

**PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY**

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Karen Miller, MD

PROTOCOL TITLE

Treatment-Resistant Depression Augmentation Therapy with An Analog of the Neuroactive Steroid Allopregnanolone: A Pilot Study

FUNDING

VERSION DATE

5/14/2018

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Specific Aim 1

Allopregnanolone levels are lower in postmenopausal women with treatment-resistant depression (n=20) as compared to those with treatment-responsive depression (n=20) and those with no history of depression (n=20). We will investigate allopregnanolone levels in a cross-sectional study of 60 postmenopausal women with the hypothesis that allopregnanolone is lower in postmenopausal women with treatment-resistant depression as compared to those with treatment-responsive depression and controls without depression, suggesting that allopregnanolone plays a critical role in treatment responsiveness.

Specific Aim 2.1

Allopregnanolone analog augmentation improves depressive symptoms in women with treatment-resistant depression. We will investigate in women with treatment-resistant depression whether allopregnanolone analog augmentation leads to a reduction in depressive symptoms, as measured by the *Montgomery-Asberg Depression Rating Scale* and *Clinical Global Impression-Severity* over an 8-week period. *Note that Aim 2.1 is not dependent on Aim 1, as pharmacologic levels of allopregnanolone could still lead to improvement in depressive symptoms even if the Aim 1 hypothesis that physiologic levels of allopregnanolone are lower in women with treatment-resistant depression is not confirmed.*

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Partners Human Subjects Research Application Form

Version Date: October 15, 2014

Major depressive disorder (MDD) is highly prevalent with significant morbidity and is more prevalent in women than men. Approximately 70% of patients do not respond to standard treatment, as demonstrated in the STAR*D trial, in which only 30% of patients with MDD achieved remission after 8-12 weeks of SSRI therapy despite adequate dosing. Therefore, the identification of an effective, well-tolerated, antidepressant augmentation therapy would have important clinical and public health implications. Steroid hormones and their metabolites act as transcription factors for parent hormone or other neurotransmitter receptors, and in some cases may also directly activate neurotransmitter receptors. Allopregnanolone, a progesterone metabolite, is a potent positive modulator of GABA action at GABAA receptors. Initial studies showed that antidepressant treatment in male rats elevated allopregnanolone levels in the brain. Investigators then demonstrated that human subjects (n=15) with treatment-naïve MDD had CSF allopregnanolone levels that were 60% lower than age- and sex-matched controls without MDD. Moreover, CSF allopregnanolone increased with SSRI treatment, and this normalization of allopregnanolone correlated with improvement in depressive symptoms as measured by the HDRS. Additionally, our own preliminary data demonstrate that allopregnanolone levels are inversely associated with severity of depression and anxiety in women across the weight spectrum, independent of BMI. Preliminary mechanistic explorations into the effects of allopregnanolone in mood disorders have shown alterations in amygdala activity and connectivity between the amygdala and dorsal medial prefrontal cortex that were correlated with reduction in anxiety in some studies. However, in these studies pregnenolone, a parent compound of allopregnanolone that was shown to subsequently increase allopregnanolone levels, was administered and the effect of pure allopregnanolone augmentation itself has not been studied. [REDACTED] has committed to provide Ganaxolone, which is a

synthetic analog of allopregnanolone with an added methyl group which prevents conversion back to the parent compound progesterone, for the proposed pilot study. Ganaxolone has been developed as an anti-epileptic medication and studied in over 1,300 individuals for up to two years in both adults and pediatric populations. Studies have reported only minor side effects, including somnolence, dizziness and fatigue.

Allopregnanolone levels are associated with severity of depression and anxiety in women across the weight spectrum. 36 women of a wide range of weights and depression severity were studied in the follicular phase of the menstrual cycle. Allopregnanolone levels measured by gas chromatography mass-spectrometry (GC-MS) were negatively associated with severity of depression ($r = -0.45$, $p = 0.03$) and anxiety ($r = -0.37$, $p = 0.04$) independent of BMI, with 15% of the variability in depression and 11% of the variability in anxiety symptom severity attributable to allo levels. Of note, there was no association between levels of progesterone, the parent compound of allopregnanolone, and depression or anxiety severity. In conclusion, greater depression and anxiety severity was negatively associated with serum allopregnanolone, but not progesterone, independent of BMI. This supports the hypothesis that neuroactive steroids such as allo may be potential therapeutic targets for depression in traditionally treatment-resistant groups.

Additionally, we have successfully conducted studies of hormone augmentation strategies in women with treatment-resistant depression and have published a pilot study investigating the effects of low-dose testosterone augmentation on treatment-resistant depression in women, which formed the basis of an ongoing, NIH-funded trial and demonstrated a marked improvement in **Montgomery-Asberg Depression Rating Scale (MADRS)** scores at 2 weeks that was sustained through the 8-week period with administration of low-dose testosterone. At this time, we have recruited more than 50 subjects for an ongoing NIH-funded randomized, double-blind clinical trial of low-dose testosterone for treatment-resistant depression in women in follow-up to this pilot study. We hypothesize that the potential antidepressant effects of low dose testosterone are mediated by neuroactive steroids, including allopregnanolone. Moreover, both the pilot and follow-up studies speak to our ability to recruit and study this specific population of women with treatment-resistant depression.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Subjects: Aim 1 will study 60 women ages 50-75 in menopause (amenorrhea >1 year or elevated FSH in women with prior hysterectomy). Aims 2.1 and 2.2 will study 10 women with treatment-resistant depression.

Aim 1 Inclusion Criteria

1. Female, age 50-75
2. Postmenopausal, defined as amenorrhea for greater than one year and/or elevated FSH for women with prior hysterectomy
3. Meet criteria for one of three subgroups:
 - **Treatment-resistant depression** (N=20): MDD diagnosed by the SCID-I/P and with MADRS ≥ 16 who are currently treated with an SSRI or SNRI at an adequate dose for at least six weeks. Meet DSM-IV criteria for a current major depressive episode, as assessed by SCID
 - **Treatment-responsive depression** (N=20): Patients with history of MDD treated with an SSRI or SNRI who have achieved remission (MADRS <10)
 - **Controls** (N=20): Patients with no current or past depression by SCID and no history of antidepressant use. Allopregnanolone levels will be measured by GC-MS.

Aim 1 Exclusion Criteria

1. Serious suicide or homicide risk, as assessed by evaluating clinician
2. Unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic
3. Substance use disorder active within last six months
4. Psychotic features (current episode or lifetime), as assessed by SCID
5. Laboratory evidence of untreated hypothyroidism
6. Use of hormones (estrogens, androgens or related hormones) within the prior three months

7. Any investigational psychotropic drug within the last two weeks
8. Alanine aminotransferase (ALT) or creatinine > 3x upper limit of normal.

Aims 2.1 and 2.2 Inclusion Criteria

1. Female, age 50-75
2. Postmenopausal, defined as amenorrhea for greater than one year and/or elevated FSH for women with prior hysterectomy
3. Meet DSM-IV criteria (by SCID) for Major Depressive Disorder
4. Meet DSM-IV criteria for a current major depressive episode, as assessed by SCID
5. MADRS \geq 16 at baseline visit
6. Currently treated with SSRI or SNRI, with or without adjunctive therapy, at an adequate dose for at least six weeks

Aims 2.1 and 2.2 Exclusion Criteria

1. Serious suicide or homicide risk, as assessed by evaluating clinician
2. Unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic
3. Substance use disorder active within last six months
4. Psychotic features (current episode or lifetime), as assessed by SCID
5. Laboratory evidence of untreated hypothyroidism
6. If treated hypothyroidism, significant change in levothyroxine dose within the prior three months
7. Use of hormones (estrogens, androgens or related hormones) within the prior three months
8. Any investigational psychotropic drug within the last two weeks
9. In the judgment of the study clinician, unlikely to be able to participate safely throughout the study period (three or more episodes of self-harm in the past year, documented history of poor treatment adherence, or frequent missed appointments (>50%) in the past year)
10. Alanine aminotransferase (ALT) or creatinine > 3x upper limit of normal.
11. History of a hormone-responsive cancer
12. Receiving strong CYP3A4 inducers or inhibitors or who intend to consume grapefruit products regularly during the study

Briefly describe study procedures. Include any local site restrictions, for example, “Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study.” Describe study endpoints.

Study visits

Aim 1

Screening Visit/ Baseline Visit (n=120): A “Screening Visit” will be conducted to determine eligibility for the protocol. It is estimated that 120 women will need to be screened to obtain 60 eligible study subjects (20 with treatment-resistant depression, 20 with treatment responsive depression and 20 controls with no depression). The screening visit and baseline visit are simultaneous, and labs will be drawn if the subject passes the psychiatric assessments and qualifies per above criteria. ○ A physical examination, medical history and urine toxicology

- Psychiatric assessments: SCID and MADRS ○ MGH Anti-depressant history form
- If qualified based on psychiatric assessment, blood draw for ALT, creatinine, cbc, thyroid function tests
- Additional aliquots will be drawn for future testing of allopregnanolone and other hormones **Aim 2**

Screening Visit (n=20): A screening visit will take place to determine eligibility for enrollment. Participants will be asked to complete the MGH ATRQ and sign release of information forms to request documentation from prescribing clinicians.

Screening visit testing will include:

- Complete medical history ○ Physical examination, including height, weight and vital signs ○ 0800h Blood draw for ALT, AST, bilirubin, creatinine, CBC, thyroid stimulating hormone (TSH) and FSH
- Urine toxicology
- Urine pregnancy test in women <55 years of age ○ Diagnostic interview with SCID ○ MDD symptom assessment with MADRS
- Completion of the MGH ATRQ

If antidepressant-resistance is confirmed following screening procedures, the subject will be scheduled for a baseline visit approximately 1-2 weeks later.

Baseline Visit for the Ganaxolone Augmentation Study (n=10): Eligible subjects will undergo baseline testing immediately before the augmentation phase of the protocol.

Baseline visit testing will include the following. However, the safety labs will not be repeated if the Baseline visit occurs within 6 weeks of the screening visit.

- Weight, vital signs, waist-to-hip ratio, and consumptive habits (alcohol, caffeinated beverages) will be recorded.
- Electrocardiogram
- Neuroactive steroid panel, including allopregnanolone, morning blood cortisol, late night salivary cortisol and 8 a.m. salivary cortisol
- Depression efficacy endpoints: MADRS, HAM-D, IDS-SR and SDQ ○ Cognitive Functioning: CPFQ
- Persistent/residual symptom assessment: SF-36, BFI, ESS, FSS, DISF, SFQ, GAD-7 ○ Safety assessments: SAFTEE-SI and CHRT ○ We will distribute the Study Drug Compliance and Hot Flash Diary ○ Cognitive testing (Probabilistic Reward and Pattern Separation Tasks) will be performed

Follow-up Visits (Ganaxolone Augmentation Phase): Subjects will then receive Ganaxolone therapy. In the case of a drop out, subjects will be asked to come in for an optional close-out visit. This visit will include all of the week 8 measures. Follow-up visits will take place at weeks 1, 2, 4, 6 and 8 post-baseline.

- Follow up visits will include:
- Weight and vital signs will be recorded (weeks 1,2, 4, 6, 8 and 10); electrocardiogram will be performed in any subject with bradycardia (HR<60) or tachycardia (HR>100)
 - Waist-to-hip ratio (week 8)
 - Depression: MADRS, IDS-SR, CGI-S, CGI-I, SDQ (weeks 2, 4, 6, 8 and 10),

- HAM-D (week 8 only) ○ Cognitive Functioning: CPFQ (weeks 2, 4, 6, 8 and 10)
- Persistent/residual symptom assessment: SF-36, BFI, ESS, FSS, DISF, SFQ, GAD-7 (weeks 2, 4, 6, 8 and 10) ○ Safety: SAFTEE-SI, CHRT (weeks 2, 4, 6, 8 and 10) ○ Salivary cortisol (week 8)
- Medication management sessions (weeks 2, 4, 6 and 8) ○ Neuroactive steroid panel (week 8)
- Blood draw for ALT, AST, bilirubin (week 8)
- We will distribute the Study Drug Compliance and Hot Flash Diary (weeks 2, 4, 6, and 8) ○ Cognitive testing (Probabilistic Reward and Pattern Separation Tasks) will be performed (week 8 only)
- Measurement of ganaxolone levels

Taper: After the 8-week visit, subjects receiving [REDACTED]

[REDACTED] A 10-week visit will be performed and will include:

- Vital signs ○ Safety: SAFTEE-SI, CHRT ○ Depression: MADRS, IDS-SR, CGI-I
- Persistent/residual symptom assessment: SF-36, BFI, ESS, FSS, DISF, SFQ, SDQ, GAD-7

3-Month Follow Up Questionnaires: Three months after the 10-week visit or last visit completed, subjects will be sent the following questionnaires to complete: ○ IDS-SR, BFI, SDQ, GAD-7

Blood collection

Aim 1

154 mL of blood will be drawn at the one study visit for Aim 1

Aim 2

Subjects will complete a blood draw at all study visits except the week 1 and week 10 visits. This will total 526mL of blood over the approximate 10-week study period from screening to the final visit

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Subjects being studied in this protocol will still have at least moderate depression. Standard care alternatives are presented in the Consent form. Subjects at MGH are offered three months of free medication management clinic services for depression treatment after completion of a clinical trial such as this one. Research staff will assist in arranging subsequent treatment by providing referrals and communications to subsequent providers.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The procedures to protect against or minimize potential risks include the following: (1) the assignment of unique study subject numbers to patients, (2) the use of these primary identifiers throughout the study, (3) storage of information in locked file cabinets, and (4) access limited to study personnel for these file cabinets and data.

We have set up exclusion criteria to minimize risks:

- Subjects must be medically stable as defined in this protocol.
- We exclude people who may be considered particularly vulnerable in clinical trials, including those at acute risk for suicide, those with active substance abuse or dependence, and those with psychosis (or treated with antipsychotic medications).
- Because we are investigating the efficacy of a hormone, it will be important to exclude patients with other endocrine abnormalities which could contribute to treatment resistance or with a changing endocrine status.

Study Subjects will be discontinued from the study if they:

- a. Score a 6 or 7 on the CGI-I on 2 consecutive study visits

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Suicide Prevention: Suicidal ideation will be assessed by the Beck Suicide Index at each visit. Patients who develop active suicidal ideation, or who are felt by the study clinician to be at high risk for suicide, will be discontinued from the study and referred for hospitalization and further treatment if clinically indicated. In addition, each study subject will be extensively interviewed at each study visit by a highly trained psychiatrist, who not only has extensive experience in the treatment of major depression, but also with these issues in the setting of clinical trial protocols. Patients in research protocols have much more access to psychiatrists than patients in the community, as a study psychiatrist is available by pager 24 hours per day. Moreover, the studies are performed in hospitals in which patients can be immediately admitted, if necessary to ensure safety.

Drug Safety:

Women with treatment-resistant depression will be administered Ganaxolone (██████████). A determination will be made at the one-week visit as to whether the Ganaxolone dose will be escalated (██████████). This will be based on tolerability and absence of side effects, including the presence of sedation and dizziness, which will be specifically asked about. The dose will not be escalated if a subject has experienced either of these – or other significant side effects. Rather, such subjects will be maintained on the lower dose (██████████). Subjects receiving (██████████) who experience daytime drowsiness may be subsequently reduced (██████████). If drowsiness continues on this lower dose, the dose will be reduced

██████████. A phone call will be made to each subject in whom a dose adjustment is made one week after the dose adjustment to determine if the subject continues to experience continuing side effects. Subjects will be advised to take Ganaxolone with food to maximize medication absorption and to avoid alcohol. In person psychiatric reassessment will occur at 2, 4, 6, 8 and 10 weeks with MADRS. Close monitoring of patients throughout the study will ensure that adverse effects from treatment, exacerbation of symptoms, or emergence of suicidality, mania or psychosis will be promptly recognized so that patients can be treated appropriately. All patients will be instructed on how to contact study clinicians in the case of an emergency. They will also be instructed on how to contact the Acute Psychiatry Service (APS) at MGH, which provides

emergent psychiatric care on a 24h/day basis. They will additionally be offered 3 months of psychiatric follow up through the [REDACTED] if desired.

Every effort will be made to keep patients in the study. Acceptable reasons for early discontinuation include: 1) request of patient, 2) decision of physician, 3) serious adverse event, 4) worsening of depression requiring hospitalization, 5) emergence of hypomania, mania or psychotic symptoms.

A Data Safety Monitoring Board will review safety data, including adverse events, twice-a-year and will be available in the interim to consider any urgent matters.

[REDACTED]

[REDACTED]
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[REDACTED]

Risks of blood sampling: Blood sampling is performed in the study, and there is always a very minor risk of infection, bruising, or syncope during a blood draw. There is also the discomfort of having one's blood drawn.

Discomforts with Questionnaires: Answering detailed questionnaires may create some inconvenience for subjects.

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