Protocol

Promoting Enhanced Pharmacotherapy Choice through Immunomarkers Evaluation in Depression: PRECISE-D

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1. Background and Introduction

1.1. Burden of Major Depressive Disorder and the Decisional Dilemma

Major Depressive Disorder (MDD) affects approximately 10% of the adult population in the United States,[1] and according to the World Health Organization, MDD is now the leading cause of disability worldwide.[2] The chronic course of the illness, which is characterized either by unremitting symptoms and dysfunction or repeated depressive episodes interspersed with periods of remission,[3,4] significantly contributes to the personal and public health costs of the disease, which total over $210 billion per year in the US alone.[5] The relative effectiveness of medications for the treatment of MDD are comparable to those for other chronic medical conditions.[6-8] However, outcomes in clinical practice continue to be poor.[9] This is related in part to the decisional dilemma faced by clinicians and patients in determining which antidepressant is right for which patient.[10] Although extensive data indicate that there are no meaningful differences among second generation antidepressants (see below), large community trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial clearly indicate that only a minority of patients respond to the initial antidepressant, and most patients require several trials of medications to achieve response.[6,11,12] Thus, while antidepressants are equally effective on average, response for a given patient is very antidepressant specific, leaving clinicians and patients guessing as to which drug is the best choice. This decisional dilemma results in a trial and error process of antidepressant selection, which can undermine the patient's confidence in the decision-making process, and ultimately contribute to multiple treatment trials, ineffective medications taken too long, treatments switched too early, or patients simply dropping out of care. This process also may inadvertently lead to patients being labeled treatment resistant, even when effective treatments may exist for them. Hence, reducing the decisional dilemma regarding antidepressant choice in primary care will increase the effectiveness of currently available antidepressant medications.

1.2. Current Practice Guidelines for Antidepressant Prescription and the Critical Evidence Gap

Based on an Executive Summary by the Effective Health Care Program of the Agency for Healthcare Research and Quality, which performed a comparative effectiveness review of second generation antidepressants, "*no substantial differences in efficacy exist among second generation antidepressants for the treatment of MDD*". [13] Accordingly, the most recent practice guidelines from the American Psychiatric Association recommend: "*Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference.*"[10] However, there is no empirical evidence that any of these or other clinical variables (such as baseline symptom severity, age of onset, presence of insomnia, chronicity, atypical or melancholic features) can meaningfully guide selection of one antidepressant medication over another.[14-19] As a consequence, a critical evidence gap exists regarding how to decide which antidepressant will be most effective for a given patient. Because of this evidence gap, patients and providers face a decisional uncertainty that can undermine treatment effectiveness and patient engagement in the treatment process.

1.3. Filling the Critical Evidence Gap: Inflammation as a Predictor of Antidepressant Treatment Response

Data indicate that inflammation plays an important role in the response to antidepressants.[20-24] A significant percentage of depressed patients exhibit increased inflammation,[25] and studies have shown that increased biomarkers of inflammation including c-reactive protein (CRP) can predict response to antidepressant treatment, including the prediction of differential response to different types of antidepressants.[21-24,26] Relevant to the mechanisms by which inflammation can affect antidepressant response, inflammatory cytokines and their signaling pathways have been shown to increase the expression and function of the transporters for serotonin,[27] thereby potentially undermining the effects of selective serotonin reuptake inhibitors (SSRIs), which act in large part by blocking these transporters.[28] Moreover, data from both laboratory animals and humans have demonstrated that inflammatory cytokines reduce dopamine neurotransmission and inhibit dopamine-mediated reward circuits in the brain that are associated with anhedonia, a core symptom of depression.[29] Interestingly, administration of medications that increase dopamine signaling have been shown to reverse anhedonic symptoms in laboratory animals exposed to inflammatory cytokines.[30] Taken together, these translational studies strongly suggest that patients with increased inflammation are less likely respond to SSRIs and are more likely respond to drugs that augment dopamine.

1.4. Inflammatory Biomarkers Can Reduce Decisional Uncertainty and Fill the Critical Evidence Gap

In the absence of data demonstrating differential efficacy among antidepressants coupled with lack of predictive power of clinical variables, there is a critical evidence gap regarding the initial choice of currently available antidepressants.[31-33] Consistent with the translational studies described above, biomarkers of inflammation may fill this gap, given that they have been shown to be effective in predicting differential response to antidepressant subtypes in MDD.[34-37] Indeed, CRP, a clinically available and inexpensive biomarker of systemic inflammation, has been shown to predict differential response to currently available antidepressants in post hoc analyses of two large community studies of over 300 patients. For example, in a study conducted by our group, MDD patients with high CRP (≥1mg/L) were found to respond better to the dopamine reuptake inhibitor bupropion in combination with escitalopram compared to patients treated with escitalopram alone, who responded better when CRP concentrations were low (<1mg/L).[22] While systematic reviews and meta-analyses have failed to find significant differences in treatment outcomes in head-to-head comparisons of SSRIs and bupropion,[38,39] the above-mentioned differential treatment response to an SSRI versus bupropion based on CRP level clearly demonstrates a heterogeneity in treatment effects (HTE). Hence, superiority of antidepressant selection informed by point-of-care (POC) CRP testing over the current practice of using clinical variables can reduce the decisional uncertainty of choosing the right antidepressant compared to the currently used “trial and error” process, ultimately closing the evidence gap and increasing the effectiveness of currently available antidepressant medications.

2. Introduction and Purpose

2.1. Study Overview

Despite the large socioeconomic impact of major depressive disorder (MDD), our ability to provide optimal antidepressant treatment is significantly limited. The lack of consistent clinical or laboratory predictors of response to antidepressants remains a major challenge. Currently, no biomarker is used in clinical care to aid in the selection of treatment, and finding the right medication for people suffering from MDD still relies on a "trial-and-error" method. There is an urgent need to better predict differential response to antidepressants.

The main objective of the proposed study is to evaluate the use of POC CRP as a predictor of differential antidepressant response (escitalopram versus bupropion extended-release [XL]) in individuals with MDD. Additionally, two optional sub-studies will be available for participants to enroll in.

The first sub-study will evaluate if capillary blood obtained via finger prick can be used for the POC CRP test instead of venous blood. Hence, our proposed study results have the potential to markedly impact antidepressant selection in routine clinical practice and allow treatment providers and patients to choose an antidepressant that is more likely to result in favorable treatment outcomes. If favorable, this study would also support personalized selection of antidepressant medications to individual MDD patients using a readily-available inexpensive blood test. Additionally, results from the sub-study could validate the use of finger prick blood for the CRP test, providing an easier and faster alternative for busy clinical practice.

The second sub-study will investigate if pre- and post-treatment connectomic profiles obtained from resting electroencephalography (EEG) are able to predict differential antidepressant treatment response. EEG also offers clinical utility as a cost-effective and rapid means of assessing neurological activity. EEG biomarkers have demonstrated ability to predict response to different interventions in depression [65, 66.] Further development of this capability has potential to rapidly advance personalized medicine.

To facilitate the understanding of the protocol, we define two commonly used terms in this protocol:

***CRP-consistent antidepressant selection*:** participants with a baseline venous CRP level greater than or equal to 1 will be prescribed bupropion XL and participants with a baseline venous CRP level less than 1 will be prescribed escitalopram.

CRP-inconsistent antidepressant selection: participants with a baseline venous CRP level greater than or equal to 1 will be prescribed escitalopram and participants with a venous baseline CRP level less than 1 will be prescribed bupropion XL.

2.2. Study Aims

- *Primary Aim 1:* To compare the efficacy of CRP-consistent antidepressant selection versus CRP-inconsistent antidepressant selection on remission rates in patients with MDD.

- *Primary Aim 2*: To compare the efficacy of CRP-consistent antidepressant selection versus CRP-inconsistent antidepressant selection on improving social and occupational functioning.

- *Primary Aim 3*: To compare CRP-consistent antidepressant selection versus CRP-inconsistent antidepressant selection on adverse antidepressant treatment effects.

- *Sub-Study Aim 1:* To investigate if capillary blood provides a valid and reliable CRP measurement by comparing the levels of POC CRP obtained by capillary blood (finger prick) with those obtained by venous blood (blood draw).

- *Sub-Study Aim 2*: To evaluate the ability of various measures of functional network connectivity obtained from resting EEG to predict treatment response.

3. Study Design

3.1. Overview

The current study is single site, randomized, open label 8-week clinical trial comparing the efficacy of CRP-consistent antidepressant selection vs CRP-inconsistent antidepressant selection. Venous levels of CRP will be measured by an FDA cleared Point of Care Smart analyzer (Diazyme Laboratories) and/or Quest Diagnostics, which provides the CRP concentration within few minutes. The study will use a stratified randomization (i.e. separate randomization schemes for patients with POC CRP ≥ 1 and POC CRP < 1). This will assure that the four study groups have similar sample sizes: 1) escitalopram with CRP < 1, 2) bupropion-XL with CRP < 1, 3) escitalopram with CRP ≥ 1, 4) bupropion-XL with CRP ≥ 1. We anticipate that participants with higher inflammation (CRP ≥ 1) will have higher remission rates with bupropion-XL than escitalopram, while individuals with low levels of systemic inflammation (CRP < 1) will remit more frequently with escitalopram when compared to those treated with bupropion XL. A sub-study will compare POC CRP levels based on the blood source: venous blood obtained by venipuncture vs capillary blood obtained via fingerstick.

3.2. Methods

70 eligible subjects will be assigned to one of two groups based on their baseline venous CRP level: CRP< 1 or CRP≥1. Participants in both groups will then be randomly assigned in a 1:1 fashion to one of two treatment arms: a) CRP consistent antidepressant selection or b) CRP inconsistent antidepressant selection. All subjects will be followed for 56 (+/- 3) days (8 weeks) to examine the efficacy of the study treatments. The treatment phase is followed by a remote follow-up call and electronic self-report questionnaires at 12 weeks.

3.3. Study Population

Number of Subjects

70 subjects will enter the open-label treatment phase of this single site study at the Center for Depression Research and Clinical Care. This trial will be conducted according to the U.S. FDA guidelines and the Declaration of Helsinki. IRB-approved written informed consent will be obtained from all patients before any protocol-specified procedures are carried out. The subjects will be drawn from an outpatient sample of patients with MDD, diagnosed with the use of the Mini International Neuropsychiatric Interview (MINI).

3.4. Subject Eligibility

Inclusion Criteria

A subject will be eligible for inclusion only if all of the following criteria are met:

- Women and men ages 18-65
- Diagnosis of Major Depressive Disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria confirmed by the Mini International Neuropsychiatric Interview (MINI).
- Have a score of 14 or higher on the Hamilton Scale for Depressive Symptomatology as assessed by trained clinicians.

Exclusion Criteria

A potential participant will NOT be eligible for participation in this study if any of the following criteria are met:

- Any antidepressant use within the last 8 weeks
- Active infection or uncontrolled autoimmune disease
- Currently on oral corticosteroids or active immune suppressive therapy (methotrexate, cyclosporine, anti-cytokines medications, etc. Note that nonsteroidal anti-inflammatory drugs - NSAIDs - will be allowed).
- Current diagnosis of uncontrolled HIV, hepatitis C or significant immunodeficiency
- Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 3 months before signing informed consent form.
- Positive urine drug test for illicit substances or substances used out of the context of prescription
- Cognitively unable to give informed consent
- Pregnant or breastfeeding women, women of childbearing potential who are not using an accepted means of birth control, or women with a positive urine pregnancy test
- History of seizure disorder
- Previous significant adverse reaction to escitalopram or bupropion
- History of non-response to adequate doses of escitalopram or bupropion XL
- Current use of concomitant psychotropic agents (anticonvulsants, benzodiazepines, hypnotics, opiates, triiodothyronine (T3), modafinil, psychostimulants, buspirone, melatonin, folate, l-methylfolate, s-adenosyl methionine, lithium) not on the same dose for at least four weeks prior to study entry or who do not agree to continue at the same dose during the acute phase of the study.
- Lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder or other psychotic disorder except for Major Depressive Disorder with psychotic features in prior episode.
- Current anorexia nervosa or bulimia nervosa per Mini International Neuropsychiatric Interview (MINI).
- Suicidal ideation of the degree that, in the opinion of the evaluating clinician, participation in the study would place them at significantly increased risk of suicide
- Unstable medical issues of such degree that, in the opinion of the evaluating clinician, participation in the study would place them at significant risk of a serious adverse event

Rationale for the Inclusion/Exclusion Criteria

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study are meaningful in support of the research hypotheses. It is imperative that subjects fully meet all eligibility criteria.

4. Study procedures

4.1. Overview

Subjects will be screened for eligibility as detailed above. Study participants will be consented prior to the administration of any procedure. Following the screening assessment and confirmation that all criteria for entry into the study are met, eligible subjects will be assigned to 2 different groups based on their baseline venous CRP level: CRP≥ 1 and CRP<1. Participants within each group will then be randomized in a 1:1 fashion to one of the two treatment arms: a) CRP-consistent antidepressant selection or b) CRP-inconsistent antidepressant selection.

Table 1.

Visit Week	**Week 0***		**Week 2+**	**Week 4+**	**Week 6+**	**Week 8**	**Week 12+**
	Screening	**Baseline**					
Visit Day Window		**0**	**14 (+/-3)**	**28 (+/-3)**	**42 (+/-3)**	**56 (+/-3)**	**84 (+/-3)**
Informed Consent and Eligibility Screening							
Informed Consent	X						
Eligibility Screening	X						
The Demographics Form	X						
Clinical, General Health, and Medical History Surveys							
The Self-Administered Comorbidity Questionnaire (SCQ)	X						
Prior and Concomitant Medication and Treatment and Adverse Events	X	X	X	X	X	X	X
Antidepressant Treatment Response Questionnaire (ATRQ)	X						
Fagerstrom Test of Nicotine Dependence	X						
Depression Severity Measurement Tools							
M.I.N.I. (7.0) Structured Diagnostic Interview	X						
Hamilton Depression Rating Scale	X					X	X
Inventory of Depressive Symptomatology (IDS)		X	X	X	X	X	X
Concise Health Risk Tracking Scale (CHRT)		X	X	X	X	X	X
Work and Social Adjustment Scale (WSAS)		X	X	X	X	X	X
The Temporal Experience of Pleasure Scale (TEPS)		X	X	X	X	X	X
Behavioral Inhibition System/ Behavioral Approach System (BIS/BAS) Scale		X	X	X	X	X	X

(TABLE 1 continued on next page)

Anxiety Symptoms							
Generalized Anxiety Disorder 7-item (GAD-7)		X	X	X	X	X	X
State Trait Anxiety Inventory (STAI)		X	X	X	X	X	X
Side Effects and Adherence							
Patient Adherence to Antidepressant Medication Questionnaire (PAQ)			X	X	X	X	X
Frequency, Intensity, and Burden of Side Effects			X	X	X	X	X
Cognition and Behavioral							
Flanker Test		X				X	
Digit Symbol Substitution Test		X				X	
Behavioral Phenotyping - 24 Hours Substance Use		X				X	
Physical Examination and Collection of Biospecimens							
Physical Examination	X						
Vital Signs (BP, HR, RR, Temperature, Pain)	X	X*	X**	X**	X**	X**	
HT/WT/BMI, Waist/ Hip Circumference	X	X*	X**	X**	X**	X	
Blood Collection: CBC, BMP, TSH, Lipid Panel, Hemoglobin A1c, CRP		X				X++	
Urine Toxicology Screen	X						
Urine Pregnancy Test	X						
Blood Based Immunomarkers							
Optional Venous Blood Draw for Biobanking		X				X	
Optional Finger Prick		X					
Electroencephalogram (EEG)							
Optional EEG: Resting State		X				X	

*Screening and baseline will take place on the same visit. If not possible, baseline will be completed within 2 weeks after screening. Vital signs, BMI, and Waist:Hip ratio will be updated.
** Obtained during in office visits only.
+ Weeks 2, 4, 6, and 12 visits may be performed remotely when necessary.
++ CRP and HbA1C only

4.2. Screening and Baseline Visit

Screening
Duration: 2 hours

The screening phase will start with the informed consent procedures. Once patients agree to participate in the study by signing the informed consent document, a medical and psychiatric history will be taken and a physical examination will be performed, as outlined in Table 1. The purpose is to ensure that only appropriate patients are entered into the study. The investigator will determine that the patients meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the patients. Patients found to be in potential need of hospitalization due to their degree of suicidal ideation at screening will be referred to the nearest emergency room.

If the participant meets all of the inclusion criteria and none of the exclusion criteria, he/she will proceed to the baseline portion of the visit.

Baseline – Week 0
Duration: 1 hour 15min **OR** up to 2 hours

1. Self-Report Questionnaires (30 min)
2. Clinician/Assessor Rated Assessments (HAM-D, M.I.N.I and ATRQ) (45min)
3. Neurocognitive and behavioral phenotyping tasks (30 minutes).
    - Including optional EEG (30 minutes)
4. Blood Draw (15 minutes)

4.3. Randomization

Patients will be assigned to one of two groups based on their baseline CRP level as measured by a venous blood sample: CRP≥1 or CRP<1. Participants from both groups will then be randomized in a 1:1 fashion to one of the two treatment arms: CRP consistent antidepressant selection or CRP inconsistent antidepressant selection.

- **CRP-consistent antidepressant selection**
  If venous blood CRP<1, then prescribe escitalopram.
  If venous blood CRP≥1, then prescribe bupropion XL

- **CRP-inconsistent antidepressant selection**
  If venous blood CRP≥1, then prescribe escitalopram
  If venous blood CRP<1, then prescribe bupropion XL

4.4. Study Visits

Week 2, 4, and 6
Duration: 1 hour

1. Self-Report Questionnaires (30 min)
2. Prior and Concomitant Medication and Treatment, Adverse Events (5-10 min)
3. Clinician General Interview (15min)
4. Assessment of vital signs and weight (10 minutes).

*Week 8 (*Exit Phase)
Duration: 2 hours **OR** up to 2 hours and 35 minutes

1. Self-Report Questionnaires (30 min)
2. Prior and Concomitant Medication and Treatment (5-10 min)
2. Clinician General Interview and Hamilton Depression Rating Scale (25 min)
4. Assessment of vital signs and weight (15 min)
5. Neurocognitive and behavioral phenotyping tasks (30 minutes).
    - Including optional EEG (30 minutes)
6. Blood draw (15 min)

Post Study Follow Up

Week 12
Duration: 1 hour

Consists of a phone call and self-administered questionnaires. The phone call will last approximately 20 minutes and will include a clinician rated Hamilton Depression Rating Scale. A series of self-report questionnaires will be sent electronically and will take approximately 40 minutes.

4.4.1. Participant Compensation

Essential to the study is appropriate support for participants' time and effort contributing to the study. Participants will receive monetary remuneration for participation in the study to compensate for time burden and travel arrangements and will be paid for each eligible visit using UT Southwestern ClinCard, per IRB regulations. Compensation for study procedures will be made each time a complete study is performed throughout the study duration. Bus passes or other help with transportation and/or parking expenses may also be available, if needed.

Participants completing a screening and baseline visit inclusive of data collection and biospecimens will be compensated ($25). Participants will be paid ($10) for completed visits at week 2, 4, 6, and 8. Participants who complete the follow up visit via telephone at week 12 will be compensated for completed assessments ($10) and self-report questionnaires ($10).

4.4.2. Costs

Participants or insurance providers will not be charged for events related to this study (i.e., screening procedures, laboratory procedures). Study medications (i.e. escitalopram or bupropion-XL) will also be provided at no cost. UT Southwestern Medical Center will not pay for doctor visits, other treatments, or tests that are NOT part of this study. Compensation for an injury resulting from the participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas. If a situation arises in which a participant is unable to collect their prescription at the designated study pharmacy, they will be reimbursed for the cost of their medication pick-up, using the receipt of the transaction as proof of purchase.

4.5. Laboratory/Diagnostic Procedures

Blood samples will be collected from participants by trained phlebotomists, who will draw the sample using standard venipuncture procedures, through a single venipuncture using a small gauge needle. Universal precautions will be observed by the phlebotomists during all draws. Each tube will be labeled and packaged for processing and storage.

Screening Phase - Week 0
Once the patient has signed the informed consent document, the urine drug screen and pregnancy test will be performed (if applicable)

Baseline Phase - Week 0
About 30 ml (~2 tablespoons) of venous blood will be collected and the following tests will be completed: Complete Blood Count, Basic Metabolic Panel, Lipid Panel, Hemoglobin A1c, TSH levels, and CRP levels. Later analysis of other immunomarkers (eg. IL-1, IL-6, TNF alpha), metabolism (eg. lipids, glucose

tolerance, amino acids, kyni), neurological function (eg. brain-derived neurotrophic factor, monoamine receptors, etc) and genetic testing will also be performed. The rest of the blood samples will be stored indefinitely until the sample runs out or it is destroyed.

Week 8 - Exit Phase
About 25 ml (~2 tablespoons) of venous blood will be collected and used for CRP and later analysis of other immunomarkers level measurements (eg. IL-1, IL-6, TNF), metabolism (eg. lipids, glucose tolerance, amino acids, etc), neurological function (eg. brain-derived neurotrophic factor, monoamine receptors, etc) and genetic testing will also be performed. The rest of the blood samples will be stored indefinitely until the sample runs out or it is destroyed.

4.6 Optional Finger Prick
Participants will have the option to participate in a sub-study that will compare venous blood CRP levels with capillary blood CRP levels. The purpose of this sub-study is to examine if the latter is accurate and can be used in future studies and clinical practice. During the baseline visit, 2-5 drops of capillary blood will be collected using a finger prick. The CRP levels on the capillary blood will be analyzed and compared to those obtained using venous blood obtained via venipuncture.

4.7 Optional Electroencephalogram (EEG)
Participants will have the option to participate in a sub-study that will acquire 10 minutes of resting state EEG at baseline and Week 8 to provide measures of functional network connectivity. The purpose of this sub-study is to determine the predictive utility of EEG-derived measures in treatment response to escitalopram and bupropion.

4.7.1 Electroencephalogram (EEG) Procedures

Participants will undergo EEG recordings at baseline and at Week 8. EEG is performed by placing an elastic cap containing electrodes on the participant's scalp. These electrodes are previously soaked in a potassium chloride saline solution (similar to salt water) in order to better conduct electrical signals at the scalp. The technician ensures correct alignment of the cap and the quality of measured signals. This process takes approximately 10-15 minutes. The participant's brain activity is then recorded for 5 minutes as they sit quietly with their eyes open, generally fixating a marked point in front of them. This procedure is repeated for 5 minutes but with the participant's eyes closed as the rest quietly but awake. The cap is then removed and the participant can pat dry their hair with a provided towel. The total time estimate for completion of the EEG collection at each visit is approximately 30 minutes. The EEG workgroup will ensure that adequate training, standardization of measures, and validation of equipment is maintained for data consistencies and quality control purposes.

5. Treatment

5.1. Overview
The current study will use two FDA-approved medication for MDD: escitalopram and bupropion-XL. Systematic reviews and meta-analyses have failed to find significant differences in treatment outcomes in head-to-head comparisons of SSRIs and bupropion. In this context, the treatment provided in this clinical trial is expected to have similar risks to standard clinical care.

Escitalopram is a widely-used SSRI, which is FDA-approved for MDD in people aged 12 or older.[40] The efficacy is similar to other SSRIs but escitalopram is known for fewer side-effects and fewer pharmacological interactions making it well-tolerated and commonly used in clinical practice.[41] The medication is commercially available in the generic form or under the brand name Lexapro. The generic medication will be provided in this study. The compound will be obtained from a commercial pharmacy. Since this is study is open-label, the medication will be dispensed to the participants in its usual commercial form. We will provide escitalopram in tablets of 5 mg, 10 mg, 15 mg and 20 mg.

Bupropion is a commonly used norepinephrine-dopamine reuptake inhibitor that is FDA-approved for MDD.[41] Its antidepressant effects are comparable to SSRIs and other antidepressants.[42-44] Bupropion has good overall tolerability.[45] Bupropion is commercially available in the generic form as well as under the brand names Wellbutrin, Zyban and Aplenzin. The medication comes in three formulations: regular bupropion, bupropion sustained-release (SR) and bupropion extended-release (XL). Bupropion-XL will be provided in this study (tablets of 150 mg and 300 mg). This formulation has the advantage of being used just once a day, while the other formulations need to be taken twice or three times a day. In addition to a better dosing schedule, bupropion-XL has theoretically fewer side-effects.[44]

5.2. Mechanisms of action

Escitalopram exerts its antidepressant actions through blockage of the serotonin reuptake pump leading to synaptic changes that result on increased serotoninergic transmission.[41] It is a "clean" SSRI - i.e. no significant secondary pharmacological actions and no known immunological effect.[23] Escitalopram usually starts working in 2 to 4 weeks.

Bupropion XL is a commonly used norepinephrine-dopamine reuptake inhibitor. As a result, this medication is believed to increase norepinephrine and dopamine neurotransmission. Evidence from in vitro and pre-clinical studies suggest that bupropion has an additional anti-inflammatory action.[46-48] Therefore, this antidepressant would be particularly useful for MDD with underlying systemic inflammation. Bupropion antidepressant effects usually start in 2 to 4 weeks after its initiation.

5.3. Dosing Schedule

Escitalopram will be started at 5 mg/day during the first week of treatment. The dose will then be increased to 10mg/day, and can be increased to 20 mg/day if side-effects allow and QIDS-C is higher than 5. Dose can be decreased to 5 mg by clinician discretion such as to increase tolerability or better manage side-effects. 5 mg will be the lowest dose allowed in the study.

Bupropion-XL will be started at 150 mg/day and increased to 300 mg/day after one week. This dose can be increased to 450 mg/day (divided in 2 doses) at Week 2 or later if side-effects allow and QIDS-C is higher than 5. Clinicians may opt to titrate bupropion-XL in a slower fashion in cases that might increase tolerability or better manage side-effects. 150 mg will be the lowest dose allowed in the study.

After study completion at week 8, participants who wish to remain on treatment will be given a four-week supply of study drug while they transition care.

The medications schedule described above is based on previous trials.[49,50]

5.4. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the Concomitant Medication Log for each patient, along with dosage information and start and stop dates. Allowed concomitant medications include any prescription or over-the-counter medication not specifically excluded by the protocol. Patients requiring excluded drugs will be discontinued from the study.

6. Sources of Research material

6.1. Outcome Measures

The primary study endpoint will be remission rates based on the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR), which will be extracted from the 30-item Inventory of Depressive Symptomatology (IDS-SR). QIDS-SR measures MDD severity; a score of 5 or less is considered remission. The secondary study endpoints will be: a) improvement in social and occupational function according to the 5-item self-administered Work and Social Adjustment Scale and b) side effect measures using the 3-item Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale.

6.2. Demographics Forms

Demographics Form: The demographics form will be administered to all participants during the screening phase. The form consists of basic demographic information (e.g., gender, race/ethnicity, education).

6.3. Clinical, General Health, and Medical History Surveys

Self-Administered Comorbidity Questionnaire (SCQ): The SCQ assesses the presence of medical problems, whether treatment is received for the condition, and whether or not the condition limits functioning. Each question is answered on a yes/no basis. Each affirmative response to the three items per medical condition is coded as a 1, with the total score being the sum of all positive responses. The medical conditions specified on the SCQ include: heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, arthritis, thyroid disease and back pain.

Prior and Concomitant Medications: The Prior and Concomitant Medications form assesses prescribed and certain over-the-counter medications taken by the participant. The Prior and Concomitant Medications form will be administered at the baseline visit and at each visit thereafter, if the participant endorses a change in medication status.

Antidepressant Treatment Response Questionnaire (ATRQ): clinician-rated scale used to determine treatment resistance in MDD. The MGH ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants.[52]

Fagerstrom Test of Nicotine Dependence: The Fagerstrom Test of Nicotine Dependence consists of six items that test for dependence to nicotine. Sample items include “How soon after you awake do you smoke your first cigarette?” with answers including “within 5 minutes”, “6-30 minutes”, “31-60 minutes” and “after 60 minutes”. A scoring algorithm has been created for all items in order to denote ranges of severity of dependence, including “very low dependence,” “low”, “moderate”, “high”, and “very high” levels.[53]

6.4. Depression Severity Measurement Tools

Mini-International Neuropsychiatric Interview: The MINI, Version 7.0. is a structured diagnostic interview designed to screen for Axis I psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Clinicians complete this structured interview to assess for the presence of various forms of psychopathology, including mood and anxiety disorders; psychotic disorders; anxiety disorders; substance use disorders; eating disorders; and antisocial personality disorders. Our study also adds in specific questions to gauge various specifiers of a major depressive episode, including with anxious distress, atypical or melancholic features. Permission to use this measure has been granted by the measure's lead author, David Sheehan.[54]

Hamilton Depression Rating Scale: a 17-item clinician-administered scale that has been widely used to determine cut-offs for clinical trials and also to determine changes overtime. The items are anchored from 0 to 4 or from 0 to 2 where higher scores indicate worse severity. There are well established cut-offs for this scale: 0-7 = normal; 8-13 = mild depression; 14-18 = moderate depression; 19-22 = severe depression and $\geq$ 23 very severe depression. The current trial will use moderate depression (i.e., total score of at least 14) as severity cut-off for eligibility.[55]

Inventory of Depressive Symptomatology: Self Report (IDS-SR): a 30-item rating scale designed to assess the severity of depressive symptoms over the past week. The questionnaire assesses the core symptoms of depression such as depressed mood and anhedonia, alongside additional items that measure, for example, anxiety, irritability, insomnia/hypersomnia, somatic complaints and other physical symptoms, panic, and reactivity to interpersonal rejection.[56]

Concise Health Risk Tracking - Self Report: The CHRT-SR is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Items are rated on a fully anchored 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree), with total scores ranging from 13 to 65. The first 13 items detail suicide propensity and include items measuring passive suicidal ideation and lack of social support. The final 3 items include suicide risk items and measure active suicidal ideation and planning. The CHRT-SR has good internal consistency (Cronbach's alpha of 0.78).[57]

Work and Social Adjustment Scale: consists of 5 items, each on a 0 ("No impairment at all") to 8 ("very severe impairment") scale, that inquiries about the impact of one's current feelings on one's employment and psychosocial functioning. Sample items include "Because of the way I feel, my ability to work is impaired" and "because of the way I feel, my ability to form and maintain close relationships with others, including those I live with, is impaired". Internal reliability was at appropriate levels, ranging from Cronbach's alpha = .70 and .94.[58]

The Temporal Experience of Pleasure Scale: this instrument is a self-reported 18-item scale that investigates the two main components anhedonia: 1) anticipatory anhedonia, and 2) consummatory anhedonia. Anticipatory anhedonia (assessed by 10 items) is related to low motivation and impaired goal-directed behavior. Consummatory anhedonia (evaluated by 8 items) is associated with lack of pleasure or inability to satiate a desire. The two components of anhedonia are specific and distinct constructs (Gard et al., 2006). Each item follows a 6-point Likert format where *1 = very false for me* and *6 = very true for me*.[59]

Behavioral Inhibition System/Behavioral Approach System Scale: this scale consists of 24 self-reported items that assesses two motivational systems: 1) avoidance/inhibition where the objective is to avoid a situation or stimuli, and 2) drive/appetite to move towards a goal, and (Carver and White, 2013). Each item follows a 4-point Likert format. Each construct (inhibition and activation) had subscales that further explore their components.[60]

6.5. Anxiety Symptoms

The Generalized Anxiety Disorder 7-item Scale (GAD-7): assesses common symptoms of anxiety and serves as an anxiety-severity scale. Participants respond on a 0 to 3 scale, from "not at all" to "nearly every day", the number of days over the past two weeks that they have been affected by problems including "worrying too much about different things" and "trouble relaxing". The total score of this scale ranges from 0-21, with scores from 5-9 indicating mild anxiety, scores from 10-14 indicating moderate anxiety, and scores 15 or higher indicating severe anxiety.[61]

State-Trait Anxiety Inventory: The 40-item State-Trait Anxiety Inventory includes 20 items indicative of state – or current levels of anxiety – and 20 items of trait – or enduring – anxiety. Items are scored on a four-point scale, ranging from "almost never" to "almost always", with higher scores indicating higher levels of anxiety. Sample state anxiety items are "I am worried" and "I feel calm" while sample trait anxiety items include "I worry too much over something that doesn't really matter." The psychometrics of this measure have been well-established.[62]

6.6. Side Effects and Adherence

The Patient Adherence Questionnaire (PAQ): two-item inventory that assesses for adherence to antidepressant medication. The first item asks how often participants have taken their medication, with responses ranging from "I have taken my medications every day without missing a day" to "I have stopped taking my medications." The second item asks about adjustments made to medication, and answer choices include various options about why individuals might have reduced or increased their dosage, or whether medication has always been taken as prescribed. The measure is scored by adding up items that encode if individuals have missed taking their medication two or more days or have reduced or increased their dosage, with any positive response classifying the patient as being "non-adherent" to medication.[63]

The Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER): used to rate side effects from antidepressant medication. The measure consists of three items, each scored on a 0 to 6 scale, that inquire about the frequency of side effects over the past week (from "no side effects" to "present all the time"); the intensity of such side effects (from "no side effects" to "intolerable"), and the interference on day-to-day functioning due to medication side effects (from "no impairment" to "unable to function").[64]

6.7. Neurocognitive and Behavioral Phenotyping Tasks

Flanker Test: series of response inhibition tests used to assess the ability of suppress responses that are inappropriate in a particular context. The target is flanked by non-target stimuli which correspond either to the same directional response as the target (congruent flankers), to the opposite response (incongruent flankers), or to neither (neutral flankers).

Digit Symbol Substitution Test: timed standardized neuropsychological test that assess processing speed.

7. Patient Recruitment and Consenting Process

7.1. IRB Review

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB for the protocol, consent form, patient recruitment materials/process (e.g., advertisements), and any other written information to be provided to patients.

7.2. Recruitment

Individuals are going to be recruited from the well-established network developed by the Center for Depression Research and Clinical Care (CDRC) and which includes the Mood Disorders Network, and current CDRC studies such as the Dallas 2K Study (D2K) and the Resilience in Adolescent Development (RAD). The Mood Disorders Network (MDN) consists of primary care practices, psychiatric care practices, charity clinics, community, schools, who are interested in collaborating with CDRC on activities and projects geared toward improving care for those suffering from depression. Many MDN clinical sites use the Vital Sign 6 (VS6) software, an application that allows screening and management of depression, using the principles of Measurement-Based Care (MBC). Using VS6 application, participants are systematically assessed for depression and treatment outcomes are monitored utilizing multi-step evidence-based treatment algorithms.

The D2K is an observational long-term study conducted by the CDRC researching the biological mechanisms of depression and antidepressant treatment response. The D2K study is comprised of 2,000 participants, over 10 years of age, with a lifetime or current diagnosis of a mood disorder. A significant part of the individuals in this study are not taking antidepressants. RAD is a 10-year study of 1,500 participants (ages 10-24) that will help uncover the factors that contribute to resilience among children, adolescents, and young adults at risk for mood and anxiety disorders. In addition to these observational studies, the CDRC conducts clinical trials for which there are standard recruitment processes. Previous participants in research at the CDRC who have provided consent for future contact will be invited to participate in this study. Participants recruited from the CDRC will already be registered under a research protocol and not a part of the principal investigator's clinical practice.

Participants will also be recruited from registries such as the UT Southwestern Research Volunteer Registry, UTSW Family Medicine Clinic, the UTSW General Internal Medicine Clinic and the UTSW Employee Assistance Program. The PI and study psychiatrist will meet with MDs and clinic managers at these sites to explain the study goals, inclusion and exclusion criteria, and study process prior to recruitment. We will provide the MDs with written information about the study and the characteristics desired in referrals. Finally, PRECISE-D will recruit from self- and clinician-referral, and IRB-approved study advertisements.

7.3. Informed Consent

All subjects will receive the consent form for the study as well as the Human Subject's Bill of Rights. First, patients interested in the study will be given a copy of the informed consent form so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. If they continue to be interested, they will visit the clinic and the investigator will meet with the potential subject to review and to discuss the details of the research study using the informed consent document as a guide. This discussion should include all

of the required elements of informed consent, e.g., the purpose of the research, the procedures to be followed, the risks and discomforts as well as potential benefits associated with participation, and alternative procedures or treatments, if any, to the study procedures or treatments. Subjects will always be given the opportunity to ask questions and have them answered by the investigator and, whenever possible, to consult with friends/family and/or their physicians. Once they have read the consent document and their questions are answered, if they agree to participate in the research, they sign and date the informed consent document. Patients will sign informed consent and only then will any study-related procedures be conducted. In order to remove any undue pressure on patients referred to the study from a study investigator who happens to be their personal clinician, such interested patients will first have an opportunity to inquire about the study from a research assistant, and obtain a copy of the consent form in advance. In addition, when presenting for screening, they can only be screened and followed during the study (if eligible) from an investigator who is different than their personal clinician.

8. Potential Risks

Human subject risk related to administration of antidepressant medication is minimal as the medications planned for use in this study, escitalopram and bupropion, are approved by the Food and Drug administration and are frequently prescribed in routine practice and for time-periods that are consistent with recommended treatment practices. Additionally, the routine assessment of side effects with measures such as the FIBSER will enable quick detection of adverse effects if they are present.

The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling around the site, bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw.

The risks of finger stick for the point of care (POC) C-reactive protein (CRP) testing include excessive bleeding, bruising/discoloration, infection, dizziness, fainting and pain. These risks are comparable to routine clinical practice where venous blood work and finger stick tests are routinely used for management of chronic medical conditions.

The risk of EEG includes discomfort from wearing a close-fitting elastic cap and the use of an electrolyte solution (KCl, similar to salt water).

The risk of loss of privacy is judged to be low. However, patients will be asked to provide personal identifying information, and there is a very rare risk of breach of confidentiality.

9. Subject Safety and Data Monitoring

9.1. Safety Measures

Minimal risk is expected from the medications as FDA approved low doses will be administered initially, side-effects to these doses monitored and dosage adjustments made according to guidelines. If physical adverse effects are intolerable at the lowest therapeutic dose, subjects may leave the study and will be offered an alternative treatment in consultation with their provider. Minimal risk is also expected from venipuncture and finger stick for POC CRP testing. These will be further minimized by having laboratory work performed only by trained and certified staff, following aseptic procedures, and ascertaining that patient does not have and active infection or taking immunosuppressive treatment (as part of eligibility criteria).

All research personnel are trained in safety precautions in the event the patient needs immediate clinical management or an imminent clinical issue is identified.

9.2. Suicide Monitoring

Participants who report risk of self-harm at any point of contact will be thoroughly evaluated by the study personnel for intent, plan and means for suicide. If the participant is in the clinic, the study clinician will be immediately notified to further assess the participant. If the participant is deemed an acute risk for suicide, the physician will direct the measures necessary to get the participant to safety, using clinic specific crisis management procedures. If study personnel learn that a participant may be at acute risk during a phone assessment, a complete evaluation of the situation will become necessary. For example, if the participant indicates thoughts of suicide/death several times a day on the CHRT scale, the study team will obtain information about the participant's intent, plan, and means at hand for suicide, as well as determine the location of the participant and whether anyone else is with the participant. Measures to keep the participant safe, including the option of calling 911 for police assistance will be implemented.

Specifically:

- In the event that a participant contacts the study and indicates suicidal ideation with intent
- Study personnel will determine if participant is alone or has supportive family or friends with him.
- Personnel will contact family members/significant friends using the contact information provided by participant at study entry.
- If family is contacted, they will be alerted to the urgency and need to limit the participant's access to the means of suicide. Personnel will review plan with family should participant need urgent care to prevent a suicide attempt.

Whether the participant presents in clinic or calls in expressing active suicidality, the clinician or study personnel will instruct the participant to go to the nearest emergency room. If family or friends are not available to take the participant to the emergency room, or if the participant refuses, the clinician/study personnel may call 911 and have the participant escorted involuntarily. In situations where participants have made initial contact with the study personnel and not the study clinician, the study personnel will notify the licensed treating clinician of the event. Following resolution of the acute suicidal status, the participant will be evaluated for continuation in the study. This will be based on the current need for best clinical care.

9.3. Reasons for Early Termination

Acceptable reasons for early termination from the randomized clinical trial include the following: 1) request of patient, 2) decision of physician, 3) serious adverse event and 4) protocol violation. Patients will be assessed for suicidal ideation at every visit. Subjects who, in the opinion of the assessing clinician have a worsening of suicidal ideation that renders them at increased risk for study participation will be removed from the study and given an appropriate clinical referral.

9.4. Evaluation of Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a study subject. The reporting period begins when a study subject signs consent and ends at Week 12 or earlier for patients who prematurely discontinue the study.

Adverse events will be recorded using the appropriate form. Patients shall be allowed to contact the investigator or a member of his staff at any time between visits concerning adverse events or worsening of symptoms.

Unanticipated problems involving risks to subjects, including adverse events, will be reported to the overall study PI and to the site IRB.

Serious adverse events, including those spontaneously reported to the site-investigator from the time a signed and dated ICF is obtained until within 30 days after the last dose of study drug must be reported using the Serious Adverse Event Form.

Pregnancy

If a subject (or subject's partner) becomes pregnant during the study, it must be reported within 24 business hours of the time the investigator becomes aware of the event to study PI and site IRB. Pregnancy in itself is not regarded as an AE unless there is a clinical suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs from the first day of treatment to 30 days following the last treatment given will be followed for gestational outcome.

Disease Progression or Worsening Depression

The development of worsening depression should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Serious Adverse Events (SAEs)

The following criteria define an SAE: a) death, b) life-threatening event, c) hospitalization or prolongation of hospitalization, d) persistent or significant disability/incapacity, or e) congenital anomaly/birth defect. The study PI are in charge of determining if an adverse event represents an SAE.

10.Procedures to Maintain Confidentiality

All investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.

All research staff will receive training through the Collaborative Institutional Training Initiative. Required courses will include: HIPAA, Good Clinical Practice, and Human Subject Protection. Staff will only have access to identifying information as needed for their role in the study. No information about or provided by the subjects will be disclosed to others without written permission. Electronic health records will be stored on password-protected, secure networks or devices.

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of all data and by security protocols for all data capture systems. As with all research data, information gathered by the study will be used only for aggregate analysis. It will not be released with any information that identifies research participants. Uses and risks related to data collection will be outlined in the informed consent and reviewed with the subjects.

11.Potential Benefits to Study Participants and Others

Study participants will have the opportunity to directly benefit from the antidepressant medications escitalopram and bupropion. It is expected that a subset of patients in both treatment arms will show either improvement in or remission of their disorder. The population of depressed patients as a whole has an opportunity to benefit from the study, as the results may be valuable in prescribing appropriate personalized treatment strategies in the long-term treatment of depression.

If we find that CRP-consistent antidepressant selection is superior to CRP-inconsistent antidepressant selection, it will reduce the decisional uncertainty associated with antidepressant selection in routine clinical practice and allow treatment providers and patients to choose an antidepressant that is more likely to result in favorable treatment outcomes. If favorable, this study would also support personalized selection of antidepressant medications to individual MDD patients using a readily-available inexpensive blood test. Additionally, if the secondary analysis demonstrates that finger stick blood can be used for the CRP test instead of venous blood, then this will represent a direct point-of-care option.

The study will also evaluate EEG connectivity measures' ability to predict differential treatment response to escitalopram and bupropion. These results have the potential to significantly impact clinical practice as EEG is an economical, rapid, and easy to administer method of obtaining treatment-guiding neurophysiological measures.

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