits at weeks 1,2,3,4,6,8. Patients will receive clinical management (MD) and complete assessment measures conducted by raters blinded to condition assignment. Measures performed at each visit will include HRSD, Quick Inventory of Depressive Symptomatology (QIDS), Hamilton Anxiety Rating Scale, CGI—Severity and Improvement, and Treatment Emergent Side Effect Scale.

3. We do not anticipate any tolerability problems with flavanol supplementation, but if a patient discontinues medication due to tolerability problems, ineffectiveness, patient preference, or other reasons, the patient will continue follow up appointments as scheduled. Appropriate medication options will be discussed with the patient based on their symptoms and history. A patient will not be considered a drop out unless they decide to discontinue follow up appointments in the study or are lost to follow up.

4. Patients in all treatment cells will be discontinued from the acute treatment phase if there is there is a rating of 6 (much worse) or 7 (very much worse) on the CGI—I for 2 consecutive weeks.

5. The blind will be broken at the end of the 8 week study period.Following the 8 week duration treatment study, endpoint assessments will be made. Patients will enter 3 month open treatment period provided free of charge as described below.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

The risk of non-response or adverse events to flavanol supplementation during the study period is addressed by having close clinical follow up of study subjects and stringent withdrawal criteria. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening as defined by a slowing assessment rating using the CGI-Improvement scale of 6 (worse) or 7 (much worse) for 2 consecutive visits; or (3) development of significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated clinically. In addition, a CGI of 6 or 7 after one week will trigger a clinical evaluation and then clinical judgment as to whether the patient should be discontinued. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. Withdrawn patients will be followed in the open treatment period and offered appropriate psychiatric treatments if they have any conditions requiring treatment (e.g., depression).

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
1.Frailty assessment: weight loss (patient report of 10 lb loss unintentionally in last year), weak grip strength (via hand dynamometer; stratified by gender and body mass index), slow walking speed, (15 feet speed stratified by gender and height), low energy expenditure (Short version of the Minnesota Leisure Time Activity questionnaire, kcals per week expended are calculated using standardized algorithm and stratified by gender), Short Physical Performance Battery--15 min
2. Hamilton Rating Scale for Depression (HSRD)--15min
3. Quick Inventory of Depressive Symptomatology (QIDS)--5min
4. Clinical Global Impression (CGI)--1min
5. Measure of Everyday Cognition (ECog)--10min
6. Wechsler Test of Adult Reading (WTAR)--5 min
7. Mini Mental State Examination (MMSE) -- 8 min
8. Stroop COlor Word Test (Stroop) -- 5 min
9. Mattis DRS- I/P subset -- 10 min
10. Digit Symbol Subtest of the WAIS III -- 2 min
11. Logical Memory Test (WMS III) -- 10min
12. Modified Benton Visual Retention Test (ModBent)--30 min
13. Mnemonic Similarity Task (MST) -- 15 min
14. Trail Making Test part A and part B

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
There is a possible delay in treatment of up to 8 weeks since an experimental agent is being investigated for the treatment of depression, and it may not be effective.

Maximum duration of delay to standard care or treatment of known efficacy
8 weeks
Treatment to be provided at the end of the study
We will provide 3 months of additional free clinic visits following the end of this project. At the conclusion of the 8 week study, a non-study clinician in our research clinic will be given the data on the subject's response to flavanol augmentation. This clinician will discuss with each subject on a case-by-case basis the risks and benefits of continuing flavanol treatment as well as other treatment options if warranted. Those who have benefited from the treatment and have not had significant side effects may elect to continue receiving flavanols after receiving an explanation of the potential risks of chronic administration. If they do not want to continue flavanols, it will be discontinued after a 3 day step-down withdrawal. Transferring after-study care to a non-study clinician protects against the development of bias in the study clinicians and offers optimal clinical care to the subjects at the study conclusion.

Clinical Treatment Alternatives

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

Risks/Discomforts/Inconveniences

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

2. Magnetic resonance imaging (MRI). the Magnetic Resonance (MR) scanner uses strong magnetic fields and radio waves to take measurements in the brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). They will be asked to lie flat on the back in the MRI scanner for approximately 60 minutes and to remain as still as possible. Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. With any MRI scan, on occasion,

some people experience nervousness or types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. If a patient experience any discomfort and wish to stop the scan, he/she can tell the MRI technologist who will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

Regarding gadolinium-based MRI scanning specifically, gadolinium compounds do have side effects. We use Dotarem (Gadoterate Meglumine). Side effects of Dotarem include nausea, headache, injection site pain, injection site coldness and burning sensation observed in fewer than 1 people out of every 100 injected (0.2% estimate). Adverse reactions that occurred with a frequency <0.2% in patients who received Dotarem include: feeling cold, rash, somnolence, fatigue, dizziness, vomiting, pruritus, paresthesia, dysgeusia, pain in extremity, anxiety, hypertension, palpitations, orophrayngeal discomfort, serum creatinine increased and injection site reactions, including site inflammation, extraversion, pruritus, and warmth. All of these side effects resolve within 20 minutes to several hours. A trained physician or licensed nurse will inject the gadolinium and remain with the patient for the entire duration and for 15 minutes after the scanning session is complete.

Some patients with acute renal failure or end-stage renal disease have developed a serious medical condition known as nephrogenic systemic fibrosis (NSF) after the use of gadolinium for MRI. The primary concern regarding risks to renal function from gadolinium-based contrast agents (GBCAs) is specific to this population of patients who have end-stage renal disease (ESRD) on hemodialysis, or acute, florid, clinical renal failure, and then are exposed to gadolinium. This population of patients is by definition excluded from this study by virtue of medical history and general review of systems. Renal dysfunction as a result of gadolinium in a population without history of end-stage renal disease or acute renal failure has not been described in the medical literature. In a retrospective study conducted at two large medical centers, 74,124 patients were injected with a standard dose of gadolinium (0.1mmol/kg, the same dose used in our research studies) who had no screening for renal function, with a rate of 0/74124 cases of renal complications (e.g., NSF or other renal dysfunction) post injection. All 15 cases of NSF that were found in this retrospective study had severe, clinical renal failure at the time of gadolinium injection. No cases of NSF have been identified in persons with normal renal function or with moderate renal dysfunction.

According to a recent report by the FDA, while gadolinium is mostly eliminated from the body after administration, recent studies have shown trace amounts of gadolinium in the brains of patients who have undergone four or more gadolinium-enhanced MRI scans. While there have been no adverse health effects associated with this finding, in order to safeguard against the potential for gadolinium accumulation, we utilize Dotarem (gadoterate meglumine) instead of Multihance (gadoebnate dimeglumine). Dotarem is a macrocylic, a class of gadolinium contrast agents, which has not been shown to remain in the body in the post-mortem studies which prompted the FDA warning. By using this macrocylic, we avoid the possibility of gadolinium accumulation. Despite the overwhelming evidence that macrocylics do not pose the same risk as other gadolinium-contrast agents, we will exclude participants who have had a history of 2 or more gado-enhanced MRI.

3. Blood draw. In the placement of a peripheral IV and the obtaining a 20 cc blood sample (3), patients can experience side effects that include pain, fainting, bruising, light-headedness, and, on rare occasions, infection.

4. Flavanol augmentation. Although we are currently unaware of any risks, there may be possible risks to the dietary intervention, such as previously unknown allergies.

5. Maintenance of antidepressant dosage: Because antidepressant medications cannot be adjusted during study participation, there is a risk that participants will not improve or will worsen.

Describe procedures for minimizing risks
Please see above for procedures to minimize risks of CBV-fMRI and contrast administration, which are discussed in the context of each individual potential risk.

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

Regarding the risk associated with blood draw, the staff will take every precaution to avoid these difficulties. The staff members are all certified at the hospital to be drawing blood from patients, and are instructed to keep the comfort and welfare of our patients as their primary priority.

Regarding the risk of worsening associated with antidepressant medication dosage not being adjusted, we have implemented stringent criteria for early discontinuation as well as criteria for discussing whether participants should be discontinued.

Finally, we will mitigate risks associated with the generally increased medical problems occurring in older adults by doing a careful interview to detect an unstable, severe, or acute medical problem and obtain parallel history from the subject's primary medical doctor. Since cognitive impairment is a condition impacting older adults, we will measure a MMSE and exclude subjects with a score lower than 24.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All records of the participating subjects will be kept in a locked room with access provided only to staff members. Patients' names will be linked with code numbers in a password protected file to which only the research assistant has access. All data collected will be kept confidential and used for professional purposes only.

Publications using these data will be done in a manner that protects the subjects' anonymity. All electronically stored data will be accessible by password known only to the principal investigator and research assistants for the study.

All MRI scans and related data will be kept on the secure, password protected, MRI server. MRI scan reports will be provided to the clinic by the MRI scanner, and kept in a locked file.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
There is no direct benefit to subjects. If flavanol treatment is effective in improving cognition and ameliorating depressive symptoms, subjects may experience improved quality of life.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Subjects will receive a total of $150 for completion of all study assessments, neuropsychological testing, and MRI scans. The payment schedule will be that they will receive $50 after completion of blood draws and psychological tests, $50 after first MRI scan, and an additional $50 for completion of the week 8 MRI scan. Given that subjects may incur travel expenses and are expected to spend several hours in the LLDC and MRI scanner completing the study procedures, we judge that this amount is reasonable.

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Uploads

Upload copy(ies) of unbolded Consent Form(s)
unstamped_Patient_CF_10_12_16.pdf
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload copy(ies) of the HIPAA form
unstamped_HIPAA 9_22_16.pdf
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MRI_result_letter_1__unstamped.pdf
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NEW YORK STATE PSYCHIATRIC INSTITUTE
FLAVANOL AUGMENTATION FOR LATE LIFE DEPRESSION

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.

Purpose of Study

The purpose of this study is to examine the effect of a nutritional supplement containing flavanols on depression and brain activity. Flavanols represent a specific group of plant derived nutrients that are found in cocoa beans, grapes, tea, berries and various other fruits and vegetables.

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.

Alternatives

You do not have to participate in this study to receive treatment for depression. Medications, psychotherapy, and their combination may be helpful for treating depression, and they are available outside this research project.

Procedures

- The study consists of blood tests and psychological tests conducted at the beginning, a magnetic resonance imaging (MRI) scan conducted at the beginning and end, and the consumption of pills containing flavanols derived from cocoa.
- MRI scans use strong magnetic fields and radio waves to take pictures of your brain. The MRI scans performed in this study also use a gadolinium contrast agent called Dotarem that will be administered to you through a catheter inserted into a vein. The psychological tests are paper and pencil and computerized tasks that will take about 2 hours to complete.
- For 8 weeks, you will be asked to consume cocoa flavanols in the form of 4 capsules daily or else placebo. A placebo is a sugar pill that is not specifically effective for treating depression.

Risks

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). These include side effects associated with the MRI contrast agent Dotarem (such as nausea, headache, and coldness or burning at the catheter site), frustration caused by the memory and thinking tasks you will perform, cocoa flavanol intake problems, and discomfort associated with the MRI scan and psychological tests.

Benefits

This research study is not meant to benefit you directly. You may contact the study doctor, Dr. Bret Rutherford at 646-774-8660 with any questions.

NEW YORK STATE PSYCHIATRIC INSTITUTE
FLAVANOL AUGMENTATION FOR LATE LIFE DEPRESSION

PURPOSE OF STUDY

You are being asked to participate in this study because you are an adult, aged 60 years or older, who has been diagnosed with Major Depressive Disorder (known in older patients as Late Life Depression) and is currently taking an antidepressant medication that has not fully treated your symptoms. We are studying whether adding a nutritional supplement containing flavanols to your current antidepressant medication helps with depression and influences brain activity linked to depression. Flavanols represent a specific group of plant derived nutrients that are found in cocoa beans, grapes, tea, berries and various other fruits and vegetables. The specific flavanols investigated in this study come from cocoa.

This research study is supported by a private philanthropic gift to Columbia University.

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.

ALTERNATIVE TREATMENT

You do not have to participate in this study. This is a study of an experimental nutritional supplement to help depression, but there are treatments for depression which are known to be effective. The alternative to participating in this study is to seek treatment outside the research project so that you would be certain of receiving a medication approved for treatment of depression. Approved medications for depression are available (e.g., fluoxetine (Prozac), sertaline (Zoloft), etc), and psychotherapy also may be helpful with depression, whether on its own or combined with medication.

Information being collected is for research purposes only and is to learn more about the effects of flavanols on depression and the brain, not about you. It is not necessary to participate in this research study to have an MRI, and the MRI done as part of this study is not the same as one done for medical purposes.

STUDY PROCEDURES

Evaluation: If you decide to participate in this study, you will have blood drawn and complete some psychological tests. 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. The psychological tests measure thought processes such as memory, language, reasoning, and attention. These tests are paper-and-pencil as well as on the computer, and they take about one hour to complete. The results of these tests are for research purposes only and will not be shared with you.

Based on these tests, it will be determined whether you are eligible for the treatment portion of the study. If you are not eligible, you will be referred to appropriate options for further treatment. If you are eligible and continue to wish to participate, you will proceed with the next part of the study.

MRI scan: You will also have 2 MRI scans as part of the study—one before treatment begins and the second one 8 weeks later, after treatment has ended. 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. You will be asked to lie flat on your back in the MRI scanner for about 30 minutes and to remain as still as possible. Before the scan, a catheter will be placed in one of your veins (usually in your arm near the elbow) so that we may administer to you a gadolinium-based contrast agent known as Dotarem during the MRI scan. These contrast agents help parts of the brain that are of interest to researchers show up better.

While in the scanner, you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong. The technologist operating the scanner and a member of the research team will be able to see you, and voice contact will be maintained throughout the scan. You may ask to stop the scan at any time if you feel uncomfortable. Your MRI scans will be reviewed by a radiologist within 1 month of the scan and the results will be shared with you and your physician.

Treatment study: After the first MRI scan, you will then begin an 8-week period during which you will be randomly assigned (like flipping a coin) to consume flavanol-containing capsules once a day with breakfast or pill placebo. A placebo is a sugar pill that is not specifically effective for depression. You will take the capsules for 8 weeks and neither you nor the investigators will know which capsules you are receiving. The flavanol capsules contain alkalized cocoa powder and other ingredients including theobromine and caffeine that are naturally found in chocolate. Your diet will not be changed in this study.

If you cannot tolerate the flavanol supplements, your participation in the study will be discontinued. If the study doctor feels your condition worsens significantly, the current treatment will be stopped, and you will be offered different treatments for your depression. The study doctor may stop your participation in the study at any time without your consent if you do not comply with the study procedures or for other reasons.

During the study, you will continue taking the same dose of your antidepressant medication that you were taking prior to the study. Your dosage of antidepressant medication may not be adjusted for the duration of the 8-week study. You may continue to receive this medication from your pharmacy, or, if you do not have the ability to get your medication, medication will be provided by the study. You will return each week to speak with the study doctor and have some tests. These appointments will last about 45 minutes. The research study will end after 8 weeks. During each visit, you will again fill out some psychological tests and have your depressive symptoms measured.

Following the study, you will still receive 3 months of free doctor visits in the clinic. The flavanols used in this study are available commercially, so it is an option to continue taking them following the study if you feel you have benefited. If you do not wish to continue the flavanols after the study, it will be discontinued.

RISKS

Regarding gadolinium-based MRI scanning, gadolinium compounds do have side effects. The gadolinium compound we use is Dotarem (Gadoterate Meglumine). Side effects of Dotarem include nausea, headache, and injection site pain. Fewer than 1 out of every 100 people injected (0.2% estimate) may experience injection site coldness and burning sensation. Side effects that occurred with a frequency less than 0.2% in patients who received Dotarem include: feeling cold, rash, feeling sleepy and fatigued, dizziness, vomiting, itching, sensation changes, pain in extremity, anxiety, elevated blood pressure, rapid or pounding heart beat, and swelling or redness around the catheter site. All of these side effects go away within 20 minutes to several hours. A trained physician or licensed nurse will administer the gadolinium through the intravenous catheter and remain with you for the entire duration of the MRI scan and for 15 minutes after the scanning session is complete.

Some patients with severe kidney problems or end-stage kidney disease have developed a serious medical condition known as nephrogenic systemic fibrosis (NSF) after the use of gadolinium for MRI. Only patients who have end-stage renal disease (ESRD) requiring hemodialysis, or current, severe kidney failure that causes significant symptoms and apparent illness have developed NSF after exposed to gadolinium. Individuals with these severe types of kidney problems will not be offered participation in this study.

The Food and Drug Administration (FDA) is currently investigating a possible risk of health problems caused by repeated use of gadolinium for MRI. Though the FDA has not reached a conclusion at this time, you should not participate in this study if you have previously had more than 2 MRI scans with gadolinium.

There are some potential risks associated with MRI in general. While there have been no reports of harmful long-term effects caused by a 3T (a measure of the magnetic field

strength) magnet, the long-term effects of being placed in a magnet of this strength are not known. Some people may experience nervousness or discomfort due to the scanner's small space and the need to lie still during the scans, but we are not aware of any other potentially dangerous effects of the MRI scan. We do not allow people with pacemakers, some types of metallic implants, and medication patches to do the MRI scans, since this may be dangerous.

Since the MRI scanner produces loud knocking noises, participants will be provided with earplugs for comfort. If you experience any discomfort and wish to stop the scan, you can inform the MRI technologist through a microphone within the scanner and he or she will stop the scan immediately.

When your blood is drawn or the catheter is placed in your vein, there is a small risk of infection, bleeding, discomfort, and that you may be left with a bruise that will resolve within a few days. Blood taken for research purposes will remain confidential. Additionally, some of the memory and thinking tasks you will be performing may be frustrating.

Although we are currently unaware of any risks of the flavanol capsules, there may be possible risks of the intervention, such as previously unknown allergies. Because your antidepressant medication dosage cannot be adjusted during your participation in this study, there is a chance that your depressive symptoms will not improve or will worsen.

RESULTS OF YOUR MRI

You also should know that 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. 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. We will contact you, or a physician whom you may designate, via telephone or letter with information about the results of your scan. 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. The main benefit of your participation in this research is that it may lead to a better understanding of how the brain changes in depression and what may be potential new treatments for depression in older adults.

CONFIDENTIALITY

Your records will be stored in a locked file and will only be available to the research staff and institutional personnel 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. All MRI scans and related data will be kept on the secure, password protected, MRI server. MRI scan reports will be provided to the clinic by the MRI scanner, and kept in a locked file.

COMPENSATION AND ECONOMIC CONSIDERATIONS

You will not be charged for any procedures that are a part of this study, including the MRI scans. To compensate you for your time, you will be paid $150 if you complete all procedures in this study, including the blood draw, psychological tests, and MRI scans. Payment will take place in the form of a check mailed to your home and may take three to four weeks to process. If you complete part of the study procedures but not all, you will receive partial compensation for the portion of the study you completed.

RESEARCH STANDARDS

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 646-774-8664. 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 participants in research studies). You may call the IRB Main Office at (646)774-7155 during regular office hours. A copy of this consent form will be provided to you.

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: _____

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7368 **Principal Investigator:** Bret Rutherford, MD

Name of Study: Flavanol Augmentation for Late Life Depression

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☑ Additional information may include:
MRI PET scans

2. **The Health Information listed above may be disclosed to:**
☑ Researchers and their staff at the following organizations involved with this Research:
NYSPI

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Bret Rutherford, MD
  1051 Riverside Dr
  New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**

Statistical Analysis plan

Descriptive statistics are expressed as means and standard deviations or percentages. Chi-square analyses and independent samples t-tests were used to compare subjects assigned to flavanol vs. placebo augmentation on categorical and continuous depression outcomes, respectively.