Precision Mental Health: Evaluating Biotype-guided Interventions for Depression

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1. PURPOSE OF THE STUDY

a. Brief Summary

The diagnosis of major depression relies on patient reports, and two patients with the same diagnosis might share only one symptom. Thus, a single mechanism is unlikely to underlie a broad descriptive diagnosis such as major depression. Our approach is anchored by a neural circuit taxonomy that proposes distinct biotypes of depression derived from functional magnetic resonance imaging (fMRI)(Williams et al., 2016). In this study, we aim to target a putative type of major depression that arises from dysfunction in cognitive control neural circuitry with a drug called guanfacine.

b. Objectives

The proposed study addresses a public health need, generated by the burden of illness from depression. Major depressive disorder (MDD) is a prevalent and disabling condition; the 1-year prevalence is approximately 17%, and lifetime prevalence is as high as 25% globally. Only a subset of individuals with depression reach symptomatic remission after adequate treatment with first-line antidepressant medication treatment, estimated at approximately 30-40%. Dysfunction in a large-scale neural circuit alternatively called the executive or cognitive control circuit is associated with cognitive symptoms, including executive dysfunction and difficulty concentrating. These are core symptoms of depression and among the most frequently reported untreated symptoms of MDD.

Cognition is central to clinical and quality of life outcomes in depression. Research has repeatedly shown that cognitive impairments are not effectively treated by antidepressant medications. A significant proportion of MDD patients continue to experience debilitating cognitive symptoms even after attaining remission of mood symptoms with antidepressant treatment. These cognitive impairments are implicated in depression relapse and associated morbidity, highlighting the need for novel treatments that improve cognitive dysfunction in depression.

Guanfacine immediate release (Brand Name: Tenex) is an FDA-approved medication for hypertension and is used off-label for ADHD. The extended-release formulation is FDA-approved for treating ADHD in children and adolescents. In this study, we aim to

determine whether guanfacine immediate release (referred to hereafter as guanfacine or GIR) preferentially increases activation in a key node (dorsolateral prefrontal cortex, dLPFC) of the cognitive control circuit in participants with MDD, low baseline activation in this node, and cognitive deficits as compared to placebo as well as guanfacine in MDD participants with high baseline activation. Furthermore, we aim to determine whether change in dLPFC activation is correlated with changes in cognition. If our hypotheses are correct, baseline activation in the dLPFC may serve as a mechanistic neural target for treatment of symptoms with guanfacine in a subgroup of patients with MDD as well as a baseline predictor of response. Thus, this study will move us toward a more personalized and brain-based model of depression.

We will use GIR as it has been used more extensively than extended-release guanfacine in adult populations with cognitive deficits and has been shown to alter task-evoked dLPFC activation.

c. Rationale for Research in Humans

The purpose of the study is to specifically assess how guanfacine affects activation in the dLPFC and whether its effects correlate with change in cognitive function, including working memory, attention, and executive function in humans. It is difficult to identify a proxy for the spectrum of cognitive impairments in depression using animal models. Additionally, much of our knowledge of brain connectivity comes from studies in nonhuman primates and rodents. The human brain, however, is more complex in its architectonics than those of non-human primates or rodents. There is significant variability among humans in regard to brain anatomy and connectivity, as ascertained with fMRI. As such, understanding neural circuits of the human brain requires its direct study.

2. STUDY PROCEDURES

a. Procedures

1. Recruitment and screening: Participants experiencing depressive symptoms and not taking any psychiatric medications as determined by a 5 half-life wash out period will be recruited from the community, including students and employees at Stanford. Recruitment will come primarily from Facebook ads, which will use only IRB approved material. A flyer will also be physically posted on boards in public locations in order to include a variety of sources for the study.
2. Individuals will need to participate in 3 screening visits in order to enroll in the study. During the first visit, participants will review informed consent, be administered a clinical interview, and be sent instructions for completing cognitive testing at home.
3. If eligibility after this initial screening visit, the second visit will be a medical screen in order to ensure participants are safe to take GIR and will include standard blood tests, medical history, vitals, and a urine drug test.
4. If the participant meets medical and cognitive criteria, functional magnetic resonance imaging (fMRI) scans will be undertaken at another study visit at The Stanford Center for Cognitive and Neurobiological Imaging (CNI). Using a participant's task-evoked activity

in the dorsolateral prefrontal cortex (dLPFC) and performance on objective cognitive testing, we will apply thresholds using established healthy norms to select participants within the cognitive biotype+ group.

5. Participants will receive GIR for a period of 8 weeks sent to their place of residence from Mariner pharmacy.
6. Participants will be seen in-person or virtually by a study clinician at weeks 2, 4, 6, 8, and 10 and an appropriately trained clinical research coordinator at weeks 1, 3, 5, 7, and 9. All subjects will have an fMRI scan after 6-8 weeks of taking GIR. During in-person visits and virtual monitoring, we will assess participants for the following: changes to symptoms, function, and suicidality, adherence to GIR, changes to concomitant medication(s), adverse events (AEs), birth control usage compliance, likelihood of pregnancy (female participants of childbearing potential), and vital signs if appropriate.
7. If participants wish to continue GIR and their psychiatrist or PCP is willing to prescribe this, they will continue with their current dose for weeks 9 and 10. If they prefer to stop taking GIR and/or they do not have a provider who is willing to continue GIR, the participant will be tapered off the medication.

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b. Procedure Risks

The research procedures outlined in this protocol comply with published protocols for clinical trial and functional imaging research, which have been developed to maximize subject safety. Following these principles, we will minimize as much as possible the risk, consistent with sound research design and good clinical practice, in the following ways:

1. **Screening for Contraindications:**
   Participants will be extensively screened for all contraindications of treatments and assessments. During screening, participants' eligibility will be established based on a full psychiatric (psychiatric and medication history, diagnostic interviews, and self-report assays to assess all areas that might put participants at risk including history or presence of mania, suicidality, and alcohol and drug abuse) and medical screening (medical history, physical exam, blood and urine tests to assess all issues that might put participants at risk including epilepsy, heart, kidney, and liver function, likelihood of drug use, and pregnancy).
2. **Safety Monitoring Plan:**
   A data and safety monitoring plan will be established, and the proposed study will be registered as a clinical trial on clinicaltrials.gov.
3. **Adherence to Treatment Guidelines:**
   The treatment protocol uses parameters described in Butterfield et al. (Psychiatry Research, 2016) in adults with ADHD.
4. **Monitoring During the Study:**
   Participants will be monitored regularly for treatment side effects and any health status changes that might put them at risk. Participants will be monitored every week for side effects generally and also specifically (i.e., with quantitative scales) for mood changes and suicidality. All significant changes described by participants and/or measured in the scales will be recorded in the patients' case report forms, immediately reported to prescribing psychiatrists (in case data were collected by other research personnel), and all necessary actions will be taken for participants' safety and well-being. Participants will be reminded and reassessed for the following:

- Use of birth control (females of childbearing potential),
- Alcohol and drug abstinence, and
- Changes to current medications.

5. **Trained Personnel:**
   The study will be conducted by experienced lead investigators and appropriately trained research personnel. All study research personnel will be adequately and appropriately trained with regard to general guidelines for research with human subjects.

Dr. Trisha Suppes, M.D., Ph.D. and Dr. Laura Hack, M.D., Ph.D. has extensive experience in clinical trials involving drug treatments for mood disorder patients. All study procedures will be detailed in the study's manual of standard operating procedures (MOP), and personnel will be required to act according to those. The study's manual will include, among others, a safety plan for reporting suicidality during screening and monitoring, safety procedures for MRI testing, and recognition and reporting of adverse events (AEs) and serious adverse events (SAEs).

c. Use of Deception in the Study

Deception will not be used in this study.

d. Use of Audio and Video Recordings

No audio or video recordings will occur during the study.

e. Alternative Procedures or Courses of Treatment

There are currently no standard-of-care medications available that specifically target or treat cognitive impairment in depression. Initiation of antidepressant medication, particularly serotonin selective reuptake inhibitors (SSRIs), the first-line treatment for major depressive disorder, may be advantageous to participants. SSRIs typically take a minimum of 6-8 weeks once titrated to therapeutic dose to show therapeutic benefit with regard to symptoms. There are risks associated with SSRI treatment including medication side effects such as nausea, gastrointestinal side effects, increased anxiety, headaches, dizziness, fatigue, and a Black box warning of increasing risk of suicidal ideation in adolescence and young adulthood.

Electing to participate in the current study will delay initiating a trial of SSRI treatment by 6 weeks, but participants will then be able to continue with first-line therapy upon study completion. This information will be disclosed in the consenting process and form as standard-of-care drug.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Upon completion of Week 8 of the treatment period, participants will have the choice of whether they would prefer to continue on the treatment or be tapered off the drug by the study MD during Weeks 9 and 10. To maintain the blind, participants who would like to continue treatment will be cross-titrated or down-titrated on their assigned medication (placebo or guanfacine) while simultaneously up-titrating on guanfacine.

Participants must have a physician willing to prescribe them guanfacine upon termination of the study and provide a note from their physician to the study clinician, or they will be tapered off the drug over the two-week safety phase. Upon request, a letter will be written to notify the physician of the participant's involvement in the study. This would facilitate the option for participants' usual care physician to continue treatment with GIR as part of their ongoing care of the participant after completion of the study.

g. Study Endpoint(s)

The endpoint for primary and secondary measures will be 8 weeks after initiation of GIR or placebo, regardless of the study outcomes. Additional measures will be collected at the final endpoint of 10 weeks. If a subject reports a significant adverse event or worsening depression, the participant will be removed from the study. The study will not be terminated prematurely in the event that participants randomized to GIR have greater improvement than participants randomized to placebo.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

A single mechanism is unlikely to underlie a broad descriptive diagnosis such as depression. Thus, our approach is anchored by a neural-circuit taxonomy that proposes distinct biotypes of depression derived from functional magnetic resonance imaging (fMRI) (Williams, Lancet Psychiatry, 2016; Williams, Depress. Anxiety, 2017).
One of these circuits is the cognitive control circuit, which has been delineated by the PI and others in human neuroimaging work to comprise the dorsolateral prefrontal cortex (dLPFC) and its projections to the dorsal parietal cortex and anterior cingulate cortex. This circuit is engaged by cognitive control tasks requiring selective attention and inhibition, such as the Go-NoGo and Continuous Performance N-back tasks.
Related neuroimaging indicates that a subset of people with depression is characterized by dLPFC hypoactivation and cognitive impairments. These cognitive symptoms result in substantial morbidity and disability in individuals struggling with depression and are a principal determinant of quality of life and function, including workforce productivity, suggested to contribute more than 60% of MDD-related economic burden.

A meta-analysis of 13 studies comparing cognitive function in first-episode MDD subjects with healthy control participants found that depressed patients had significant impairments in psychomotor speed, attention, and most aspects of executive function (including attentional switching, verbal fluency, and cognitive flexibility). A substantial subset of these patients (approximately 20%) exhibited cognitive deficits of two standard deviations below the mean on two or more cognitive domains. These patients also appear to be poor responders to standard antidepressants (Lee et al. Journal of Affective Disorders 2012, Gualtieri et al., Journal of Clinical Psychiatry 2008). Thus, there remains a critical need to find effective treatments for this subset of MDD patients.
Cognitive dysfunction greatly contributes to the ongoing burden of disability and functional impairment in MDD after mood symptoms attain remission (McIntyre et al.,

Journal Anxiety and Depression, 2013). Our research group has previously reported results of the International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial, a randomized controlled study investigating the effects of three different antidepressant medications in 1008 depressed patients. These patients demonstrate ongoing impairment in five domains of cognitive function – attention, response inhibition, verbal memory, decision speed, and information processing – after 8 weeks of antidepressant medication treatment, irrespective of the antidepressant treatment group, including patients who attained remission based on clinical outcome measures (Shilyansky et al., Lancet Psychiatry, 2016).

Guanfacine is an α2A-adrenergic receptor agonist that has been shown to selectively facilitate plasticity in frontal norepinephrine pathways. In preclinical studies, guanfacine binds more preferentially to postsynaptic α2A-adrenergic receptors than clonidine. Preclinical studies and clinical trials indicate that guanfacine acts directly by enhancing noradrenaline functioning via α2A-adrenoceptors in the PFC, primarily at postsynaptic receptors, through inhibition of cyclic adenosine monophosphate, closing hyperpolarization-activated cyclic nucleotide-gated channels, modulating synaptic functioning, and strengthening PFC-network connectivity, thereby improving PFC cognitive functions.

b. Findings from Past Animal Experiments

Over three decades of animal research has demonstrated that working memory can be improved by alpha-2-adrenoceptor agonists such as guanfacine, while infusions of alpha-2 antagonists into the PFC impair working memory (Arnsten et al., 1988; Arnsten and Goldman-Rakic, 1985; Franowicz and Arnsten, 1998; Rama et al., 1996; Ramos et al., 2006; Tanila et al., 1996; Wang et al., 2007). Furthermore, animal studies show that guanfacine has robust antidepressant effects and can reverse a depression-like state induced by cholinergic signaling (Minuer et al., 2015). In particular, both acute and chronic guanfacine administration decreased immobility time of mice in the forced swim test.

4. RADIOISOTOPES OR RADIATION MACHINES

a. Standard of Care (SOC) Procedures

Identify Week/Month of Study	Name of Exam	Identify if SOC or Research
NA	NA	NA

b. Radioisotopes

i. Radionuclide(s) and chemical form(s)

NA

ii. Total number of times the radioisotope and activity will be administered (mCi) and the route of administration for a typical study participant

NA

iii. If not FDA approved: dosimetry information and source documents (package insert, Medical Internal Radiation Dose [MIRD] calculation, and peer reviewed literature)

NA

c. Radiation Machines – Diagnostic Procedures

i. Examination description (well-established procedures)

NA

ii. Total number of times each procedure will be performed (typical study participant)

NA

iii. Setup and techniques to support dose modeling

NA

iv. FDA status of the machine and information on dose modeling (if procedure is not well-established)

NA

d. Radiation Machines – Therapeutic Procedures

i. Area treated, dose per fraction/number of fractions, performed as part of normal clinical management or due to research participation (well-established procedures)

NA

ii. FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions (if procedure is not well-established)

NA

5. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Sigma MR750 3T scanner
Description:	The MR research being conducted requires highly specialized equipment and imaging software that does not exist in the clinical MR market, so it is designed and manufactured by researchers at the Lucas Center and other hardware companies.
Significant Risk? (Y/N)	Yes
Rationale for Non-Significant Risk	Although some of the imaging software and equipment are not FDA approved, they have been tested for safety and are very similar to what is used regularly in clinical MR examinations. The MR personnel are highly trained in the set-up, utilization, and monitoring of this equipment.
Investigational Device 2	
Name:	GE 3 Tesla Ultra-High Performance (UHP) scanner
Description:	The MR research being conducted requires highly specialized equipment and imaging software that does not exist in the clinical MR market so it is designed and manufactured by researchers at the Lucas Center and other hardware companies.
Significant Risk? (Y/N)	Yes

Rationale for Non-Significant Risk	The 3T UHP scanner from GE is an upgrade to the 3T MR750 which was a commercial FDA-approved system. The UHP system utilizes many components from GE's 3T Signa Premier, including gradient drivers, power supply, transmit and receive system electronics, but uses a higher performance gradient coil. The 3T UHP system is not FDA approved, and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-2-33 (ed 3.1) -- meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. In addition, the MR research being conducted requires highly specialized software that does not exist in *the* clinical MR market so it is designed and implemented by researchers at the CNI. Any such software will be considered investigational, will function as a nonsignificant risk device, and is subject to the 21 CFR 812 investigational device (IDE) regulations as well as 21 CFR 50 and 56. The investigational image acquisition software will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation (dB/dt), and acoustic noise. - The scanner is for investigational use only and will not be used in to diagnose, cure, treat or prevent the impairment of human health. Additionally, the magnet has been tested by GE and meets the limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point according to medical equipment and flammability standards. - The MRI scans in this study will utilize operational parameters within FDA guidelines for Nonsignificant Risk, same as before the upgrade.

b. IDE-Exempt Devices

IND-Exempt Device 1	
Name:	NA
Description:	NA

6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

Investigational Product 1	
Name:	NA
Dosage:	NA
Administration Route:	NA

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Guanfacine hydrochloride immediate release
Dosage:	0.5mg nightly, increase every 3 days until 2mg nightly
Administration Route	Oral
New and different use? (Y/N)	Y

7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

NA

8. PARTICIPANT POPULATION

a. Planned Enrollment

25

b. Age, Gender, and Ethnic Background

18-69 years old, male and female, all ethnic backgrounds

c. Vulnerable Populations

Children younger than 18 are not included due to the fact that many of the clinical and biological measures that will be used in subsequent research studies in our clinic are validated for use in people 18 and older.

d. Rationale for Exclusion of Certain Populations

NA

e. Stanford Populations

If any Stanford employees, and/or students qualify and wish to participate, they will be treated the same as any other participant.

f. Healthy Volunteers

NA

g. Recruitment Details

Dr. Williams' ongoing imaging trials will be leveraged. Recruitment pipelines include flyering, online advertisements, Facebook ads, and participants from an IRB-approved R01 grant, where approximately one participant per two weeks meets study criteria. Psychiatric symptoms are assessed during recruitment.
We will also use online advertisements through the lab's Facebook platform, where all comments are private to prevent inadvertent PHI sharing. Advertisements will be IRB-approved before launch.

Participants will provide written informed consent, adhering to Stanford IRB guidelines and the Declaration of Helsinki

h. Eligibility Criteria

i. Inclusion Criteria

- 18-69 years of age (inclusive)

- Go-NoGo fMRI task-evoked dLPFC ≤ - 0.5 SD below the mean of normative sample
- Behavioral cognitive control performance ≤ - 0.5 SD below the mean of normative sample on a Maze, Digit Span, and/or Verbal Interference (Stroop) task administered using WebNeuro
- Score ≥ 14 on the 17-item Hamilton Depression Rating Scale-17 (HDRS-17)
- Meets DSM-5 diagnostic criteria for current, past, or recurrent nonpsychotic major depressive disorder established by MINI Plus
- Medication naïve to guanfacine
- Fluent and literate in English, and show non-impaired intellectual abilities to ensure adequate comprehension of the task instructions
- Written, informed consent
- fMRI scanning eligibility, including no evidence of any form of metal embedded in the body (e.g., metal wires, nuts, bolts, screws, plates, sutures), as these produce artifacts when brain imaging. All potential subjects will need to successfully complete the screening forms at the Stanford Center for Cognitive and Neurobiological Imaging (CNI).

ii. Exclusion Criteria

- Presence of suicidal ideations representing imminent risk, defined by a score of > 8 on the MINI-Plus, or by clinician judgement
- Lifetime history of medical illness or injury that may compromise cognitive functioning or interfere with assessments as deemed by the study physician (such as neurological disorders such as seizures or stroke, Parkinson's disease, dementia, or traumatic brain injury)
- Severe impediment to vision, hearing, and/or hand movement likely to interfere with ability to complete the assessments, or are unable and/or unlikely to follow the study protocols
- Pregnant, breastfeeding or unwilling or unable to use adequate birth control throughout the study
- Loss of consciousness for > 10 minutes during lifetime
- Any contraindication to being scanned in the 3.0T scanner at the CNI such as having a pacemaker or implanted device that has not been cleared for scanning at 3.0 Tesla
- Previous or current DSM-5 bipolar disorder (I, II, not otherwise specified) or psychosis
- Meets criteria for DSM-5 alcohol or substance use disorder within the last 12 months
- Meets criteria for current DSM-5 PTSD, OCD, or eating disorder
- Concurrent participation in other intervention or treatment studies
- Current use of psychotropic medications. If their usual treating physician is supportive, participants who are currently on psychotropics that can be safely tapered may be tapered off to participate but participant must wait 5 half-lives prior to first scan
- Current use of a strong CYP3A4 inhibitor or inducer (macrolide/ketolide antibiotics [clarithromycin, telithromycin], azole antifungals [itraconazole,

ketoconazole, posaconazole, voriconazole], protease inhibitors [atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ombitasvir, paritaprevir, ritonavir, saquinavir], ceritinib, cobicistat, and idealisib), or inducer (apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, lumacaftor-ivacaftor, mitotane, phenobarbital, phenytoin, primidone, rifampin)

- Hypotension as defined by SBP ≤ 90 and/or DBP ≤60 on 2 of 3 separate measurements at least 5 minutes apart, bradycardia as defined by HR ≤55 on 2 of 3 separate measurements at least 5 minutes apart
- General medical condition, disease, or neurological disorder as reported by participant or found on in-person screenings that is deemed by the study physicians to be unsafe for GIR treatment, including kidney or liver impairment that is deemed to be unsafe, EKG abnormalities that are deemed to be unsafe, or cardiovascular disease deemed to be unsafe.
- History of sudden cardiac death in first degree relatives
- Positive drug screen for any substance deemed by the study physician to be unsafe for use with GIR in combination with other information obtained during screening

i. Screening Procedures

Participants will complete an online eligibility survey, provide informed consent, and attend two screening visits. Screenings include clinical interviews, medical history, cognitive testing, and functional MRI scans to assess dLPFC activation.

j. Participation in Multiple Protocols

Participants will first be screened via an online REDCap survey in order to determine initial eligibility. Once participants have completed the survey and have been determined eligible, they will continue to an in-person visit where consenting will take place and further screening procedures will be completed.
Participants will be screened for assessment of inclusion and exclusion criteria at the in-person baseline visit. We will ensure that consent is obtained and enrollment completed before personal health information is collected.
We also screen using the following physical and laboratory tests:
a) **Physical Exam:**

- Participants will be asked to provide additional details of their medical history specifically relevant to the treatment contraindications (exclusion criteria). For standard monitoring, we will assess height, weight, vital signs, systems assessment, and general medical presentation during the physical exam.

b) **Laboratory Testing:**

- For standard monitoring, we undertake the following:
    - **Blood sample:** Analyzed for CBC, CMP, LFTs, TSH, and serum pregnancy test.
    - **Urine sample:** For urine drug screen.
    - **Electrocardiogram (EKG):** To assess cardiovascular health.

k. Payments to Participants

Research subjects will be offered [redacted] for the pretreatment fMRI session, self-report questionnaires, and cognitive assessments; and [redacted] for the subsequent MRI session at Week 8 of the treatment phase. Participants who complete the Monetary Incentive Delay (MID) task in the three MRI sessions will be offered an additional payment depending on their performance on the task, for a maximum total of [redacted] per session.

Participants will be compensated [redacted] for each of the 5 phone visits with completed questionnaires, [redacted] for the virtual or in-person physician check-ins at Weeks 2 and 8, and [redacted] for the physician check-ins at Weeks 4, 6, and 10.

l. Costs to Participants

No protocol-related costs will be charged to participants.

m. Planned Duration of the Study

The probable duration of the entire study is three years.

1. **Individual Participant Duration:**
    - Screening: Approximately four hours.
    - Active Participation: Approximately 24 hours total over 12 weeks, with 10–12 days of active engagement.
    - Total Study Duration: Participants will spend about 12 weeks enrolled in the study, including an 8-week treatment phase and follow-up activities.
2. **Study Completion Timeline:**
    - The study is planned to be conducted over three years, with data analysis for each participant requiring approximately 160 hours.

9. RISKS

a. Potential Risks

i. Investigational devices

NA

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

Guanfacine Side Effects and Potential Risks in Children and Adolescents with ADHD: Drowsiness (28% to 57%), headache (16% to 28%), fatigue (10% to 22%), dizziness (4% to 16%), insomnia (2% to 13%), abdominal pain (8% to 19%), decreased appetite (5% to 15%), hypotension (4% to 9%), bradycardia (2% to 5%), orthostatic hypotension (1% to 5%), first-degree atrioventricular block (≥2%), sinus arrhythmia (≥2%), tachycardia (≥2%), syncope (1% to ≥2%), irritability (5% to 8%), lethargy (3% to 8%), anxiety (2% to 5%), nightmares (3% to 4%), emotional lability (2% to 3%), agitation (≥2%), depression (≥2%), increased blood pressure (≥2%), loss of consciousness (children: ≥2%), skin rash (2% to 3%), pruritus, weight gain (2% to

3%), xerostomia (3% to 8%), nausea (5% to 7%), vomiting (2% to 7%), diarrhea (2% to 6%), constipation (2% to 4%), abdominal distress (≥2%), dyspepsia (≥2%), stomach discomfort (≥2%), urinary incontinence (2% to 5%), asthma (≥2%), fever (8%; Biederman 2008).

iv. Procedures

Risks Associated with fMRI
Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. Participants will be screened for having cardiac pacemakers or any other biomedical device in or on their body, including any metal objects (especially surgical clips), devices, or implants before entering the magnet room. All such objects will be removed (if possible) before entering the magnet room. In some cases, having those devices means participants should not have an MRI scan performed. Participants will also be screened for history of head or eye injury involving metal fragments, having worked in a metal shop, or for being pregnant. They will also be asked for any tattoos on their body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. There is a possibility that participants will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful. There is a small risk of heating from the cables associated with these devices. Dizziness or nausea may occur if participants move their head rapidly within the magnet. The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal.

Distress During Interviews
The interviews are time consuming and about personal matters. It is possible that participants will feel upset, tired, or anxious.

Phlebotomy
There is a minimal risk of infection with blood draw as well as the risk of minor discomfort.

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

NA

vii. Psychological well-being

Some participants may experience distress or anxiety related to participating in the procedures. Participants will be monitored throughout the procedures and encouraged to report any concerns. A psychiatrist will be available to assist the participant if

needed, and participants will be removed from the protocol if their distress or anxiety becomes intolerable.

viii. Economic well-being

NA

ix. Social well-being

NA

x. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

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b. International Research Risk Procedures

NA

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c. Procedures to Minimize Risk

Participants are safeguarded from undue risk by procedures to obtain informed consent, ensure confidentiality, and minimize possible risks associated with the study. Each is described below.

Potential risks associated with participation in this study may include the potential for the following:

1. Distress from completing cognitive and psychological questionnaires and from being in an fMRI scanner.
2. Risks associated with blood, saliva, and urine sampling.
3. Risks associated with GIR administration.

The risks are reasonable in relation to the anticipated benefits and will be minimized by using procedures that are consistent with sound research design, that do not unnecessarily expose participants to risk, and that are based on established research and trial protocols.

Questionnaires:

The risks associated with the self-report and clinical assessments are minimal. Research personnel are trained to manage any distress that is generated by completing these assessments, and protocols for managing any distress have been well established in prior studies. Some participants might experience discomfort with discussing personal information with a person they do not know.

Behavioral and Cognitive Assays:

The risks associated with the behavioral and cognitive assessments are also minimal. Research personnel are trained to manage any distress that is generated by completing these assessments, and protocols for managing any distress have been well established in prior studies.

Brain Imaging Assays:

The principal piece of equipment used in this protocol is a 3 Tesla GE fMRI scanner. A small number of people may feel claustrophobic inside the machines. The study will be

immediately stopped via button press if this occurs. Study personnel and technicians will be on-site during all acquisitions to address any such discomfort. To minimize fatigue, sufficient breaks are provided to participants during the scanning procedure, and the experimenter regularly inquires as to whether there is anything that they can do to facilitate the participant's comfort. The risks associated with fMRI are minimal. Routine contraindications to MRI include the presence of any metal implants (pacemaker, aneurysm clips, neurostimulators, cochlear, eyes, tattoos with ink contraindicated for fMRI scanning). The scan will be immediately stopped via button press if this occurs. Study personnel and MRI technologists will be on-site during all acquisitions to address any such discomfort.

Blood and Urine Sampling:

Blood and urine samples will be required prior to entry to assess for health problems, drug use, and pregnancy (in females). Participants may experience minor discomfort.

Saliva and Hair Sampling:

Saliva and hair samples will be collected as optional components of the study. Participants may experience minor discomfort.

Guanfacine:

GIR studies have reported blood pressure changes in patients with ADHD as well as in healthy control participants. Any medical risks from decreased blood pressure will be minimized through the careful screening of potential participants. Potential participants with baseline hypotension, history of cardiovascular illness, or concerning findings on EKG will be excluded. If a participant experiences distressing side effects, GIR will be discontinued. Participants will be closely monitored through in-person and bi-weekly phone assessments to assess safety and tolerability, specifically asking about known side effects detailed above. Bloodwork and physician examination with their PCP will be arranged as needed. Participants will be reminded that they can elect to terminate study participation at any time, and if experiencing significant distressing side effects, drug administration will be discontinued.

Other Considerations:

- **Incidental Findings on MRI**:
  Although this study and scans from this study will be used for research purposes, we will also collect T1-weighted anatomical images from each participant. We will follow the IRB-approved protocol of CNI or the Lucas Center, whereby any indications of an incidental finding are sent to a neuroradiologist for a clinical report.
- **Emergencies:**
  If, during the course of interviewing and assessment procedures, study staff identifies a condition that mandates immediate clinical intervention or official reporting, all necessary steps will be taken, and the emergency procedures of the institution will be followed. In the event that a research participant expresses suicidal ideation during a clinical interview or when completing a questionnaire, a suicide risk assessment will be performed, and a licensed clinical psychologist or psychiatrist will be consulted in order to determine the level and immediacy of risk. If the research subject is deemed an imminent danger to self, they will be placed on a 5150 LPS psychiatric hold and transferred to Stanford Hospital Emergency Department for comprehensive clinical evaluation and assessment.

d. Study Conclusion

Emergencies:
If, during the course of interviewing and assessment procedures, study staff identifies a condition that mandates immediate clinical intervention or official reporting (e.g., homicidality or suicidality), all necessary steps will be taken, and the emergency procedures of the Department of Psychiatry and Behavioral Sciences will be followed. In the case that staff determine that the participant is at significant risk for self- or other-destructive behavior, necessary treatment steps will be taken (e.g., hospitalization, referral to a care provider, etc.). All participants will be given numbers to call in the event of an emergency during treatment: the primary phone number of the treating clinician and the number for the clinic. If the treating clinician is immediately unavailable, participants will be instructed to not delay and to go to their nearest Emergency Room.

Safety Measures Upon Termination:
After a participant's completion of or early termination from the study, participants will be followed up only in the case of an adverse event. If an adverse event occurs, the participants will be followed by the study MD until the adverse event is resolved. Referrals will be given if needed.

Termination Due to Loss to Follow-Up:
Staff will call participants who miss a visit on the same day to inquire about reasons for the absence, help problem-solve, and reschedule the missed visit. Staff will be persistent in attempting to re-engage noncompliant participants in subsequent follow-ups via phone and/or email. Participants are considered lost to follow-up if they miss a scheduled visit and are unresponsive to three subsequent attempts to reach them. Staff will encourage participants lost to follow-up to contact their standing psychiatrist for ongoing care. Additionally, we will email any participants lost to follow-up our mental health resource guide to provide them with local and national mental health care resources.

e. Data Safety Monitoring Plan (DSMC)

The PI will utilize a standardized approach employing contemporary biostatistical, medical, and ethical principles to review study design and interim data before trial inception and every year thereafter; the PI will also have the ability to ask for more frequent reviews at any time during the study if they deem this necessary. The PI, data manager, and study statistician will prepare a specific report for the IRB. Specific attention will be given to data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, and other factors that can affect study outcome, including scientific developments that may have an impact on the safety of the participants or the ethics of the study. The procedures in place for monitoring adverse events as well as for site, data and statistical management will enable us to generate a timely report to the IRB. The data safety report to the IRB will include:

1. All serious and unexpected adverse events (for example, inpatient hospitalizations) or other unanticipated problems that involve risk to study participants or others at either site, and whether these appeared related to the research assessment protocols. Reports will not specifically disclose the session/dose arm of the study unless this is required for safety reasons;

2. Whether participants' safety, privacy, and confidentiality has been consistently assured by the investigator;
3. Whether the PI recommends an interim analysis pertinent to evaluating participants' safety;
4. Judgments as to whether research instruments have been administered in a uniform manner and in a way that maintains participants' confidentiality;
5. A review of the study's progress toward recruitment goals, quality of data (e.g., appropriate completion of forms), medication treatment adherence, and participant retention/attrition rates;
6. A review of new scientific literature pertinent to the safety of participants or the ethics of research participation (for example, new therapeutic developments).

These reports will be filed with the PI, who will file them with the Human Participants IRBs. The annual reports will also be filed with the IRB. The reports will enumerate the dates that the committee met and its procedures for monitoring participants' safety and confidentiality and data integrity. There will be regular, ongoing communication between the PI and the IRB. IRB protocols and informed consent documents will be annually reviewed by the IRB. The PI will take responsibility for reporting any serious adverse event (SAE) to the IRB within 24 hours according to standard regulations. A SAE is defined as follows: death, life-threatening adverse event, inpatient hospitalization, persistent or significant disability/incapacity, and medically significant event.

i. Person(s) responsible for Data and Safety Monitoring

The PI.

ii. Frequency of DSMB meetings

NA

iii. Specific triggers or stopping rules

See study endpoints.

iv. DSMB Reporting

A summary of the report will be submitted to the IRB for review.

v. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vi. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

N

f. Risks to Special Populations

NA

10. BENEFITS

Participants may find that the study drug improves cognitive impairment and depressive symptoms, potentially benefiting future participants who struggle with MDD and cognitive impairment.

11. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.