Adherence to Antidepressant Treatment in Subjects with Depression

Protocol Identifying Number: 2017-007-00

Principal Investigator: Martin P. Paulus

Sponsor: Laureate Institute for Brain Research

Funded by: The William K Warren Foundation

Draft or Version Number: v.1.0

November 7, 2017

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
GCP	Good Clinical Practice
US	United States
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
QIDS-SR	Quick Inventory of Depressive Symptomatology
MPH	Methylphenidate
Mg	Milligrams
MEMS	Medication Electronic Monitoring System
BMQ	Beliefs about Medicine Questionnaire
MAR	Medication Adherence Reasons
LIBR	Laureate Institute for Brain Research
CGI	Clinical Global Impression
PDSQ	Psychiatric Diagnostic Screening Questionnaire
MHRP	Mental Health Research Panel
PHQ-9	Patient Health Questionnaire (Depression)
CTQ	Childhood Trauma Questionnaire
PANAS-X	Positive and Negative Affect Schedule- Expanded Form
WHO HPQ	World Health Organization Health and Work Performance Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System
CBC	Complete Blood Count
CMP	Complete Metabolic Panel
TSH	Thyroid Stimulating Hormone
STAR-D	Sequenced Treatment Alternatives to Relieve Depression
SDS	Sheehan Disability Scale
DF	Degrees of Freedom

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6 All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.
- The principal investigator will assure that no protocol deviation from, or changes to the protocol take place without prior agreement from the sponsor and Institutional Review Board (IRB).

Principal Investigator: _____Martin P. Paulus_____

Signed: _____ Date: _____11/07/2017_____

PROTOCOL SUMMARY

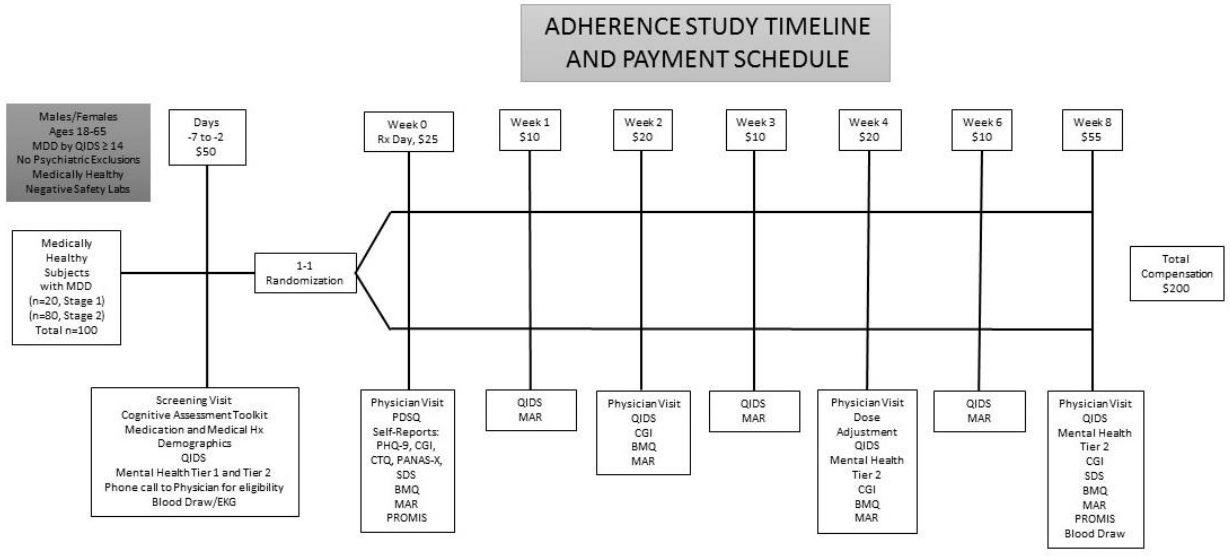
Title:	The Effect of Methylphenidate on Adherence to Antidepressant Treatment in Subjects with Depression
Précis:	This study aims to determine whether a combination a first-line antidepressant plus methylphenidate (MPH) in a capsule relative to a first-line antidepressant plus placebo in a capsule results in higher rates of medication adherence in individuals with moderate to severe depression. In this double-blind randomized placebo controlled trial, 100 individuals with a Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) scale score ≥ 14 will be enrolled to participate in an 8 week treatment study. Participants will be randomized with a 1-1 ratio to receive 5 milligrams (mg) MPH + 10 mg escitalopram or placebo + 10 mg escitalopram to be taken orally once per day. Participants will undergo a 3 hour baseline evaluation visit at week 0, two 30-minute office visits (week 2 and 4), one 60-minute office visit (week 8) and three 5-minute phone calls (weeks 1, 3, and 6) during which clinical assessments and measures will be obtained. The trial is designed with two stages: 20 participants in Stage 1 will be used to estimate the adherence effect size; Stage 2 is designed with an interim analysis to test our hypotheses.
Objectives:	Primary Objective: To determine whether MPH + escitalopram results in higher rates of medication adherence relative to placebo + escitalopram Secondary Objective: To determine whether MPH + escitalopram results in greater consistency of adherence relative to placebo + escitalopram
Endpoint	Primary Endpoint: • % Pill count = 100 * [number of prescribed pills – number of pills remaining]/[number of days between dispensing date and return date] Secondary Endpoint: • Medication Electronic Monitoring System (MEMS) (Aardex) - % of doses taken on schedule within 25% of the expected time interval, defined as ± 6 hours from participant's breakfast time. Exploratory Endpoints: • Beliefs About Medicine Questionnaire (BMQ) – Accepting/ambivalent vs. indifferent/skeptical • Blood level monitoring – blood level outside the 75- 125% range of the therapeutic window • Revised Medication Adherence Reasons (MAR) scale • Response - Reduction in symptoms on the QIDS-SR • *PROMIS* Measures
Population:	Individuals with depression seeking treatment
Phase:	Proof of Concept (Phase 2a)
Number of Sites enrolling participants:	Single site – Laureate Institute for Brain Research (LIBR)

Description of Study Agent : Subjects will receive a compound capsule containing either (1) 5 mg MPH + 10 mg escitalopram or (2) placebo + 10 mg escitalopram. At week 4, the escitalopram dose may be increased to 20 mg, based on clinical evaluation. The capsule will be provided by a local compounding pharmacy (Tulsa, Oklahoma).

Study Duration: 3 years

Participant Duration: 2 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Principal Investigator:

Martin P. Paulus M.D.
Scientific Director and President
Laureate Institute for Brain Research
6655 S Yale Ave Tulsa, OK 74136-3326
Phone: 918 502 5120, FAX: 918 502 5135
Email: mpaulus@laureateinstitute.org
Web: http://www.laureateinstitute.org

Sub-Investigator:

Sahib S. Khalsa M.D., Ph.D.
Director of Clinical Studies
Laureate Institute for Brain Research

Assistant Professor, University of Tulsa, Oxley College of Health Sciences
Tulsa, Oklahoma
6655 S Yale Ave Tulsa, OK 74136-3326
Phone: 918 502 5743 Fax: 918 502 5135
Email: skhalsa@laureateinstitute.org

Site investigators:

Martin P. Paulus M.D.
Scientific Director and President
Laureate Institute for Brain Research
6655 S Yale Ave Tulsa, OK 74136-3326
Phone: 918 502 5120, FAX: 918 502 5135
Email: mpaulus@laureateinstitute.org
Web: http://www.laureateinstitute.org

Sahib S. Khalsa M.D., Ph.D.
Director of Clinical Studies
Laureate Institute for Brain Research
Assistant Professor, University of Tulsa, Oxley College of Health Sciences
Tulsa, Oklahoma
6655 S Yale Ave Tulsa, OK 74136-3326
Phone: 918 502 5743 Fax: 918 502 5135
Email: skhalsa@laureateinstitute.org

Teresa A. Victor. Ph.D.
Staff Scientist, Research Core
Laureate Institute for Brain Research
6655 South Yale Ave.
Tulsa, Oklahoma USA 74136
Phone: 918 502 5108 Fax: 918 502 5135
Email: tvictor@laureateinstitute.org

Biostatistician:

Hung-wen Yeh Ph.D.
Associate Investigator
Laureate Institute for Brain Research
6655 S Yale Ave
Tulsa, OK 74136-3326
Phone: 918 502 5119
Fax: 918 502 5135
Email: hyeh@laureateinstitute.org

Biostatistician:

Wesley Thompson
Statistical Consultant
University of California, San Diego
9500 Gilman Drive #0725
La Jolla, CA 92093
Phone: 858 534 6748
Email: wkthompson@ucsd.edu

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Adherence to treatment, i.e. the extent to which the patient's history of therapeutic engagement coincides with the prescribed treatment [1], is among the most important problems in mental health care [2,3]. It is estimated that nearly half of all prescribed medications are not taken, that about 125,000 deaths annually are attributable to non-adherence, and that non-adherence costs are estimated between $100 and $300 billion each year [4]. Thus, non-adherence is a profound clinical challenge that incurs adverse psychosocial consequences, enormous costs, and poor outcomes that are shared by patients, family members, providers, healthcare systems, payers, and society [5]. It is estimated that only one out of five patients comply with antidepressant treatment for over four months [6], and that the majority of patients discontinue antidepressant medication within the first 30 days [7]. Some have estimated that the median time to discontinuation of an antidepressant is about two [8] to four months [9]. Unfortunately, the majority of clinical trials do not report rates of adherence and for those that do only 4 out of 5 participants adhere to the treatment regimen [10], which significantly affects reported efficacy [11] and safety assessments [12]. There are slight differences between antidepressant medication classes [13] but low adherence is not limited to medication treatment for depression [14], or even mental health [15,16]. For example, there is evidence for 25-90% adherence rates for headache treatments [17]. Moreover, non-adherence extends to other therapeutic modalities, with about 20% to 70% of individuals who initiate psychosocial mental health services discontinuing treatment prior to clinicians' recommendations [18]. Whereas continued antidepressant treatment reduces recurrence risk [19], cardiovascular [20] and overall mortality [21,22] as well as suicide rates [23], non-adherence has profound consequences for the course of depression by increasing relapse [24] or recurrence [25]. Taken together, adherence to treatment has to be one of the most important targets of research seeking to improve therapeutic outcomes.

There are numerous measures for adherence. Most are of moderate quality [26], and there is not one gold-standard approach for measuring and predicting adherence[27]. For example, adherence scores reported by patients do not agree well with those obtained from physicians [28]. Moreover, non-adherence is not limited to initiation of antidepressant treatment but is also common among individuals on maintenance treatment [29]. A number of socio-demographic factors have been proposed to contribute to the rates of adherence, among them are age [30] (younger individuals are more likely to discontinue), gender (males are more likely to discontinue) [31], race (adherence to antidepressants is 40%

lower among African-Americans than Caucasians) [32], lower levels of education [31], employment [33], being from a lower-income neighborhood [30] or part of an immigrant group [34], lower levels of quality of life [8], and other psychosocial stressors [35]. Sexual side effects [36], substance use comorbidity and personality disorders also contribute to non-adherence of individuals with mood disorders [37]. However, recent data suggest that demographic or clinical factors [38] are not consistently associated with non-adherence [39]. Unfortunately, there is little evidence from randomized controlled trials that educational [40,41] counseling [42], coaching[43], or other types of interventions improve adherence in general [44] and may have – at most – small effects [2]. Recently, however, based on a meta-analysis some have reported moderate effect size outcomes using multi-component, i.e. combining cognitive behavioral and educational aspects, interventions [3].

These findings raise several issues about treatment non-adherence. First, there is no optimal way to measure it. Second, socio-demographic characteristics are unlikely to provide single-subject level predictions for those individuals who are likely to be non-adhererent. Third, there is no “one-size-fits-all” approach to characterizing and reducing non-adherence, particularly when it comes to psychoeducational interventions. Therefore, further research into individual differences are likely to contribute substantially to our understanding of the underlying processes that influence adherence to treatment.

Metacognition is an individual difference process which includes beliefs and attitudes about self-related events such as thoughts, feelings, memories, images, sensations, and perceptions [45]. The 'necessity-concerns framework'[46] is a metacognitive approach and provides a heuristic to understand patients' adherence behavior. This framework proposes that the decision to take a medication is mediated by two opposing beliefs, i.e. beliefs about the necessity of taking the medication for a particular condition versus concerns about negative effects associated with taking medications. Psychometric scales to measure these metacognitive aspects of adherence have identified several components. The revised Medication Adherence Reasons Scale (MARS) [47] (with Cronbach alphas ranging from 0.827 – 0.953) can identify between 50% to 70% of individuals taking medications. It comprises four medication related domains: practical issues, belief of necessity, forgetfulness, concerns over side effects. The Beliefs about Medicines Questionnaire (BMQ) [46] contains two sections: the BMQ-Specific, which assesses representations of medication prescribed for personal use such as beliefs about the necessity of the medication and beliefs about danger associated with a specific medication, and the BMQ-General, which assesses generic beliefs about medicines such as beliefs of harm and overuse. Low scores in the BMQ-Harm and -Concern subscales are associated with greater non-adherence to antidepressants[48]. In a meta-analysis across different medical conditions and treatments, this framework significantly and differentially predicted rates of adherence [49]. For example, for each standard deviation increase in necessity beliefs, the odds of adherence increases by a factor of 1.7 and for each standard deviation increase in concerns, the odds of adherence decreases by a factor of 2 [50]. Moreover, depression [51] has been shown to moderate this relationship [52] and influences particularly the concerns aspect of the framework [53]. The antidepressant-specific "necessity-minus-concerns" composite has been proposed as a predictor for adherence [54] and there is evidence that attitudes and beliefs are at least as important as side effects in predicting adherence [55]. For example, those individuals who have higher levels of

concerns about antidepressant medications are less likely to be adherent [56] whereas those who report high initial expectations show greater adherence, even to placebo interventions [57]. Non-initiators also have lower belief scores for perceived impact of illness, intention to take medication, and positive attitude towards medication[58]. Others have found that while intentional non-adherers had higher concerns scores unintentional non-adherers did not, which emphasizes the heterogeneity of non-adherence[59]. Moreover, those individuals who reported high necessity and high concern beliefs, i.e. were ambivalent, also showed lower levels of adherence [60]. Not surprisingly, greater non-adherence is related to higher depression scores at follow up [61]. These beliefs adjust dynamically during the course of treatment such that individuals who adhere to treatment have greater perceived benefit and reduced concerns [62]. Taken together, metacognition [45] is an individual difference metric that appears to play a central role in treatment adherence by providing self-relevant and value-based attributes to the actions that can guide policies for the individual, i.e. whether to take or not take a medication.

2.2 RATIONALE

Building new habits is an important aspect of adherence to any treatment (medication or psychotherapy). Successfully accomplishing this motivational feat basically means that new treatment related behaviors need to be changed from a reward-related to a habit-based strategy. New habits can be typically reinforced either by an immediate positive outcome (positive reinforcement), or by the avoidance of a negative outcome (negative reinforcement). Both processes are likely to involve top-down prefrontal cortex control over hippocampal activity, and require the concerted establishment of a set of behavioral contingencies, heuristics, and internal representations of how the behavior positively affects the individual. With respect to depression, there are several barriers to the formation of new treatment related habits (i.e., adherence behaviors). First, depressed individuals have reduced hedonic processing mediated by the dopaminergic system, meaning they are less driven by what feels “good” or what is “good for the individual”. Therefore, it is often difficult to utilize tools that may typically act as positive reinforcers in other individuals (e.g. financial payment). Second, habits evolve from the strong association of a cue (situation or stimulus) with an action. The strengthening of a habit relies primarily on the degree to which a behavior is expressed “automatically” (without necessary thinking about it), occurs frequently, and is clearly self-identified. Successfully cemented habits are highly efficient behaviors, and usually associated with a lack of awareness, unintentionality, and uncontrollability during their performance. Habit-formation is therefore a complex process and is likely to take weeks. Prior research suggests that successful habit-formation likely involves a transition from reinforcement driven hippocampal circuit activity to stimulus-response driven basal ganglia driven circuit activity, indicating that it requires a broad shift in patterns of neural activity [63,64]. Unfortunately, the functioning of these circuits is preferentially impaired in depressed individuals [65,66]. It is presently unclear whether interventions capable of modulating activity in these same neural circuits can improve treatment related habit formation. Third, educational interventions to enhance adherence have failed to demonstrate a clear benefit on adherence and depression outcome [40]. Fourth, community pharmacy-based coaching program showed no intervention effect on adherence [43]. Based on these considerations, the current study aims to investigate the influence of pairing a pharmacological agent with an acute positive

reinforcing dopaminergic/noradrenergic effect with a standard antidepressant on the rates of medication treatment adherence.

MPH has been widely used to treat attention-deficit/hyperactivity disorder (ADHD) for the last half century [67]. The drug is a monoaminergic reuptake inhibitor, i.e. it blocks the blocking dopamine transporters [68] and increases dopamine and norepinephrine availability in the synaptic cleft [69]. Methylphenidate has strong affinity at the norepinephrine transporter [70], which exceeds its affinity for the dopamine transporter. However, its ability to increase NE is much less than that of amphetamine and it has virtually no effect on serotonin [71]. Moreover, it does not produce a subjective euphoria, which has been related to its relatively weak ability to reduce D2 receptors in the striatum [72,73]. However, it may have different properties after repeated administration [74]. Methylphenidate has weaker reinforcing properties [75] and has different pharmacokinetic profile [76] than amphetamines or cocaine, which lowers its relative abuse liability. In healthy volunteers, methylphenidate induced improvements in working memory performance [77], which were associated with reductions in rCBF in the dorsolateral prefrontal cortex and posterior parietal cortex, reduced the impact of emotionally arousing material on memory [78], however, it did not affect fear conditioning. Interestingly, methylphenidate has long been considered as a potential treatment for anxiety based on human and animal studies. Moreover, there is a long history of using methylphenidate for treating mood, behavior, and cognitive symptoms in individuals with organic brain changes [79] and traumatic brain injury [80]. In particular, several studies have shown improvement of cognitive symptoms after treatment with methylphenidate in patients with acute brain injury [81] including speed of mental processing [82,83], response accuracy [84], improved shifts of attention [85], caregiver ratings of attention [86], level of depressive symptoms [87], however, its effects on sustained attention, distractibility, and memory are less clear [88,89].

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

A. Risks associated with the study medications:

1. METHYPHENIDATE

Common side effects:

Nervousness, difficulty falling asleep or staying asleep, dizziness, nausea, vomiting, loss of appetite, stomach pain, diarrhea, heartburn, dry mouth, headache, muscle tightness, drowsiness, uncontrollable movement of a part of the body, restlessness, numbness, burning, or tingling in the hands or feet, decreased sexual desire

Rare side effects:

- Fast, pounding, or irregular heartbeat, chest pain, shortness of breath, excessive tiredness, slow or difficult speech, fainting, weakness or numbness of an arm or leg, seizures, changes in vision or blurred vision, agitation, believing things that are not true, feeling unusually suspicious of others, hallucinating (seeing things or hearing voices that do not exist), motor

tics or verbal tics, depression, abnormally excited mood, mood changes, frequent, painful erections, erection that lasts longer than 4 hours, numbness, pain, or sensitivity to temperature in the fingers or toes, skin color change from pale to blue to red in the fingers or toes, unexplained wounds on the fingers or toes, fever, hives, rash, blistering or peeling skin, itching, swelling of the eyes, face, lips, mouth, tongue, or throat, hoarseness, difficulty breathing or swallowing

Methylphenidate may cause sudden death in children and teenagers, especially children or teenagers with heart defects or serious heart problems. This medication also may cause sudden death, heart attack or stroke in adults, especially adults with heart defects or serious heart problems. Development of substance use/dependence is a possible, but uncommon side effect.[90]

2. ESCITALOPRAM

Common side effects:

Drowsiness, tired feeling, sleep problems (insomnia), mild nausea, diarrhea, constipation, upset stomach, dry mouth, cold/flu symptoms such as stuffy nose, sneezing, sore throat, cough, increased sweating or urination, dizziness, heart burn, increased appetite, weight changes, changes in sex drive or ability

Rare side effects:

Very stiff (rigid) muscles, high fever, sweating, confusion, fast or uneven heartbeats, tremors, agitation, hallucinations, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, feeling like you might pass out, headache with chest pain and severe dizziness, fainting, fast or pounding heartbeats; or headache, slurred speech, severe weakness, muscle cramps, feeling unsteady, seizure (convulsions), shallow breathing, serotonin syndrome, extrapyramidal symptoms, QT prolongation, hyponatremia, withdrawal symptoms on abrupt discontinuation, abrnomal bleeding, suicidality, paresthesia, anaphylaxis

B. Risks Associated with Screening and Evaluation:

The risks and discomforts of the screening evaluations are minimal. Some of the questions in the interviews may be painful or uncomfortable to answer.

C. Risks Associated with Blood Draw:

The risks of blood drawing are minimal. Possible mild side effects include mild pain or bruising at the site of venipuncture. There is a very small risk of fainting or infection in the area of the needle insertion.

D. Risks Associated with Delaying Treatment:

Participants will NOT be asked to discontinue any medications for the purposes of this study and will be informed that they should not participate in the study if it will be difficult for them to delay treatment.

E. Risks Associated with Discontinuation

Symptoms associated with discontinuation of Lexapro have been reported, including flu-like symptoms, insomnia, nausea, imbalance, paresthesias, and hyperarousal. Participants should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. At the time of consent and study visits 5 & 6, participants will be requested to follow-up with their primary care physician following completion of the study to continue receiving a prescription for escitalopram, if desired. Participants will be reminded to contact their primary care physician and possible side effects from abrupt cessation will be discussed.

2.3.2 KNOWN POTENTIAL BENEFITS

There may be no immediate personal or medical benefit derived from participation, as we do not expect every participant's symptoms to improve. The results of these studies, however, will further the scientific community's understanding of mood disorder pathophysiology and treatment adherence in depression. By increasing understanding of pathophysiology and adherence rates, this study the potential to improve treatment modalities, diagnostic capabilities, and methods of adherence compliance. The study may aid in de-stigmatizing psychiatric illness and convincing noncompliant patients that medications are likely to be helpful. As such, participants may derive personal satisfaction from their contribution to the discovery process.

3 OBJECTIVES AND PURPOSE

Primary Objective: To determine whether MPH + escitalopram results in higher rates of adherence relative to placebo + antidepressant.

Secondary Objective: To determine whether MPH + escitalopram results in greater consistency of adherence relative to placebo + escitalopram.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This Phase 2a randomized placebo-controlled clinical trial will include two principal study arms, with an option to escalate the dose of escitalopram at week 4 (see 6.1.7):

1) Study Drug A: 5mg placebo + 10mg escitalopram (encapsulated into one capsule)
2) Study Drug B: 5mg methylphenidate (MPH) + 10mg escitalopram (encapsulated into one capsule)

In the proposed protocol, 100 MDD subjects will be randomized to one of the two conditions: escitalopram with placebo (n=10) or escitalopram with methylphenidate (n=10) in Stage 1 and escitalopram with placebo (n=40) or escitalopram with methylphenidate (n=40) in Stage 2. Participants randomized to either condition will be prescribed medication over the course of 8 weeks, with in-person follow-up visits at weeks 0, 2, 4 and 8, with follow-up phone calls on weeks 1, 3 and 6.

Participants randomized to each condition will continue receive will receive usual care as defined by the individual clinician, with the restriction that participants in this group will not be allowed to receive certain new treatments during the study period.

4.2.1 PRIMARY ENDPOINT

Adherence [91]:

- % Pill count = 100 * [number of prescribed pills – number of pills remaining]/[number of days between dispensing date and return date]

4.2.2 SECONDARY ENDPOINTS

Secondary Outcome (STAR-D [92])

- Medication Electronic Monitoring System (MEMS) (Aardex) - % of doses taken on schedule within 25% of the expected time interval, defined as ± 6 hours from participant's breakfast time.

4.2.3 EXPLORATORY ENDPOINTS

- BMQ[46] – Accepting/ambivalent vs. indifferent/skeptical
- Blood level monitoring – blood level outside the 75 – 125% range of the therapeutic window
- MAR[93] scale
- Remission - a score of 5 on the QIDS-SR
- Response - 50% reduction in symptoms on the QIDS-SR

PROMIS Measures [94,95]:

- PROMIS Anxiety
- PROMIS Depression
- PROMIS Anger
- PROMIS/Neuro-QOL Positive Affect and Well-being
- PROMIS Cog Abilities
- PROMIS Cog General
- PROMIS Fatigue
- PROMIS Sleep Disturbance
- PROMIS Sleep-related Impairment
- PROMIS Social Satisfaction DSA
- PROMIS Social Satisfaction Role

- PROMIS Ability to Participate Social
- PROMIS Emotional Support
- PROMIS Information Support
- PROMIS Satisfaction Roles Activities
- PROMIS Social Isolation
- PROMIS Physical Function
- PROMIS Pain Interference
- PROMIS PAIN Behavior

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Participants must meet all of the following inclusion criteria to be considered eligible to participate in the study (closely matched on STAR-D):

- Baseline QIDS-SR > 14 (moderate depression [96])
- Age 18 – 65
- Written Informed Consent
- MDD single-episode/recurrent, not in remission

5.2 PARTICIPANT EXCLUSION CRITERIA

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- MPH-related exclusions [97]
    - Uncontrolled hyperthyroidism
    - Glaucoma
    - Motor tics
    - MAOI treatment
    - Serious coronary artery disease, cardiomyopathy, serious cardiac arrhythmias
    - Uncontrolled HTN
    - Peripheral vasculopathy
    - Pregnancy
- Bipolar Disorder
- Psychotic Disorder
- History of intolerability of study medications
- Currently taking psychiatric medications
- Current Substance Use Disorder (other than nicotine)
- Current Alcohol Use Disorder

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Study participants will be recruited through the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), local service providers for behavioral health and mental health (e.g. Family and Children's Services, local psychiatrist and physician offices), and through online, newspaper, flyer, radio or other media advertisements in the Tulsa metropolitan area. Participants will also be recruited through a pre-approved LIBR Screening protocol (WIRB #20101611) and through the Laureate Institute for Brain Research REDCap database. Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms. These exam rooms at LIBR are secured from public areas via combination locked doors that are only accessible to authorized personnel.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Efforts will be made to continue follow-up of withdrawn or terminated participants or participants who prematurely discontinue assigned study intervention but remain in the study for follow-up. Follow-up efforts will include contacting participants to complete the 8-week in-person follow-up assessment.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, and study sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination of futility

If suspended, the study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the sponsor, and/or IRB.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The study medications will be acquired through a local compounding pharmacy in Tulsa, Oklahoma.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study medications will be formulated into identical compound capsules containing either (1) 5 mg MPH + 10 mg escitalopram, (2) placebo + 10 mg escitalopram, (3) 5 mg MPH + 20 mg of escitalopram, (4) placebo + 20 mg escitalopram. The study medications will be packaged in standard bottles with a MEMS tracking cap. The bottles will be labeled with “Study Drug A”, “Study Drug B”, “Study Drug C” or Study Drug D”, the number of capsules in the bottle and the administration date. At the 4-week visit, participants will have the option to increase the escitalopram dose to 20 mg based on clinical improvement assessed by the study psychiatrist.

6.1.3 PRODUCT STORAGE AND STABILITY

The study medications will be stored behind at least two differently keyed locks at all times. The medication will be stored in a safe or steel cabinet of substantial construction. If the safe or cabinet is less than 750 pounds, it will be mounted or secured to a wall, floor or base embedded in concrete. The safe/cabinet will have an inner and outer door with the locks for each door keyed differently. The room where the safe/cabinet will be stored will also be lockable and locked after hours.

6.1.4 PREPARATION

A compounding pharmacy will dispense and label the individual bottles of study medication. A study psychiatrist will provide the medication to the subject at each in-house study visit.

6.1.5 DOSING AND ADMINISTRATION

The dosing and administration method are detailed below (see 6.1.7).

6.1.6 ROUTE OF ADMINISTRATION

Participants will receive the study medication in a compound capsule for oral administration.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

The compound capsules will contain either (1) 5 mg MPH + 10 mg escitalopram, (2) placebo + 10 mg escitalopram, (3) 5 mg MPH + 20 mg of escitalopram or (4) placebo + 20 mg escitalopram. At the 4-week visit, participants will have the option to increase the escitalopram dosage to 20 mg based on clinical improvement assessed by the study psychiatrist.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Dose adjustments, modifications and delays will be determined by the study psychiatrist at the 4 week time point.

6.1.9 DURATION OF THERAPY

The expected duration of the study will be 8 weeks of treatment, plus a screening visit for eligibility that may occur up to one week prior to study start.

6.1.10 TRACKING OF DOSE

The dose will be tracked by the study coordinator and Principal Investigator and included in the study's REDCAP database.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

NONE

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

A separate and current record will be maintained for the storage and use of each controlled substance (use meaning to administer, dispense, professionally use, or otherwise dispose of), indicating the date, building and room, specific research experiment, controlled substance's application in the research, and type, strength and quantity of each controlled substance use. The record must also include the name and address of the person to whom, or for whose use, the substances were administered or dispensed. By noting starting quantity of substance, each use is a subtraction from the starting quantity, and the running (decreasing) amount should equal the total amount remaining on-hand.

Each record of use must be signed by the person working with the controlled substance. The inventory should also include a detailed list of any controlled substances lost, destroyed, or stolen, including the type, strength, and quantity of such substances, and the date of the discovery of such loss, destruction, or theft. The record of use will be stored on a LIBR computer with daily back-up and password protected access by designated research personnel.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

• Medical and psychiatric history – obtained by self-report questionnaire and from review of medical records

• Medication history – only medications currently taken should be included; this includes prescription and over-the-counter medications. Assessment of eligibility will include a review of permitted and prohibited medications.

• Vital sign assessment – temperature, heart and respiratory rate, systolic and diastolic blood pressure, echocardiogram (EKG), height and weight.

• Oral administration of the study medication: either (1) 5 mg MPH + 10 mg escitalopram or (2) placebo + 10 mg escitalopram. At week 4, the escitalopram dose may be increased to 20 mg, based on clinical evaluation.

• Assessment of study medication adherence – conducted during scheduled visits and phone calls and by MEMS tracking cap

• Administration of questionnaires or other instruments for patient-reported outcomes

7.1.2 STANDARD OF CARE STUDY PROCEDURES

All participants in each study arm will continue to receive usual care from their primary care provider

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

• Safety labs: CBC, CMP and TSH levels will be determined by blood collection prior to dispensing the study medication at Week 0 and collected again at Week 8.

• Blood levels of study medications: At the Week 8 visit, levels of escitalopram will be determined by blood collection.

• Pregnancy test: Conducted during screening evaluation. If positive, participants will be excluded from further study participation.

7.2.2 OTHER ASSAYS OR PROCEDURES

NONE

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

The blood collection will be obtained in appropriate Vacutainer tubes by a trained phlebotomist using sterile techniques and transported to Saint Francis Hospital Outreach Laboratory for processing. The pregnancy test will be obtained by a trained LIBR staff member.

7.2.4 SPECIMEN SHIPMENT

Blood samples will be transported to Saint Francis Hospital Outreach Laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING/ENROLLMENT/BASELINE

Screening/Enrollment Visit (Week 0, 3 hours):

• Obtain informed consent of potential participant verified by signature on written informed consent form for screening and study consent form.
• Record vital signs including temperature, heart rate, systolic and diastolic blood pressure.
• Record height and weight.
• Collect urine for evaluation of pregnancy status (if applicable).
• Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
• Review medical history and medications history to determine eligibility based on inclusion/exclusion criteria.
• Collect self-report scales
• Collect blood safety labs (CBC, CMP, TSH)
• Schedule study visits for participants who are eligible and available for the duration of the study.
• Provide participants with instructions for taking the study medication

7.3.2 FOLLOW-UP

Weeks 1, 3 and 6 (phone call)

- Administer the QIDS-SR and MAR questionnaires

Weeks 2 and 4 (in person visits)

- Verify inclusion/exclusion criteria.
- Record vital signs including temperature, heart rate, systolic and diastolic blood pressure.
- Record current medications and interim medical procedures
- Collect self-report scales including QIDS-SR and medication adherence measures
- Dispense the study medication

7.3.3 FINAL STUDY VISIT

Final Visit (Week 8, 1 hour):

- Verify inclusion/exclusion criteria.
- Record vital signs including temperature, heart rate, systolic and diastolic blood pressure.
- Record current medications and interim medical procedures
- Collect self-report scales and medication adherence measures
- Collect blood levels of the antidepressant medication and repeat of safety labs obtained at Week 0.

7.3.4 EARLY TERMINATION VISIT

If early termination occurs and the participant is willing, schedule a final visit to collect follow-up visit measures.

7.3.5 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8						
Informed consent	X													
Assessment: Medical History and Diagnosis, Physician Visit	X													
Cognitive Assessment Toolkit	X													
Inclusion: QIDS-SR	X		X	X	X	X	X	X						
Psychiatric Diagnostic Screening Questionnaire (PDSQ)		X												
Self-Report Measures: Demographics and Mental Health Tier 1 and 2	X													
Tobacco, Alcohol and Substance Use	X					X		X						
Self- Report Measures: PHQ-9, CTQ, PANAS-X, SDS		X												
CGI		X		X		X		X						
BMQ		X				X		X						
Pill Count				X		X		X						
Blood Level of Study Medication								X						
MEMS Monitoring				X		X		X						
MAR Scale		X	X	X	X	X	X	X						
PROMIS Measures		X		X		X		X						
Safety Labs	X							X						
EKG	X													
Escitalopram levels								X						

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Data pertaining to concomitant medications, treatments, and/or procedures utilized by participants will be collected during each in-person visit.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

The addition of psychoactive medications that affect brain function or evidence-based behavioral interventions will be prohibited during the duration of the study. Participants will be instructed to tell the study psychiatrist of any change in medication or treatment.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

See 7.5.1. above.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will no longer have access to the study medications at the study closure. Participants desiring to continue accessing this type of intervention will be instructed to contact their primary care physician and/or given information on treatment centers and physicians in their local area.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

This study involves the use to two FDA-approved medications (MPH and escitalopram).

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or

substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

• Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

• Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

• Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

An example of an adverse event (AE) that might conceivably occur as a result of the oral administration of the study medications due to side effects that would require treatment in an emergency room.

All AEs will be assessed by the clinician using the following guidelines to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible. The event must be phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related " as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS

The study Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the

appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Event Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the IRB and study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.

Other SAEs regardless of relationship, will be submitted to the IRB and study sponsor within 72 hours of site awareness. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for Unanticipated Problems (UPs) require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

A detailed description of the event, incident, experience, or outcome;

An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP

A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs that are SAEs will be reported to the IRB and to the study sponsor within 10 working days of the investigator becoming aware of the event.

Any other UP will be reported to the IRB and to the study sponsor within 10 working days of the investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and study sponsor within 10 working days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable

8.4.5 REPORTING OF PREGNANCY

Any participants found to be pregnant on screening will be informed and excluded from further study participation.

8.5 STUDY HALTING RULES

Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the IRB.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the Western IRB, via monitoring of study information provided by the PI.

9 CLINICAL MONITORING

Monitoring for this study will be performed by the study PI. The study PI will engage in weekly discussions of the study progress with the clinical research coordinator, perform random reviews of study endpoint, safety, and other key data to verify completeness of data acquisition.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This Phase 2a trial contains 2 stages. Stage 1 aims to estimate dropout rate and the effect size of outcome measures, while Stage 2 aims to evaluate for statistical significance the primary, secondary, and exploratory endpoints. Stage 2 is designed with an interim analysis. Hence, there will be two Go/No-Go decisions: one at the end of Stage 1, and the other in the middle (the interim analysis) of Stage 2. Depending on the results of Stage 1, the trial may or may not proceed to Stage 2. If dropout rate and/or the effect size suggest 80 participants for Stage 2 (100 total study participants) is under-powered, the study will be discontinued. Even if the study proceeds to Stage 2, the trial may still be terminated if the interim analysis suggests the trial to be futile. To avoid biased decision-making, data will be analyzed by two statisticians: (1) the consultant statistician Dr. Thompson will analyze Stage 1 data to obtain effect size and attrition rate, (2) before initiation of Stage 2, the primary statistician Dr. Yeh will re-evaluate the power/sample size of Stage 2 based on the effect size and attrition rate provided by Dr. Thompson from Stage 1, (3) if Stage 2 procedes, Thompson will conduct the interim analysis, and (4) if the interim analysis is inconclusive and Stage 2 proceeds to the end, Dr. Yeh will perform the final analysis. For statistical details, see Section 10.4.

10.2 STATISTICAL HYPOTHESES

[For Stage 2 only]

1. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show a lower % Pill count at the end of the study.

2. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show a higher % of doses taken on schedule within 25% of the expected time interval.

3. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show higher accepting/ambivalent vs. indifferent/skeptical on the Beliefs About Medicine Questionnaire at the end of the study.

4. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show lower blood level for escitalopram at study endpoint.

5. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show higher Revised Medication Adherence Reasons (MAR) scale at study endpoint.

6. Individuals treated with antidepressant + MPH relative to antidepressant + placebo will show greater reduction in symptoms on the QIDS-SR at study endpoint.

7. Individuals treatment with antidepressant + MPH relative to antidepressant + placebo will show greater outcome improvement as measured by the PROMIS scales.

10.3 ANALYSIS DATASETS

We will use the full analysis set which includes data of all participants who meet inclusion/exclusion criteria, provide consent form, and are randomized to either treatment arm. The only exception is that participants will be excluded from the analysis set only if they have no single follow-up visit.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

At the end of Stage 1, effect size of the primary outcome measure for group difference at Week 8 will be expressed as Hedges' G, and non-parametric bootstrap will be applied to obtain its 95% confidence interval (CI); attrition rate and its exact 95% CI will also be estimated. These two measures will be used to re-evaluate the power of Stage 2 before initiation of Stage 2. If no combinations of Hedges' G and attrition rate within their 95% CI ranges provide 80% power in Stage 2 based on the proposed 80 participants, the trial will be terminated, otherwise we will proceed to Stage 2. If the study proceeds to Stage 2, an interim analysis will be performed once we reach half completers of Stage 2 (n=40). All outcome measures will be analyzed in their continuous scales without dichotomization.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For this study, the primary "efficacy" endpoint is an adherence measure—specifically, the pill count percentage at Week 8. If the trial proceeds to Stage 2, group differences will be evaluated by 2-sample t-test first at the interim analysis (10 placebo + escitalopram, 10 methylphenidate + escitalopram) and at the final analysis if the trial proceeds to the end (also see Section 10.4.7). Regardless of whether and/or when the trial is terminated, we will compute 95% confidence intervals for group differences using all available data including those from Stage 1 to maximize precision.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be analyzed in the same way as the primary endpoint in 10.4.2.

10.4.4 SAFETY ANALYSES

Adverse events leading to premature discontinuation from the study and/or serious treatment-emergent AEs will be presented in either a table or a listing.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Because the primary outcome is adherence, only retention will be discussed here. The 8-week retention rate will be computed for each group and for both groups combined, and the corresponding 95% confidence interval will be estimated by the exact binomial method. The 8-week retention rate will be compared between two groups by the "mid-P" value method instead of the conservative Fisher exact test[98].

10.4.6 BASELINE DESCRIPTIVE STATISTICS

For each group, demographic variables and baseline characteristics will be summarized in a table by mean and standard deviation for continuous variables or by frequency and percentage for categorical variables. Following the CONSORT guideline, Item 15, baseline characteristics will be described but not tested between groups [99].

10.4.7 PLANNED INTERIM ANALYSES

Stage 2 is designed with an interim analysis, which will be performed when we achieve half completers. Assuming the primary endpoint follows a Gaussian distribution, we controlled overall Type I error rate at 0.05 two-sided level using the Hwang-Shih-DeCani spending function [100] with γ parameter -4 for the upper bound and -2 for the binding lower bound. This analysis was conducted using R gsDesign package, version 3.0-1, function gsDesign(k=2, test.type=3, alpha=0.025, beta=0.2) where alpha is 1-sided. The resulting lower and upper bounds for the interim z-statistic are 0.4 and 2.75, respectively. Because we will use t-tests instead of z-tests for unknown variance, the lower and upper bounds of the z-statistic will be converted to corresponding quantiles in t-distribution using the quantile substitution method [101] and the actual number of available observations (e.g. the bounds will be 0.404 and 2.960 if we have 32 participants or 30 degrees of freedom); if the t-statistic falls below the lower bound, we will terminate the trial for futility; if it falls above the upper bound, the trial will be claimed as successful; if the interim t-statistic falls between bounds, then Stage 2 will be continued to the end.

10.4.7.1 SAFETY REVIEW

Safety endpoints such as the occurrence and frequency of AEs or SAEs will be monitored. For action plans related to the safety review, see Section 5.5, Premature Termination or Suspension of Study and Section 8.5 Study Halting Rules.

10.4.7.2 EFFICACY REVIEW

The primary endpoint will be evaluated with an interim analysis.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Not proposed.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Considering this proof-of-concept trial, no adjustment will be implemented for multiple secondary and exploratory endpoints.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

In addition to tables and graphs representing group data, individual response data and other relevant study information will be presented in tables. The data listings accompanying the report will include, for each patient, a patient identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the time during the study (e.g., days on therapy and time of day, if relevant) when the measurements were made, the drug/dose at the time, measures of

adherence, and any concomitant medications at the time of, or close to the time of, measurement or assessment.

10.4.11 EXPLORATORY ANALYSES

As an exploratory analysis, linear mixed-effect models (LMM) will be used to compare group differences across time points, using group and time and their interaction as fixed-effects and a patient-specific intercept. We will conduct post hoc comparisons to assess how early the treatment effect may start to appear.

10.5 SAMPLE SIZE

We propose 20 participants for Stage 1 and 80 participants for Stage 2, both in 1:1 ratio for the two groups.

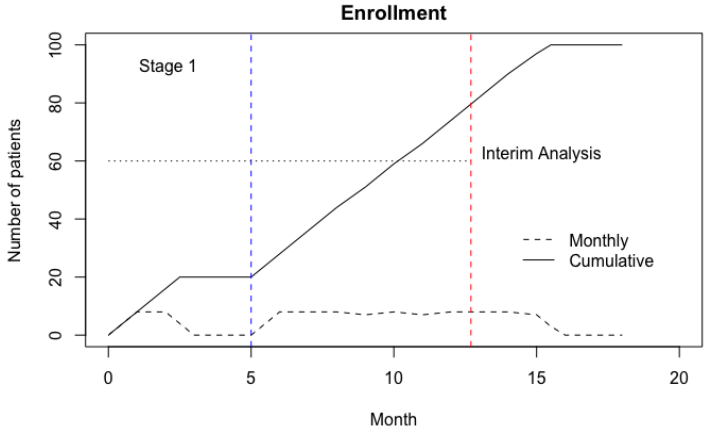
In Stage 1, the proposed sample size of 10 patients per group will provide an estimate of mean with margin of error equivalent to $t_{10-1,0.975}\sqrt{1/10} = 0.72$ times of standard deviation for each group at 95% confidence, or $t_{10+10-2,0.975}\sqrt{1/10 + 1/10} = 0.94$ times of common standard deviation for between-group difference. Assuming 20% dropout rate for both groups at Week 8, the margin of error for the between-group difference becomes $t_{8+8-2,0.975}\sqrt{1/8 + 1/8} = 1.07$ times of common standard deviation.

Stage 2 is designed with an interim analysis. Assuming the primary endpoint follows a Gaussian distribution, we control overall Type I error rate at 0.05 two-sided level using the Hwang-Shih-DeCani spending function *_ENREF_96* with γ parameter -4 for the upper bound and -2 for the binding lower bound. We propose a sample size of 40 patients per group and anticipate 20% dropout rate at Week 8, giving 32 patients per group or 64 in total. We set n.fix in gsDesign() to 62 instead of 64 to obtain a final sample size of 64. Because gsDesign() uses 1-sample z-statistic for continuous endpoint, the resulting effect size $\theta = 0.3558$ needs be converted to 2-sample Hedges' G by a factor of 2, i.e., $g \approx 0.71$. For the maximum sample size of 64, this design leads to an expected sample size of 54.7 under this alternative hypothesis, or 42.8 under null hypothesis. Also, the variance of the primary endpoint is unknown and will be estimated from the sample, so z-tests will be replaced with t-tests in analyses and the bounds will need to be revised accordingly. Based on the quantile substitution method [101], the interim boundaries 0.40 and 2.75 for z-distribution are converted to 0.404 and 2.960 for t-distribution with 32-2=30 degrees-of-freedom (df), and the critical z-value 1.96 for the final analysis be converted to 1.999 for t-distribution with 64-2=62 df. We evaluated these boundaries by 10,000-run simulation and confirmed that (1) under null hypothesis, there will be a 65.5% chance to stop the trial for futility and 0.3% chance to claim it successful at interim analysis, and 0.024 one-sided Type I error rate at final analysis; (2) under alternative hypothesis with an effect size of Hedges' G 0.714, there will be only 5.4% chance to stop the trial for futility and 19.8% chance for success at the interim analysis, and 80.1% power at the final analysis.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Enrollment: To achieve the proposed sample size of 100 patients and to complete the study within the 18-month study window, we will aim for an enrollment rate of 7 to 8 patients/month. The figure below shows the monthly and cumulative enrollment. The first 20 patients for Stage 1 will be enrolled within the first 2.5 months, followed by 8 weeks or 2 months of intervention for the 20th participant, and then another 2 weeks or 0.5 months for data preparation, cleaning, and analysis (including power re-evaluation for Stage 2). Thus, Stage 1 is planned to be finished within 5 months (the blue dashed line). If a satisfactory effect size and retention rate are suggested by Stage 1 data, another 80 patients will be recruited over the next 10.5 months. Half of target participants for Stage 2 (40) will be enrolled at Month 10.2. Followed by 2 months of intervention, an interim analysis will be performed between Months 12.2 and 12.7 (the red dashed line). If the interim analysis reveals the trial to be futile, the trial will be abandoned; at this point, we will have enrolled around 80 participants. If the interim analysis suggests otherwise, enrollment will continue and end at Month 15.5. Followed by another 2 months for intervention and 0.5 months for analysis, the whole trial will be completed within 18 months.



Randomization/Masking: Participants who meet inclusion and exclusion criteria and sign the consent form will be randomized to receive either 5 mg MPH + 10 mg escitalopram or placebo + 10 mg escitalopram. To ensure balance in-group size, we will use block randomization with block size two. The randomization sheet will be provided by the primary statistician (Yeh) directly to the pharmacist. Investigators and participants will be kept blinded during the study window until data collection and analysis are completed.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

All study physicians, nurses and research assistants who work directly with participants will be blinded to treatment allocation. The study statistician and one additional staff member who will be assigned to work with the compounding pharmacy will be unblinded. Participants will be asked to guess their treatment assignment and indicate their degree of certainty and reasoning at each in-person visit (Weeks 0, 2, 4 and 8).

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

During interviews or any time during the study, subjects may report psychological distress, suicidal ideation, or intent to harm self or others. If this occurs, Dr. Paulus, or his licensed designee, will be contacted immediately to ensure appropriate care and compliance with mandated reporting to authorities. Subjects may be referred for professional intervention and the blind may be broken to provide necessary information about study participation, as deemed appropriate, including calling emergency personnel (911) if needed. A current list of local mental health programs will be available for all participants. Information reported will be kept in confidence with the exception that disclosure of suicidality, homicidality, or child or elder abuse that warrants reporting to appropriate authorities.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

LIBR will maintain appropriate medical and research records for this trial, in compliance with LIBR's institutional requirements for the protection of confidentiality of participants.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The study PI will be responsible for addressing Quality Assurance issues (e.g., correcting procedures that are not in compliance with the protocol). The research coordinator will be responsible for Quality Control issues (e.g. correcting errors in data entry).

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Western IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A separate screening consent may be used in order to register and track potential participants within LIBR's screening protocol. If a separate screening procedure is not used, the study consent must be signed prior to conducting study screening procedures.

Written informed consent is required for all participants. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements posed by LIBR and the Western IRB. Prior to the beginning of the trial, the PI should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Participant confidentiality will be assured via multiple measures: data will be coded so that identifying features are unlinked. The key for this code will be kept in a password-protected database. Any data

shared in publications and/or with other researchers will maintain the anonymity of participants, and will only link them according to their code.

No human samples or specimens will be stored as a result of this study. Data related to this study will be retained, and stored in a password-protected database.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Electronic data capture will represent the primary source data. Any paper source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Copies of the electronic case report forms (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including self-report scales, AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the RedCap electronic data capture system provided by LIBR. Data will be collected using a HIPAA compliant interface. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

All research documents containing Personally Identifiable Information (PII) and collected research data will be stored electronically on the LIBR Network and/or REDCap. Access to the LIBR network and to REDCap is granted only to authorized personnel. The LIBR Network is protected by the Palo Alto PA-5250 Layer 7 firewall with licenses for Wildfire, AV, Threat Prevention, and URL filtering. All LIBR network data is stored on site. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations. The REDCap Consortium, a vast support network of

collaborators, is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap in various ways.

14.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice, or Manual of Procedure requirements. The noncompliance may be on the part of either the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

In accordance with these policies, the study PI will register the study with clinicaltrials.gov prior to data collection, so the research results may be considered for publication in ICMJE member journals.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

This study will be led by the LIBR PIs.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the biomedical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures (which mirror the policies for managing such conflicts proposed by the NIH) for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 LITERATURE REFERENCES

Please see below.

APPENDIX

Version	Date	Significant Revisions

1. Organization WH. *Adherence to long-term therapies: evidence for action.* Geneva, Switzerland: World Health Organization;2003.

2. Pai AL, McGrady M. Systematic review and meta-analysis of psychological interventions to promote treatment adherence in children, adolescents, and young adults with chronic illness. *Journal of pediatric psychology.* Sep 2014;39(8):918-931.

3. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. *Journal of pediatric psychology.* Jul 2008;33(6):590-611.

4. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. *Am Heart J.* Sep 2011;162(3):412-424.

5. Bosworth HB, Fortmann SP, Kuntz J, et al. Recommendations for Providers on Person-Centered Approaches to Assess and Improve Medication Adherence. *J Gen Intern Med.* Jan 2017;32(1):93-100.

6. Serna MC, Cruz I, Real J, Gasco E, Galvan L. Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. *Eur Psychiatry.* May 2010;25(4):206-213.

7. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with depression in the United States. *Am J Psychiatry.* Jan 2006;163(1):101-108.

8. Novick D, Montgomery W, Moneta V, Peng X, Brugnoli R, Haro JM. Antidepressant medication treatment patterns in Asian patients with major depressive disorder. *Patient preference and adherence.* 2015;9:421-428.

9. Milea D, Guelfucci F, Bent-Ennakhil N, Toumi M, Auray JP. Antidepressant monotherapy: A claims database analysis of treatment changes and treatment duration. *Clinical therapeutics.* Nov 2010;32(12):2057-2072.

10. Zhang Z, Peluso MJ, Gross CP, Viscoli CM, Kernan WN. Adherence reporting in randomized controlled trials. *Clinical trials (London, England).* Apr 2014;11(2):195-204.

11. Satpute S, Mehta M, Bhete S, Kurle D. Assessment of adherence to the statistical components of consolidated standards of reporting trials statement for quality of reports on randomized controlled trials from five pharmacology journals. *Perspectives in clinical research.* Jul-Sep 2016;7(3):128-131.

12. Dodd S, White IR, Williamson P. Nonadherence to treatment protocol in published randomised controlled trials: a review. *Trials.* Jun 18 2012;13:84.

13. Poluzzi E, Piccinni C, Sangiorgi E, et al. Trend in SSRI-SNRI antidepressants prescription over a 6-year period and predictors of poor adherence. *European journal of clinical pharmacology.* Dec 2013;69(12):2095-2101.

14. Corrigan PW, Rusch N, Ben-Zeev D, Sher T. The rational patient and beyond: implications for treatment adherence in people with psychiatric disabilities. *Rehabilitation psychology.* Feb 2014;59(1):85-98.

15. Marengoni A, Onder G, Esposti LD, et al. Adherence to Selective Serotonin and Serotonin-Norepinephrine Reuptake Inhibitor Prescriptions Affects Overall Medication Adherence in Older Persons: Evidence From the Italian Nationwide OsMed Health-DB Database. *J Clin Psychiatry.* Dec 2016;77(12):1712-1718.

16. Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. *Patient preference and adherence.* 2012;6:499-507.

17. Ramsey RR, Ryan JL, Hershey AD, Powers SW, Aylward BS, Hommel KA. Treatment adherence in patients with headache: a systematic review. *Headache.* May 2014;54(5):795-816.

18. Gearing RE, Townsend L, Elkins J, El-Bassel N, Osterberg L. Strategies to Predict, Measure, and Improve Psychosocial Treatment Adherence. *Harv Rev Psychiatry.* Dec 12 2013.

19. Kim KH, Lee SM, Paik JW, Kim NS. The effects of continuous antidepressant treatment during the first 6 months on relapse or recurrence of depression. *J Affect Disord.* Jul 2011;132(1-2):121-129.

20. Yue Z, Cai C, Ai-Fang Y, Feng-Min T, Li C, Bin W. The effect of placebo adherence on reducing cardiovascular mortality: a meta-analysis. *Clin Res Cardiol.* Mar 2014;103(3):229-235.

21. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ.* Jul 01 2006;333(7557):15.

22. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ.* Sep 11 2008;337:a1344.

23. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry.* Feb 2005;62(2):165-172.

24. Glue P, Donovan MR, Kolluri S, Emir B. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. *Aust N Z J Psychiatry.* Aug 2010;44(8):697-705.

25. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry.* Dec 1998;55(12):1128-1132.

26. Jeffery RA, Navarro T, Wilczynski NL, et al. Adherence measurement and patient recruitment methods are poor in intervention trials to improve patient adherence. *Journal of clinical epidemiology.* Oct 2014;67(10):1076-1082.

27. Dunbar-Jacob J, Rohay JM. Predictors of medication adherence: fact or artifact. *J Behav Med.* Dec 2016;39(6):957-968.

28. Loayza N, Crettol S, Riquier F, Eap CB. Adherence to antidepressant treatment: what the doctor thinks and what the patient says. *Pharmacopsychiatry.* Jul 2012;45(5):204-207.

29. ten Doesschate MC, Bockting CL, Schene AH. Adherence to continuation and maintenance antidepressant use in recurrent depression. *J Affect Disord.* May 2009;115(1-2):167-170.

30. Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Med Care.* Apr 2007;45(4):363-369.

31. Sundell KA, Waern M, Petzold M, Gissler M. Socio-economic determinants of early discontinuation of anti-depressant treatment in young adults. *European journal of public health.* Jun 2013;23(3):433-440.

32. Wu CH, Erickson SR, Piette JD, Balkrishnan R. The association of race, comorbid anxiety, and antidepressant adherence among Medicaid enrollees with major depressive disorder. *Research in social & administrative pharmacy : RSAP.* May-Jun 2012;8(3):193-205.

33. Trivedi RB, Ayotte BJ, Thorpe CT, Edelman D, Bosworth HB. Is there a nonadherent subtype of hypertensive patient? A latent class analysis approach. *Patient preference and adherence.* Jul 21 2010;4:255-262.

34. Cruz I, Serna C, Rue M, Real J, Soler-Gonzalez J, Galvan L. Duration and compliance with antidepressant treatment in immigrant and native-born populations in Spain: a four year follow-up descriptive study. *BMC Public Health.* May 11 2012;12:256.

35. Buus N, Johannessen H, Stage KB. Explanatory models of depression and treatment adherence to antidepressant medication: a qualitative interview study. *International journal of nursing studies.* Oct 2012;49(10):1220-1229.

36. Murata A, Kanbayashi T, Shimizu T, Miura M. Risk factors for drug nonadherence in antidepressant-treated patients and implications of pharmacist adherence instructions for adherence improvement. *Patient preference and adherence.* 2012;6:863-869.

37. Pompili M, Venturini P, Palermo M, et al. Mood disorders medications: predictors of nonadherence - review of the current literature. *Expert Rev Neurother.* Jul 2013;13(7):809-825.

38. Lee MS, Lee HY, Kang SG, et al. Variables influencing antidepressant medication adherence for treating outpatients with depressive disorders. *J Affect Disord.* Jun 2010;123(1-3):216-221.

39. Vangeli E, Bakhshi S, Baker A, et al. A Systematic Review of Factors Associated with Non-Adherence to Treatment for Immune-Mediated Inflammatory Diseases. *Advances in therapy.* Nov 2015;32(11):983-1028.

40. Vergouwen AC, Bakker A, Katon WJ, Verheij TJ, Koerselman F. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry.* Dec 2003;64(12):1415-1420.

41. Akerblad AC, Bengtsson F, Ekselius L, von Knorring L. Effects of an educational compliance enhancement programme and therapeutic drug monitoring on treatment adherence in depressed patients managed by general practitioners. *Int Clin Psychopharmacol.* Nov 2003;18(6):347-354.

42. Peveler R, George C, Kinmonth AL, Campbell M, Thompson C. Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. *BMJ.* Sep 04 1999;319(7210):612-615.

43. Brook OH, van Hout H, Stalman W, et al. A pharmacy-based coaching program to improve adherence to antidepressant treatment among primary care patients. *Psychiatr Serv.* Apr 2005;56(4):487-489.

44. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* Nov 20 2014(11):CD000011.

45. Toneatto T. Metacognition and substance use. *Addict Behav.* Mar-Apr 1999;24(2):167-174.

46. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & health.* 1999/01/01 1999;14(1):1-24.

47. Unni EJ, Olson JL, Farris KB. Revision and validation of Medication Adherence Reasons Scale (MAR-Scale). *Current medical research and opinion.* Feb 2014;30(2):211-221.

48. De las Cuevas C, Penate W, Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. *European journal of clinical pharmacology.* Jan 2014;70(1):89-98.

49. Foot H, La Caze A, Gujral G, Cottrell N. The necessity-concerns framework predicts adherence to medication in multiple illness conditions: A meta-analysis. *Patient education and counseling.* May 2016;99(5):706-717.

50. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One.* 2013;8(12):e80633.

51. Brown C, Battista DR, Bruehlman R, Sereika SS, Thase ME, Dunbar-Jacob J. Beliefs about antidepressant medications in primary care patients: relationship to self-reported adherence. *Med Care.* Dec 2005;43(12):1203-1207.

52. Brandstetter S, Riedelbeck G, Steinmann M, Loss J, Ehrenstein B, Apfelbacher C. Depression moderates the associations between beliefs about medicines and medication adherence in patients with rheumatoid arthritis: Cross-sectional study. *Journal of health psychology.* May 04 2016.

53. Russell J, Kazantzis N. Medication beliefs and adherence to antidepressants in primary care. *The New Zealand medical journal.* Nov 07 2008;121(1286):14-20.

54. Aikens JE, Nease DE, Jr., Nau DP, Klinkman MS, Schwenk TL. Adherence to maintenance-phase antidepressant medication as a function of patient beliefs about medication. *Annals of family medicine.* Jan-Feb 2005;3(1):23-30.

55. Pompili M, Serafini G, Del Casale A, et al. Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Rev Neurother.* Jul 2009;9(7):985-1004.

56. Burnett-Zeigler I, Kim HM, Chiang C, et al. The association between race and gender, treatment attitudes, and antidepressant treatment adherence. *Int J Geriatr Psychiatry.* Feb 2014;29(2):169-177.

57. Stetler C. Adherence, expectations and the placebo response: why is good adherence to an inert treatment beneficial? *Psychology & health.* 2014;29(2):127-140.

58. van Geffen EC, Heerdink ER, Hugtenburg JG, Siero FW, Egberts AC, van Hulten R. Patients' perceptions and illness severity at start of antidepressant treatment in general practice. *The International journal of pharmacy practice.* Aug 2010;18(4):217-225.

59. Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the Necessity-Concerns Framework. *J Psychosom Res.* Jan 2008;64(1):41-46.

60. Phillips LA, Diefenbach MA, Kronish IM, Negron RM, Horowitz CR. The necessity-concerns framework: a multidimensional theory benefits from multidimensional analysis. *Ann Behav Med.* Aug 2014;48(1):7-16.

61. Bosworth HB, Voils CI, Potter GG, Steffens DC. The effects of antidepressant medication adherence as well as psychosocial and clinical factors on depression outcome among older adults. *Int J Geriatr Psychiatry.* Feb 2008;23(2):129-134.

62. Aikens JE, Klinkman MS. Changes in patients' beliefs about their antidepressant during the acute phase of depression treatment. *Gen Hosp Psychiatry.* May-Jun 2012;34(3):221-226.

63. Bayley PJ, Frascino JC, Squire LR. Robust habit learning in the absence of awareness and independent of the medial temporal lobe. *Nature.* Jul 28 2005;436(7050):550-553.

64. Broadbent NJ, Squire LR, Clark RE. Rats depend on habit memory for discrimination learning and retention. *Learn Mem.* Mar 2007;14(3):145-151.

65. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol.* 2002;53:545-574.

66. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism.* May 2005;54(5 Suppl 1):20-23.

67. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc.* 2000;75(7):711-721.

68. Volkow ND, Wang GJ, Fowler JS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am.J.Psychiatry.* 1998;155(10):1325-1331.

69. Volkow ND, Wang G, Fowler JS, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J.Neurosci.* 2001;21(2):RC121.

70. Markowitz JS, DeVane CL, Pestreich LK, Patrick KS, Muniz R. A comprehensive in vitro screening of d-, l-, and dl-threo-methylphenidate: an exploratory study. *J Child Adolesc Psychopharmacol.* 2006;16(6):687-698.

71. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *Journal of Neurochemistry.* 1997;68(5):2032-2037.

72. Volkow ND, Fowler JS, Wang GJ. Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *J.Psychopharmacol.* 1999;13(4):337-345.

73. Volkow ND, Wang GJ, Fowler JS, et al. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of "high&quot. *J.Pharmacol.Exp.Ther.* 1999;288(1):14-20.

74. Volkow ND, Wang GJ, Fowler JS, et al. Differences in regional brain metabolic responses between single and repeated doses of methylphenidate. *Psychiatry Res.* 1998;83(1):29-36.

75. Chait LD. Reinforcing and subjective effects of methylphenidate in humans. *Behav Pharmacol.* 1994;5(3):281-288.

76. Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. *Arch.Gen.Psychiatry.* 1995;52(6):456-463.

77. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci.* 2000;20(6):RC65.

78. Brignell CM, Curran HV. Drugs, sweat, and fears: a comparison of the effects of diazepam and methylphenidate on fear conditioning. *Psychopharmacology (Berl).* 2006;186(4):504-516.

79. Branconnier RJ, Cole JO. The therapeutic role of methylphenidate in senile organic brain syndrome. *Proc Annu Meet.Am Psychopathol.Assoc.* 1980;69:183-196.

80. Kraus MF. Neuropsychiatric sequelae of stroke and traumatic brain injury: the role of psychostimulants. *Int J Psychiatry Med.* 1995;25(1):39-51.

81. Kaelin DL, Cifu DX, Matthies B. Methylphenidate effect on attention deficit in the acutely brain-injured adult. *Arch Phys.Med Rehabil.* 1996;77(1):6-9.

82. Whyte J, Hart T, Schuster K, Fleming M, Polansky M, Coslett HB. Effects of methylphenidate on attentional function after traumatic brain injury. A randomized, placebo-controlled trial. *Am J Phys.Med Rehabil.* 1997;76(6):440-450.

83. Warden DL, Gordon B, McAllister TW, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma.* 2006;23(10):1468-1501.

84. Kim YH, Ko MH, Na SY, Park SH, Kim KW. Effects of single-dose methylphenidate on cognitive performance in patients with traumatic brain injury: a double-blind placebo-controlled study. *Clin Rehabil.* 2006;20(1):24-30.

85. Pavlovskaya M, Hochstein S, Keren O, Mordvinov E, Groswasser Z. Methylphenidate effect on hemispheric attentional imbalance in patients with traumatic brain injury: a psychophysical study. *Brain Inj.* 2007;21(5):489-497.

86. Whyte J, Hart T, Vaccaro M, et al. Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. *Am J Phys.Med Rehabil.* 2004;83(6):401-420.

87. Lee H, Kim SW, Kim JM, Shin IS, Yang SJ, Yoon JS. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Hum Psychopharmacol.* 2005;20(2):97-104.

88. Whyte J, Vaccaro M, Grieb-Neff P, Hart T. Psychostimulant use in the rehabilitation of individuals with traumatic brain injury. *J Head Trauma Rehabil.* 2002;17(4):284-299.

89. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother.* 2005;39(7-8):1309-1313.

90. Forrester MB. Methylphenidate abuse in Texas, 1998-2004. *J Toxicol Environ Health A.* 2006;69(12):1145-1153.

91. Bosman J, Ter Horst PG, Smit JP, et al. Adherence of antidepressants during pregnancy: MEMS compared with three other methods. *Therapeutic advances in psychopharmacology.* Apr 2014;4(2):61-69.

92. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Can J Psychiatry.* Mar 2010;55(3):126-135.

93. Unni EJ, Farris KB. Development of a new scale to measure self-reported medication nonadherence. *Research in social & administrative pharmacy : RSAP.* May-Jun 2015;11(3):e133-143.

94. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *Journal of clinical epidemiology.* Nov 2010;63(11):1179-1194.

95. Hilton TF. The promise of PROMIS((R)) for addiction. *Drug Alcohol Depend.* Dec 15 2011;119(3):229-234.

96. *http://www.ids-qids.org/index2.html#table2*

97. https://*www.drugs.com/pro/ritalin.html*

98. Turnbull B. The empirical distribution function with arbitrarily grouped, censored and truncated data. *JRSS-B.* 1976;38:290-295.

99. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother.* Jul 2010;1(2):100-107.

100. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med.* Dec 1990;9(12):1439-1445.

101. Whitehead J, Valdes-Marquez E, Lissmats A. A simple two-stage design for quantitative responses with application to a study in diabetic neuropathic pain. *Pharm Stat.* Apr-Jun 2009;8(2):125-135.