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EMORY UNIVERSITY SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES

TITLE: InSuLa Assessed Needs for Depression: The ISLAND Study

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Precise/Abstract:

Introduction and Background:

Imaging-based diagnostic tests are routinely used in the clinical management of many medical illnesses. In ischemic heart disease, for example, evaluation of the integrity and caliber of the coronary arteries combined with tests of myocardial function are critical determinants of the interventional strategy initiated following the diagnosis of an acute myocardial infarction [1]. The decision by a cardiologist to treat medically or surgically is neither arbitrary nor conciliatory. Rather, they are based on objective measurements of the primary organ of interest considered in context of other contributing risk factors, including genetics, co-morbid medical conditions (i.e., hypertension, diabetes, hyperlipidemia) life-style factors (smoking, diet, exercise) and past cardiac problems. Currently, the choice of treatment for major depression (MDD) is based on 1) trial-and-error, 2) the skills and preferences of the clinician treating the patient (i.e. psychiatrist or therapist) who chooses a treatment based on their training and ideology, or 3) patient treatment preferences [2].

For a patient presenting with a major depressive episode as part of major depressive disorder (MDD), an antidepressant medication or evidence-based psychotherapy is the recommended first-line treatment. However, fewer than 40% of patients achieve remission with any initial intervention (monotherapy), and choosing the "wrong" treatment has significant individual and societal costs due to continued distress, risk of suicide, loss of productivity, wasted resources, and potential unintended neural effects associated with two to three months of an ineffective strategy [2]. To minimize these costs and improve the clinical care of patients with MDD, a crucial goal is to develop a dependable treatment selection algorithm that matches an individual patient to the treatment option most likely to be successful. To have meaningful clinical impact, such an algorithm must lead to remission rates that exceed the usual 35-40% commonly reported with usual care. Critically, such an algorithm should select the best treatment while also avoiding the worst treatment, and also identify patients that require other alternatives.

In developing a reliable biomarker to guide initial treatment stratification to standard first-line treatments such as CBT or sCIT, it is also necessary to differentiate those patients that require non-standard treatment options. A 35-40% non-remission rate is typical of trials where a randomized treatment is followed by a second medication or combination medication and psychotherapy. Given that further increases in medical and psychosocial costs are associated with two failed standard first-line treatments, it is essential to know in advance if a patient is a poor candidate for these usual options.

We previously conducted a trial of 82 patients with MDD who were randomly assigned to 12 weeks of treatment with either cognitive behavioral therapy (CBT) or the antidepressant escitalopram (ESC). Using a pre-treatment fluorodeoxyglucose positron emission tomography (FDG-PET) measure of metabolic activity, we found that the ratio of metabolic activity in the insula relative to whole brain metabolism predicted remission and non-response to the two treatments. Specifically, patients whose insula activity was below the whole brain mean were highly likely to remit with CBT and have a poor response to ESC. Conversely, those with relatively high insula activity required ESC to remit, and responded poorly to CBT [3]. This earlier trial also contained an additional 12-week combination treatment phase for patients who did not remit to their original 12 weeks of treatment with ESC or CBT. In this phase, we found that for patients were more likely to achieve remission if their added second treatment (whether

ESC added to CBT non-remitters, or CBT added to ESC non-remitters) matched the baseline insula activity signal predictive of remission [4]. This trial provided the first evidence that a biomarker could predict differential outcomes to two contrasting treatment approaches for MDD. The current study aims to replicate the findings of the earlier trial, with the long-term goal of achieving a personalized medicine approach to MDD, in which individual patients receive treatments most likely to help them specifically, based on their brain activity.

Objectives

Aim 1*a*. To prospectively test the efficacy of the anterior insula TSB to assign individual MDD patients to 12 weeks of treatment with either CBT or sCIT.

Hypothesis 1*a*. Assigning treatment based on the anterior insula TSB will result in remission rates of 50% or greater, exceeding current benchmarks.

Exploratory Aim 1b. To characterize metabolic change patterns associated with successful and unsuccessful treatment in the insula-defined depression subgroups.

Hypothesis 1*b*. Insula activity will change as a function of remission status within each treatment. Differential treatment and remission specific changes in depression-relevant regions will also be seen.

Aim 2. To further characterize baseline biomarkers predictive of treatment non-response after completing 24 weeks of two first-line treatments for MDD.

Hypothesis 2. Non-response to both 12 weeks of insula TSB-assigned monotherapy and 12 weeks of combined CBT and sCIT will show a baseline metabolic pattern distinct from remitters to TSB-defined monotherapy and from remitters to combined treatment, defining a treatment resistant subtype.

Study Design and Methods:

a. Sample

The target number of patients with MDD without psychotic symptoms to be entered into treatment is 100. We will consent up to 150 patients to allow for patients who are found to be ineligible for the study during the screening process. Their ages may range from 18-55 and patients will have to be in good physical health or, if they have major medical conditions, these conditions will be stable.

Inclusion Criteria:

1. Men or women aged 18-55 years.
2. Primary psychiatric diagnosis of Major Depressive Disorder, without psychotic features, confirmed via SCID-IV structured diagnostic interview.
3. Screening Hamilton Depression Rating Scale (HAMD) ≥ 18; and Baseline HAMD ≥ 15
4. If the patient is a woman of child-bearing potential, she must agree to use an acceptable form of birth control for duration of study participation.
5. Able to understand and provide informed consent for participation.

Exclusion Criteria:

1. Lifetime history of Bipolar Disorder, Dementia, Autism Spectrum Disorder, Schizophrenia, or any other Psychotic Disorder.
2. Psychotic symptoms occurring at any time during the current major depressive episode.
3. Current (past 12 months) diagnosis of Panic disorder, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Anorexia Nervosa, or Bulimia Nervosa.

4. Alcohol or Drug Dependence within 12 months or Abuse within 3 months (excluding nicotine and caffeine) of baseline visit, as assessed by history and urine drug screen.
5. Clinical evidence of a severe Personality Disorder, as assessed by the study psychiatrist, which would impede participation or completion of the trial.
6. Known neurological disorders or documented serious head injury.
7. Serious and unstable medical illnesses including cardiovascular disease and cancer.
8. Active medical conditions with known mood changes (endocrine, autoimmune disorders).
9. Current diabetes mellitus.
10. For women, pregnancy, lactation, or unwillingness to comply with birth control requirements.
11. Use of any of the following treatments or any other alternative therapy within 2 weeks of the pre-treatment PET scan that may have beneficial effects on mood, including St John's Wort, S-adenosyl methionine (SAMe), n-3 fatty acids, or light therapy.
12. Use of antidepressant medication within 1 month of the pre-treatment PET scan (within 5 weeks for fluoxetine and protryptyline).
13. Failure to achieve a much improved status (i.e. equivalent to >50% symptom reduction) with any lifetime treatment course of CBT (defined as a minimum of 4 sessions of a specified manual-driven therapy by a CBT-trained therapist) or escitalopram (defined as a minimum of 6 weeks of at least 10 mg/day).
14. Clinically significant active suicidal ideation or self-injurious behavior necessitating immediate treatment, as determined by the investigator.
15. Received electroconvulsive therapy in the past 6 months or during the current depressive episode.
16. Currently responding to medication treatment, without clinical reasons to change.
17. Current treatment with weekly individual or group psychotherapy of any type targeted at depressive symptoms.
18. QTc >500 milliseconds on EKG at screening.
19. Contraindications for MRI, including, but not limited to pacemaker, aneurysm clips, neurostimulators, cochlear implants, metal in eyes, steel worker, intra-uterine devices for birth control.
20. Use of concomitant medications with the exception of:
    a. Maintenance or prophylactic therapy for stable medical conditions.
    b. Hypnotic medication prescribed or approved by the study physician, (up to a three doses per week) for insomnia, as long if not the night before a PET/MRI or clinic ratings visit. Antipsychotic medications, whether prescribed for sleep or other indications, are prohibited.

b. Setting

The clinical care and assessments of patients will occur in the Mood and Anxiety Disorders Program (MAP) at the Emory University Executive Park campus. PET and MRI scans will be performed at the Center for Systems Imaging (CSI) at the Wesley Woods Health Center.

c. Recruitment

Patients will be recruited through advertisements, media campaigns, and clinician referral.

d. Procedures

The schedule of events is listed in **Table 1.**

PHASE 1

Screening Visit

The screening visit will require approximately 3 hours. Patients will start by signing the informed consent form after all their questions about the study have been answered to their satisfaction. A study rater will administer the HAMD to assess depression severity. Patients with a HAMD ≥18 will go on to complete the SCID-IV to confirm MDD diagnosis and ensure any exclusionary psychiatric diagnosis is not present. A medical history, physical exam, electrocardiogram (EKG), blood tests (15cc for complete blood count, comprehensive metabolic panel, thyroid function screen, pregnancy test) and a urinalysis and urine drug screen, will be performed to ensure the patient is medically appropriate for the study. An additional 10cc plasma tube will be collected for genetics analysis. Additional questionnaires regarding personal and family history of depression, smoking history, beliefs about depression, and concomitant medications will be administered. Patients who meet all inclusion and no exclusion criteria at the end of this visit will be scheduled for the Scanning Visit within 10 days.

Questionnaires completed by the patient at this visit include the following:

- Edinburgh Handedness Scale
- Hollingshead Scale of Socioeconomic Status
- Childhood Trauma Questionnaire
- Patient Attitudes and Beliefs Scale
- Reasons for Depression Questionnaire
- MRI Safety Form (Required by CSI)

Scanning Visit

This visit will require approximately 3 hours and will occur at the Wesley Woods Center. Patients unwilling or unable to do the FDG-PET scan and the MRI scan on the same day will have the scans scheduled over a 2-day period. The FDG-PET scan will be performed prior to the MRI scan whenever possible. The Positive and Negative Affective State scale (PANAS) will be rated at the beginning and end of each scan to monitor fluctuations over the scanning session. Analogue Mood Scales (10-point Likert) will be used to rate euthymia, anxiety and sadness and the start and finish of each scan.

Baseline Visit

This visit will require approximately 90 minutes. Vital signs will be measured and inquiry about any concomitant medication changes will be made.
Patients will be assessed by a trained interviewer with the following instruments:

- HAMD
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Rating Scale for Anxiety (HAM-A)
- Clinical Global Impression-Severity (CGI-S) scales

Patients will complete the following questionnaires:

- Beck Depression Inventory-II (BDI-II)
- Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
- Sheehan Disability Scale (SDS)
- Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)

- Multidimensional Locus of Control Inventory (MLCI)
- Life Orientation Test – Revised (LOT-R)
- Emotion Regulation Questionnaire (ERQ)
- Dunlop Emotional Blunting Scale (DEBS)
- Ruminative Response Scale (RRS)
- Pittsburgh Sleep Quality Index (PSQI)
- Frequency, Intensity and Burden of Side Effects Rating (FIBSER)
- Childhood Trauma Questionnaire (CTQ)
- PROMIS Depression Scale
- PROMIS Anxiety Scale
- Body Awareness Questionnaire

Blood will be collected for the following measures:

- Methylation (6cc)
- Immune measures and metabolomics (10 cc)
- RNA (6 cc)

Additionally, study patients will complete an extended vital sign assessment, consisting of 3 heart measure tasks (two subjective, one objective):

- Heart Rate Measure
- 7 Minute Heart Rate Recording Task
- Affective Bias Task

Upon completion of all questionnaires and interviews, the patient will meet with a study physician to be informed of their treatment assignment. The study physician will answer any questions about the treatment or future study visits.

Phase 1 Post-baseline Visits

Patients will return weekly for the first four weeks (Visits 3-6) and the every other week for weeks 5-12 (Visits 7-10). These visits will last approximately one hour. Vital signs and changes in concomitant medications will be assessed. At each visit, patients will be assessed by an interviewer with the HAMD, MADRS and HAMA. Patients will complete the BDI-II, QIDS-SR, FIBSER and self-report forms. They will meet with a study physician, who will administer the CGI-S and CGI-Improvement (CGI-I) scales. Adverse events will be discussed with the study physician, and dosing adjustments, if permitted (see below), will be made.

At the week 6 (Visit 7) visit, patients will also complete the SDS, Q-LES-Q, DEBS and PSQI. They will also complete the PROMIS Anxiety and the PROMIS Depression Scale.

At the week 12 visit (visit 10), patients will undergo repeat FDG-PET scanning at the CSI and then come to the come to the MAP offices to complete the visit assessments. In addition to all the measures collected at week 6, patients will also complete the Body Awareness Questionnaire, PABS, RFDQ, MLCI, LOT-R, RRS, and ERQ. Blood will also be collected to repeat the methylation, immune, metabolomics and RNA measures, as well as to measure pharmacokinetic values of escitalopram (10 cc, for total blood volume draw of 32cc). Total time for completion of all components at Visit 10 is approximately four hours. If patients have

insufficient time to complete both the PET scan and the clinic visit on the same day, the PET scan will be scheduled as close as possible to the clinic visit, with a maximum of 7 days between the PET scan and clinic visit.

Patients who are non-responders to treatment will cross-over to the alternate treatment and will have the week 12 blood draws and questionnaires repeated at week 24.

PHASE 2

Visit procedures in Phase 2 will depend on whether or not the patient remitted (defined below) in Phase 1.

Remitters at the end of Phase 1 will return at monthly intervals to measure their vital signs and report concomitant medications, and will complete the HAMD, MADRS, HAMA, CGI-S, CGI-I, BDI-II and QIDS-SR. Total time for this visit is about one hour. Patients on escitalopram will receive one month's supply of medication at this visit, and patients receiving CBT will have a CBT booster session if they desire it.

Non-Remitters at the end of Phase 1 will enter another 12 week treatment course that replicates the treatment course and visit frequency of Phase 1 (see **Table 1**). The only differences from Phase 1 are that in Phase 2 there are no PET scans, and the patients continue with their Phase 1 treatment in addition to starting the Phase 2 treatment (see **Study Treatments**, below).

Heart Rate Monitoring

As a potential non-imaging surrogate for insula activity, we will ask patients to count their heart beats while their actual pulse rate is monitored. A soft tone will indicate the start and end point for each counting interval. Actual pulse will be monitored with electrodes on their left and right wrists and clavicle. The test will be administered at the baseline and week 12 scans, as well as a third time for patients completing the week 24 visit. Subjects will complete the Body Awareness Questionnaire each time they perform the heart rate monitoring task.

Heartbeat perception will be measured using the Mental Tracking Method [15]. Between onset and offset of a soft tone, the subject counts his/her heartbeat by concentration on bodily feelings. The subject is not to take his/her own pulse to try any other physical manipulation, which might facilitate the detection of heartbeats. The task will be repeated 3 times, for intervals lasting 25, 35, and 45 seconds respectively. After the termination of each perception interval, participants will report the counted/estimated number of heartbeats. The subject will not be informed about how many seconds the 3 trials lasted or about their performance.

The following intervals will be used:
Rest (60 sec); Perception (25 sec)
Rest (30 sec); Perception (35 sec)
Rest (30 sec) Perception (45 sec)
Rest (60 sec)

Stationary objective 7 Minute Heart Rate Recording

The patient's heart rate will be recorded for 7 minutes while they sit stationary and look at a printed cross on a sheet of paper. Prior to beginning this recording, patients will be asked to be seated for 5 minutes.

Affective Bias Task

Participants will be asked to rate the level of emotion on faces presented on a computer screen. To rate the level of emotional intensity, participants will use the mouse to move a horizontal marker on a scale ranging from very sad to very happy. The emotion and intensity portrayed on each face will vary for each trail. During this task, participants' heart rate will be recorded.

Table 1. Schedule of Events

		PHASE I				PHASE II FOR NON-REMITTERS			
Assessment/ Procedure	**Screen**	**Visit 1** (Imaging) **Day-3 to -7**	**Visit 2** (Baseline) **Wk 0**	**Visits 3-6** (Weekly) **Wks 1-4**	**Visits 7-9** (Biweekly) **Wks 6-10**	**Visit 10** (Endpoint) **Wk 12**	**Visit 11- 14** (Weekly) **Wks 13-16**	**Visits 15-17** (Biweekly) **Wks 18-22**	**Visit 18** (Endpoint) **Wk 24**
Demographics/ Consent	X								
Medical History, Physical Exam	X								
Vital Signs	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X
Safety Labs/ EKG/ UDS	X								
Pregnancy Test	X					X			X
SCID for DSM-IV	X								
PABS, RFDQ	X					X			X
CTQ, Handednedss, Hollungshead	X								
HAMD, MADRS, HAMA	X		X	X	X	X	X	X	X
CGI-S, CGI-C			X	X	X	X	X	X	X
QIDS,BDI-II			X	X	X	X	X	X	X
MDLCI, LOT-R, RRS, ERQ			X			X			X
Q-LES-Q, DEBS, PSQI, SDS			X		X (wk 6)	X		X (wk 18)	X
PROMIS-Anx, PROMIS-Dep, WAI-C, WAI-T				X (wk 1&4)		X	X (wk 13&16)		X
AEs, FIBSER			X	X	X	X	X	X	X
FDG PET, PANAS		X				X			
Heart rate monitoring, Body Awareness Questionnaire, Affective Bias Task		X				X			X
MRI, MRI Safety Form		X							
Genetics Blood Sample	X								
Pharmacokinetic Sample						X			X
Methylation, Immune, RNA, Metabolics			X			X			X

Brain Imaging Procedures

1. FDG PET scans

Regional cerebral glucose metabolism will be measured using a 18F-fluoro-deoxyglucose method (10 mCi FDG dose/scan; scan duration 60 seconds) [7-9]. Data will be acquired on a Siemens ECAT 921 PET scanner, operating in 3D mode Axial FOV 14.5 cm; 47 reconstructed slices). A total of 2 scans (Visit 1 and Visit 10) will be acquired, each lasting approximately 90 minutes. For each scan, a 5 mCi dose of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) will be injected intravenously, with image acquisition beginning after 40 minutes (scan duration 20 minutes). Arterialized-venous blood sampling will be used to calculate absolute glucose metabolic rates. All subjects will be scanned during CSI business hours. under identical conditions: supine, awake, in the resting state with eyes closed and ears uncovered. Patients will be advised to fast and avoid caffeine for four hours prior to the scan. Patients will be checked every ten minutes to ensure they are not asleep. Patients will not be explicitly instructed to monitor internal mood state or to perform any specific cognitive task. This approach aims to examine regional effects associated with the baseline depressed state without the potential interpretive confounds introduced by explicit manipulation of affective or cognitive state. A debriefing session will follow the uptake period to document compliance with the instructions. PET scans will be performed prior to the fMRI scans.

2. fMRI Bold scans

MRI acquisitions will be acquired using a Siemens 3T whole body scanner (Tim Trio) with a 60 cm diameter bore. The MR imaging protocol includes an (1) anatomic image (7 min), (2) Two sets of different phase encoding DTI (16 min) and (3) two sets of resting state functional connectivity (15 min) acquisition [12] and a magnetic resonance spectroscopy scan (15 min). The anatomic imaging will be conducted for anatomic reference in fMRI and DTI data analysis, and volumetric analysis. The DTI images will be used to refine selection of regions-of-interest (ROI) for model-based analyses. Positive and negative affect will be assessed using the PANAS before and after the scanning session. These measures will be used for correlational analyses with brain data.

To provide precise anatomical localization of identified functional differences between groups, a high-resolution anatomical image of the whole brain will be acquired. High-resolution anatomical imaging will be performed with a T1-weighted MPRAGE sequence optimized at 3T: TE/TR=5/35, matrix=256 x 208 x 196, FOV=256 x 208 x 192 mm2, 1mm isotropic resolution. Diffusion Tensor Imaging (DTI) will also be acquired to allow structural connectivity inferences between areas identified with the functional images. DTI images will be acquired using diffusion weighted single-shot spin echo-planar imaging (EPI) sequence in 66 axial slices covering the whole brain (TR/TE=3292/96 ms, matrix=128×128, FOV=256 mm×256 mm, slice thickness=2 mm; 66 slices, and two opposite phase encoding directions). Diffusion weighting will be applied in 128 directions with a b-value of 1000 s/mm2. Resting BOLD imaging will collect T2*-weighted images: 10 oblique axial slices covering the subgenual cingulate, amygdala, hippocampus, hypothalamus and ventral striatum, and frontal cortical areas of interest (orbital frontal, medial prefrontal, dorsolateral prefrontal) to investigate areas of known abnormalities in previous PET studies.

3. TSB Determination

Following PET scan preprocessing, anterior insula activity values will be extracted using a standardized region of interest (237.35 mm3 spherical ROI centered on MNI coordinates x= +28.5, y= -21, z= -9) based on the original study findings. Patients with insula metabolism higher than their WBM (insula/WBM ratio >1) will be assigned to the escitalopram group; patients with insula metabolism lower than their WBM (insula/WBM ratio <1) will be assigned to the CBT group.

Study Treatments

1. Treatment Assignment for Phase I

Once the PET scan data have been analyzed to determine the TSB, patients will return for their baseline visit to receive their treatment assignment. Upon completion of the baseline visit study procedures, patients will meet with a study psychiatrist to be informed of their treatment assignment to escitalopram or CBT. Importantly, to minimize placebo response emerging from expectation bias, and to maximize comparability with our original dataset, patients will NOT be informed that they are being treated according to their PET scan result. Instead, patients will be informed that while we are studying the utility of imaging to improve patient care, they are being randomized to treatment. This will replicate exactly what was done in our original study to develop this biomarker. This safeguard is crucial to ensure that any increase in remission rates we observe in our trial are the result of matching patients to the TSB, and not due to non-specific effects. Assessors administering the clinical rating scales will be blind to treatment group and method of treatment assignment.

2. CBT Treatment

All clinical guidelines for MDD include Cognitive Behavior Therapy (CBT) as a recommended treatment. For patients treated with CBT, therapy visits will occur twice weekly for 4 weeks and then weekly for weeks 5-12, for a total of 16 therapy sessions. Using a standardized protocol [5] enhanced with behavioral strategies, patients will learn to develop an awareness of how attitudes, beliefs or ways of thinking and thoughts produce and maintain depressed or anxious moods. CBT pursues alleviation of depression through a systematic effort to change depressed patients' automatic and maladaptive beliefs or ways of thinking. At the heart of this approach is the assumption that distorted beliefs about the self, the world, and the future maintain depressive affect. Initially, patients focus on becoming aware of these thinking styles, and they then learn how to respond to them in ways that are more adaptive. Patients will be asked to monitor their thoughts, attitudes and beliefs, especially those accessed in the midst of problematic emotional situations. During the course of treatment, the therapist focuses on modifying these habitual patterns of thinking through explicit cognitive or behavioral interventions and correcting maladaptive patterns such as perfectionism and excessive need for approval from others.

The typical course of treatment comprises 16-20 sessions (16 planned in this study) and the sequence of treatment involves three stages. In the early stage (sessions 1-4) the emphasis is on establishing a therapeutic relationship with the patient, educating the patient about the CBT model and emotional lability, setting goals, and identifying and evaluating automatic thoughts. The middle phase (sessions 5 to 12) involves a gradual shift towards the identification of dysfunctional beliefs and compensatory strategies the patient may be employing, helping the patient to identify core beliefs and practicing skills at responding to and modifying depressogenic views. Tasks in the late stages of CBT (sessions 13-16) revolve around

preparing the patient for termination, predicting high-risk situations relevant to relapse and consolidation of learning thought self-therapy tasks. All therapy sessions will be recorded on DVDs. Dr. Craighead or the treating psychologists will be available by phone to address any clinical concerns between clinical visits. In addition, the Working Alliance Inventory, therapist and client versions, (WAI-T and WAI-C), which measure the quality of the therapeutic relationship between therapist and patient, will be completed by both the therapist and patient after 2, 8 and 16 sessions of therapy have been completed.

3. Escitalopram Treatment

Patients assigned to escitalopram will receive 10 mg/day for the first 3 weeks of treatment. Patients who show less than a 50% improvement from their baseline HDRS-17 item score by week 3 will have their dose increased to 20 mg/d. Patients who demonstrated 50% improvement at week 3 will be maintained on the 10 mg/day dose. Any patient who has failed to achieve the remission threshold (HDRS-17 ≤ 7) by week 6 will have their dose increased to 20 mg/day at the week 6 visit. Patients unable to tolerate 20 mg/d will be down-titrated to 10 mg/day. The escitalopram dose will not be changed during the last four weeks of each the treatment phase (week 8 in phase I, or week 20 in Phase II). Patients unable to tolerate 10 mg/d will be discontinued from the trial. This approach to dosing will ensure all escitalopram-treated patients are either treated to remission or receive at least 6 weeks at the 20 mg/day (or maximally tolerated dose), which is identical to the dosing schedule we used in our initial study. Side effects will be monitored at every study visit.

4. Phase II Treatment

a. Remitters

Remitters in Phase I (defined below) will return at weeks 16, 20 and 24 during Phase II for ongoing monitoring of symptoms. Patients remitting with escitalopram will continue to receive that medication; CBT-remitters will receive 3 therapy booster sessions at monthly intervals. All remitters will complete the following procedures at each of these three visits:

- Vital signs
- HAMD, MADRS, HAMA, and CGI assessments
- QIDS-SR, BDI-II, FIBSER, and SDS questionnaires

b. Non-Remitters

Patients who do not meet the remission criteria at week 12 will enter Phase II, during which they will continue their Phase I treatment, and start a course with the alternative treatment. Thus patients in Phase II will receive a combination of escitalopram and CBT. For patients receiving escitalopram in Phase I, the dose cannot be increased in Phase II, but may be reduced if side effects are intolerable. Patients receiving CBT in Phase I will have monthly CBT booster sessions at months 4, 5 and 6 with their therapist. As shown in Table 1, the schedule of events in Phase II replicates that of Phase I, with the exception that there is no repeat PET scan at the end of Phase II.

At week 24, phlebotomy will be performed for pharmacokinetics, methylation, inflammation and RNA, and women of child-bearing potential will complete a urine pregnancy test.

A study psychiatrist will be available by phone to address any clinical concerns between clinical visits for all patients.

5. Early Terminating Patients

Patients who terminate their participation prior to week 12 in Phase I will complete the week 12 assessments (with the exception of the PET scan). Patients who terminate the trial early in Phase II will complete the week 24 assessments. All early terminating patients will receive assistance transferring their clinical care to another clinician. The date the patient is withdrawn from the study and the reason for the discontinuation will be recorded. When a patient is lost to follow-up, extensive efforts will be made to contact the patient in order to determine why the patient failed to return.

6. Patient Instructions

Each patient will be advised of the importance of treatment adherence. For patients on escitalopram, pill counts to confirm adherence will be conducted at each study visit. A missed dose may be taken within the same day. A missed dose the previous day should not be made-up (i.e. doubled) the next day. If the patient has any questions about the study or other medications, the research physician may be contacted, if necessary through a 24 hour emergency number. In the event that a study visit is missed, it will be rescheduled within 3 days whenever possible.

7. Post-study follow-up

To ensure that study participants are safely transitioned to alternative sources of care, the study physicians will offer additional brief visits as needed for up to one month following the patient's completion of study participation. No additional research data will be collected at these visits. The visits will be conducted as standard of care visits until the patient's care has been transferred to another clinician.

8. Treatment Adherence and Rater Reliability

As in our first study, we will ensure that the treatments delivered in this study adhere to their respective treatment protocols, using standard measures for pharmacotherapy and CBT, respectively. Medication adherence will be monitored using pill counts and pharmacokinetic sampling at weeks 12 and 24 for patients receiving escitalopram. CBT competence will be assessed by Leslie Sokol, PhD using the Cognitive Therapy Scale (CTS) [6] to rate a randomly selected sample (15%) of video recordings from each treatment, blocked on early, middle and late phases of intervention. Ongoing reliability data will be gathered for rating scales. New clinicians joining the treatment team will go through MAP's standard apprenticeship for the ratings and special training for reliability prior to performing independent ratings.

IV. Data Analyses

A. Treatment Response Assessments

Definitions.
Remission (RR) is categorically defined as a final score on the HAM-D scale for the week 10 and 12 visits (which are separated by 2 weeks) of less than 8.
Response (R) is defined as 50% reduction from baseline and a final score <15 at the week 10 and 12 visits.
Non-response (NR) is defined as a <30% improvement in HAM-D score from baseline to week 12. For non-remitters in phase II, NR is defined as failure to as a <30% improvement in HAM-D score from baseline to week 24.

Sample Size Calculation and Efficacy Thresholds

Aim 1

The efficacy of the biomarker to assign best treatment will be tested in this protocol using Simon's 'two-stage' design [7] using exact binomial calculations. Simon's two-stage design is commonly used for testing treatment stratification biomarkers; for example, for estimating remission rates of different established cancer treatments [8]. For the insula TSB being tested here, if the overall remission rate is below the threshold set for the first stage (see sample size in the next 2 paragraphs), then TSB-based assignment will be halted and treatment switched to assignment by randomization for the remaining patients.

Sample size for this design is determined by first setting the threshold level at which we will consider the remission rate a failure. For our purposes, we set the threshold level to a remission rate of 35%, which is roughly equivalent to the remission rate expected from randomized or naturalistic treatment in depression [9 -11].The sample size is then calculated by setting the type I error=0.05, the minimum acceptable target level of remission (in this case, 50% or a 15% increase in remission rate over threshold level) and the Type II error (beta=0.2 or power=0.80).

With these parameters, the total sample size needed for the first stage of the Simon's 2-stage design is n=27 completers with 12 weeks of treatment. If 10 or more of those 27 subjects remit (i.e. 37%), the design will continue to stage 2 using the "treat by insula type" paradigm. The continuation will then require an additional 50 subjects for a total of 77 subjects. If a total of 39 or more of the 77 subjects remit, then the stratification strategy will be considered worthy of further future testing. If less than 10 of the first 27 subjects remit, the trial will revert to randomized treatment allocation in order to complete data collection. This futility design ensures that we don't continue to treat by the TSB if we cannot meet the 50% target remission rate in the full sample. At minimum, we require 77 subjects to complete all 12 weeks (i.e. have remission status) in order to test the efficacy of the biomarker to assign best treatment. If we allow for a 20% dropout rate, which is consistent with our earlier trial, we will need to recruit a total of 96 (approximately 100) subjects at baseline.

Aim 2

Given the expected 77 completers of the initial treatment phase and the projected 50% remission rate, we will have approximately 40 subjects enter the second 12-week (combined) treatment phase, and based on our original sample,16 will be non-responders (dual failures). Evidence from the original study points to several candidate dual-failure biomarkers significant at the 0.005 corrected level with a sample size as small as 11 (computed effect size range [1.2 to 1.8]). We expect to have enough data from this study to define the dual failure biomarker as described.

Heart rate accuracy analysis

Formula for heartbeat perception score: Mean score across 3 heartbeat perception interactions as follows (direction of error is ignored)

$1/3\sum(1- (|\text{recorded heartbeats} – \text{counted heartbeats}|)/\text{recorded heartbeats})$

Scores vary from 0 to 1, with high scores indicating only small differences between recorded and counted heartbeats.

Source of Materials.

Research information will be gathered using face to face interviews including past medical and psychiatric history, presenting complaints, current symptoms, standardized psychiatric and functional assessments. Patients will have a routine physical examination, and complete blood and urine assessments to assess their general medical condition. Specific research blood tests of potential relevance to treatment response will also be obtained. Assessment and treatment sessions will be audiotaped and videotaped. PET and fMRI scans will be obtained using standard research protocols within each respective laboratory.

Protection again risks.

Risks to participation include experiencing side effects from the study medications for the MDD subjects, exposure to radiation from the PET scan, and exposure to magnets in the MRI scanner. Every effort will be made to protect against and minimize potential risks. All information gathered will be coded by patient number rather than by name and research information will be kept under lock and key. Information will not be divulged unless specifically requested by the patient in writing. A certificate of confidentiality and sensitive study request will be pursued for this study.

The main potential risk of a PET scan is exposure to low dose radiation. Based on published dosimetry, the total effective dose equivalent for 2 FDG PET scans (10mCi/scan= 20mCi/study) is 17.6 mSv. This dose is less than the allowed dose for research subjects in a single year. Subjects will be educated regarding radiation exposure from PET scans. Placement of the IV needle required for injection of the radiotracer during the PET study can cause a small amount of bruising or pain. Pregnancy is contraindicated for participation. Nonetheless, a pregnancy test will be done immediately prior to the PET session to ensure a non-pregnant status prior to radiation exposure.

The risks associated with MRI are minimal. Subjects will be screened for absolute contraindications to MRI, including presence of a pacemaker, aneurysm clips, neurostimulators, cochlear implants, metal in eyes, steel worker, metallic inter-uterine devices for birth control, or other implants. Patients and volunteers will be briefed prior to the scan day to alleviate anticipatory anxiety regarding the procedure. Claustrophobia is possible. The study can be immediately terminated if this is not tolerated. Study investigators and MRI technologists will be on site at all times during study acquisition to intervene under such circumstances.

The treatment risks are consistent with the standard-of-care for MDD. Similarly to all antidepressant medications, escitalopram has common known side effects, including headache, nausea, anxiety, and sleep and appetite disturbances. In patients under age 25, there is a small increased risk of developing thoughts of self-harm or suicidal ideas.

Adverse event monitoring

Adverse event information will be captured via two methods. At each visit, the study staff will ask the patient if they have experienced any changes in their mental or physical health. Any reported adverse events will be assessed and, if needed, treated by a study physician. In addition, patients will complete the FIBSER, which provide more quantitative measures of side adverse effect occurrence.

Benefits to subject or future benefits

Patients who participate will receive an expert psychiatric assessment and treatment. With treatment, patients may experience an improvement in their symptoms of depression along with a potential improvement in their cognition. Patients will have the benefit of participating in a clinical trial that could inform future treatment of patients with MDD

Training

No training is currently necessary for MAP staff for the rating scales used in this study because all research personnel involved in this project are currently trained on the scales used. New staff involved in patient assessment will be trained in scale administration according to the MAP's usual training methods.

Confidentiality

Patients' confidentiality will be maintained throughout the duration of their study participation. Patient names and other identifiers will not be included in assessment tools and datasets; a unique ID will be assigned. Patient files will be kept in locked offices, and the computerized data is kept on password-protected computers in the locked Mood and Anxiety Disorders Program offices.

Informed consent

At the screening visit, patients will be provided with an informed consent form that will outline the risks and benefits of participating in this study. It will also outline which assessments occur at the various study visits.

Deception

Deception is a crucial and necessary component for this project. A major confounder of trials studying treatments for depression is the placebo response. Although placebo response has many sources, a major driver is the expectation of improvement, which can be enhanced by the use of expensive procedures or new technologies that inspire greater confidence [12-14]. In this study we are using FDG-PET scans to assign patients to the specific treatment they will receive. We need to tell participants that their treatment is being randomly assigned to minimize the added expectation-effect on placebo response that would result from being told a new technology was guiding their treatment decision. It is important to understand that we do not know if this approach really is superior to randomized treatment – this study is designed as a proof of principle study, with the outcome being that if we achieve greater than 50% remission rates, this will reflect preliminary prospective proof of the method. If we were to achieve those high remission rates through exaggerated placebo responding, the point of the study would be undermined, and future resources inappropriately directed. There are currently no methods to select best treatments for individual patients in clinical use. Therefore, withholding the information about how treatment in this study is assigned does not represent a compromise of usual clinical care. We have no evidence or reason to suspect that the PET scan-indicated treatment is likely to be worse than randomized treatment assignment. Thus, there are no anticipated harms to participants that would result from this deception; all participants will receive a standard-of-care treatment for depression, either evidence-based psychotherapy or medication. In order to prevent information about the trial design from disseminating into the general public, we will not debrief patients about the deception at the end of the trial. Because

this trial allows all participants to receive both treatments if the initially assigned treatment does not lead to remission in Phase 1, there is no harm in withholding this aspect of the study design. The treatment outcome assessors administering the HAMD, MADRS and HAMA scales will also be blind to the design of the study and the means of treatment assignment. This blinding is necessary to prevent distortions of ratings accuracy due to expectations arising from knowledge that treatment is assigned based on the FDG-PET measurement.

Debriefing
Patients will be debriefed by the study team following their study participation outlining the reasons for the deception need of this study.

Plans to inform participants of new findings or research results that might affect health

If new findings emerge regarding risks or benefits of the study medications used in our study, patients will be informed of this information as soon as possible and reminded of their ability to continue participation in the study at their own will.

Data and safety monitoring plan (DSMP)

The proposed study is most appropriately considered the equivalent of a Phase IV clinical trial. The Departments of Psychiatry and Neurology Data Safety Monitoring Board will provide annual review of the safety and confidentiality components of the study. All serious adverse events will be reported to the DSMB within 10 days of learning of their occurrence, and any deaths will be reported within 24 hours. The DSMB includes physicians who are experienced in clinical research, a nurse, and administrative support. Statistical help is available as needed. Study clinicians serving on the DSMB will recuse themselves when the current studied is being reviewed by the DSMB.

Plans for data management and monitoring

Data will be collected and stored in a password-protected Microsoft Access database, on password-protected computers, stored in the MAP offices.

Pharmaceutical, biologic, and device information:
The package insert for escitalopram is attached, and can be found at:
http://dailymed.nlm.nih.gov/dailymed/about.cfm

Reference and appendices:

1. Am College Cardiology and Am Heart Association. Management of Patients w/ Acute Myocardial Infarction. 2000. http://www.acc.org/gap/downloads/Pocket_Guide.pdf

2. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, 3rd ed. 2010.

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Questionnaires and scales attached include:

- Hamilton Depression Rating Scale (HAMD)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Rating Scale for Anxiety (HAM-A)
- Clinical Global Impression-Severity and –Improvement scales (CGI-S, CGI-I)
- Positive and Negative Affect Scale (PANAS)
- Beck Depression Inventory-II (BDI-II)
- Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
- Sheehan Disability Scale (SDS)
- Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)
- Multidimensional Locus of Control Inventory (MLCI)
- Life Orientation Test – Revised (LOT-R)
- Childhood Trauma Questionnaire (CTQ)
- Emotion Regulation Questionnaire (ERQ)
- Dunlop Emotional Blunting Scale (DEBS)
- Ruminative Response Scale (RRS)
- Pittsburgh Sleep Quality Index (PSQI)
- Frequency, Intensity and Burden of Side Effects Rating (FIBSER)
- PROMIS Depression Scale
- PROMIS Anxiety Scale
- Body Awareness Questionnaire
- MRI Safety Form