Testosterone Antidepressant Augmentation in Women

NCT01783574

Version Date: May 19, 2017

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
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PROTOCOL TITLE
Collaborative Study: Testosterone Antidepressant Augmentation in Women

FUNDING
[redacted]

VERSION DATE
5/19/2017

SPECIFIC AIMS

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

Inadequate response to antidepressant therapy in major depressive disorder (MDD) is disabling and highly prevalent, particularly among women. Although the use of antidepressant augmentation strategies is common, there are few effective therapies and few strategies that have been studied in a rigorous, controlled fashion.

Because studies in other female populations suggest that low-dose testosterone administration (in which testosterone levels are raised within the normal female range) has antidepressant effects with minimal side effects, testosterone is a candidate for a novel augmentation treatment for women with MDD. Preliminary studies from our group demonstrate antidepressant efficacy of low-dose testosterone administration in women with inadequate response to inhibitors of serotonin uptake, as well as in other female relatively androgen-deficient populations. We propose to test the efficacy and tolerability of testosterone as an augmentation treatment for depressed women with inadequate response to antidepressant therapy in a randomized, placebo-controlled trial, which, if positive, will form the basis of a future, large, randomized, controlled trial.

An additional potential benefit of testosterone therapy is that it targets two specific persistent/residual symptoms of MDD – fatigue and sexual dysfunction. Fatigue/loss of energy and reduced libido/sexual function are common symptoms associated with MDD and ones for which few effective therapies are available. Moreover, data suggest that libido and sexual function may be independently and adversely affected by antidepressant therapy administration in a substantial subset of women. Our preliminary data suggest that low-dose testosterone may be an effective therapy for these two target symptoms in depressed women with partial/nonresponse to antidepressant therapy. In addition, data suggest that low-dose testosterone therapy increases energy and improves libido and sexual function in women. However, the specific therapeutic potential of low-dose testosterone augmentation has not been tested with a randomized, placebo-controlled study in MDD women with inadequate response to antidepressant therapy.

Rigorous, randomized, placebo-controlled trials are necessary to determine whether low-dose testosterone augmentation will be an effective treatment for depression in women with inadequate response to antidepressant **therapy**. In this application, a double-blind, placebo-controlled trial of adjunctive low-dose testosterone for inadequate response to antidepressant **therapy** among MDD women is proposed.

Specific Aim 1. Low-dose testosterone augmentation improves depressive symptoms in women with MDD and partial/nonresponse to antidepressant therapy.

Aim 1A. We will investigate in female antidepressant therapy partial/nonresponders whether low-dose testosterone augmentation for 8 weeks leads to a significantly greater reduction in depressive symptoms than placebo.

Aim 1B. We will investigate whether a key mechanism underlying the effects of testosterone administration on depressive symptoms is an increase in neuroactive testosterone metabolites, including 3alpha-diol.

Specific Aim 2. Adjunctive low-dose testosterone is safe and well-tolerated in women with MDD and partial/nonresponse to antidepressant therapy. We will investigate whether low-dose testosterone augmentation therapy for 8 weeks is safe and well-tolerated in female antidepressant therapy partial/non-responders compared to placebo.

Specific Aim 3. Low-dose testosterone augmentation improves two specific RDoC construct symptoms (in the Arousal/Physiologic Processes Domain) in women: fatigue and sexual dysfunction. We will investigate in female antidepressant therapy partial/nonresponders whether low-dose testosterone augmentation for 8 weeks improves associated fatigue and sexual dysfunction compared to placebo.

Specific Aim 4. Low-dose testosterone therapy in women with treatment resistant depression will cause functional changes in the brain. We will investigate the mechanisms and functional neuroanatomy of the effects of testosterone on different regions of the brain in women with treatment resistant depression. This will serve as preliminary data for future studies and grants.

Exploratory Aim: We will investigate androgen and other hormonal correlates of functional and structural neuroanatomy in women with treatment resistant depression compared with healthy, non-depressed controls. This will serve as preliminary data for future studies.

Specific Aim 5. **Androgen and neuroactive steroid levels will be lower in postmenopausal women with treatment resistant depression than in healthy controls.**

We will investigate androgen and neuroactive steroid levels in postmenopausal women with treatment resistant depression in comparison to androgen and neuroactive steroid levels in postmenopausal healthy controls without significant psychiatric disease.

BACKGROUND AND SIGNIFICANCE

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

Although a number of potential augmentation strategies for MDD patients with partial/nonresponse to antidepressant therapy have been studied, few have been shown to be effective and fewer have acceptable side-effect profiles. The development of low-dose physiologic testosterone therapy for women is an innovative and potentially important approach to the prevalent problem of partial/nonresponse to antidepressant therapy among women with MDD. This is an approach that has never been pursued previously in any double-blind, randomized fashion. Furthermore, examination of the effects of experimental manipulation of peripheral gonadal hormone concentrations on RDoC candidate constructs (anergia/fatigue and

sexual dysfunction) within the domain of Arousal/Regulatory Processes reflects an innovative approach. The RDoC perspective we propose involves focus on these constructs independent of depression diagnosis, to generate data that may contribute to a larger body of findings supporting new ways of classifying mental disorders based on observable behavior and neurobiological measures. The classic gonadal steroid dichotomous paradigm (estrogens as the female hormone/testosterone as the male hormone) has only recently been understood to be an oversimplified framework. Although testosterone levels in women (and estrogen levels in men) are much lower than that in the opposite sex, there is increasing evidence that their role in the regulation of brain function may be important. This new area of investigation is an innovative approach that may have important clinical implications and may identify new potential targets for drug development in MDD. Investigation of neuroactive, GABAergic steroid metabolites of testosterone as a possible mechanism responsible for brain effects is another innovative component.

Partial/nonresponse to antidepressant **therapy** is extremely prevalent in the U.S., disproportionally affects women, and is associated with substantial morbidity and functional impairment. An effective, well-tolerated therapy would have a significant impact on public health. Antidepressant treatments with novel mechanisms of action and benign side effect profiles are needed. Preliminary data suggest that low, physiologic doses of testosterone may be effective to improve mood among women with partial/nonresponse to antidepressant therapy, yet with few side effects. If these preliminary findings are confirmed, results from the proposed study would form the basis for a larger, multi-center trial with active comparators to definitively establish that low-dose testosterone augmentation in women with antidepressant therapy partial/non-response is effective, well tolerated and exerts durable effects on mood in antidepressant-treated women with MDD, through effects on neuroactive steroids.

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."

Study Design: After antidepressant therapy partial or nonresponse is established by documentation of failure to at least 8 weeks' treatment with an adequately dosed antidepressant therapy, A minimum of 100 subjects study-wide (60 from MGH) with MADRS≥12 will enter the double-blind augmentation randomized-placebo-controlled treatment study. 50 of these subjects will be on active study drug and 50 will be control subjects on placebo. Eligible subjects will undergo baseline assessment of symptoms and biological measures and then be randomized to 1 of 2 groups: low-dose physiologic testosterone augmentation by transdermal preparation [redacted] or placebo. Antidepressant dose will be held steady during the trial. Outcome measures will examine the antidepressant efficacy of physiologic testosterone treatment (Aim 1), its tolerability (Aim 2) and its effects on 2 specific RDoC symptoms (Aim 3).

Subject Enrollment: A total of 330 women will be enrolled study-wide, of which 100 women with antidepressant-resistant MDD and 50 women with no psychiatric history will be eligible study-wide. Study subjects for the depressed population will be women, ages 21-75 with failure to remit following at least 8 weeks antidepressant trial documented by past treatment history. [redacted]

[redacted] In addition, 20 healthy controls without depression will be recruited for the fMRI substudy healthy control population.

Up to 60 postmenopausal women who do not have current or past psychiatric disorders will also be screened to obtain 30 women who will be enrolled [redacted] as healthy controls.

Randomized Study Subject Population (n=60)

Inclusion Criteria for Randomized Study Subjects:
1. Female, age 21-75, who provide written informed consent
2. Free testosterone level no higher than the third quartile of the normal range
3. Meet DSM-IV criteria (by SCID) for current Major Depressive Disorder and have MADRS≥12
4. Currently treated with an antidepressant (1^{st}, 2^{nd} or 3^{rd} trial in current episode), that has been taken at an adequate dose[103] for at least eight weeks with sufficient source documentation to confirm high level of confidence in treatment details (using the MGH ATRQ). Current treatment may include a combination therapy as long as the subject has not exceeded three failed trials in the current episode.
5. Persistent depression symptom burden of the same dose of the currently (ineffective) antidepressant therapy, evidenced by MADRS≥12.

Exclusion Criteria for Randomized Study Subjects**:**
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, or clinical suspicion of ongoing substance use disorder at the discretion of the study clinician at time of screening based on history and/or laboratory results.
4. Any history of psychotic features, bipolar disorder, or primary obsessive compulsive disorder, as assessed by SCID
5. Untreated hypothyroidism. If treated hypothyroidism, change in levothyroxine dose within the prior 3 mos
6. Use of androgens, including testosterone, DHEA and methyltestosterone, within the prior three months
7. Any investigational psychotropic drug within the last 30 days
8. 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)
9. Alanine aminotransferase (ALT) > 3x upper limit of normal or creatinine> 3x upper limit
10. History of a hormone-responsive cancer
11. History of testosterone abuse
12. Almond allergy (AndroFeme contains almond oil)
13. History of hypercalcemia or thromboembolism
14. Women who are breastfeeding
15. Pregnant women, women who desire to become pregnant, or women of child bearing potential who are not using a medically accepted means of contraception (to include condom, diaphragm, spermicide, intrauterine device, tubal ligation, or partner with vasectomy)

Additional Exclusion Criteria for Randomized study subjects in fMRI Substudy Only (n=20)

Exclusion criteria for the fMRI substudy participants include routine MRI exclusion criteria as listed below:

- Cardiac pacemaker
- Surgical aneurysm clips
- Neurostimulator
- Implanted pumps
- Metal fragments in body / eyes
- Pregnancy
- Nitroglycerin patch (if non-removable)
- Weight >250
- Severe claustrophobia

Healthy Control fMRI Population (n=20)

Inclusion criteria for fMRI Healthy Control Subjects

- Match a randomized subject based on:
    - Age (+/- 2 years)
    - BMI (+/- 2 kg/m^2)
    - Hormonal status

Exclusion criteria for fMRI Healthy Control Subjects

- Any history of psychiatric illness including major depressive disorder, bipolar disorder, psychotic features, or obsessive compulsive disorder, as assessed by SCID
- Current or prior use of any psychiatric medications
- Current or prior substance use disorder
- Unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic
- Hypothyroidism
- Use of androgens, including testosterone, DHEA and methyltestosterone, within the prior three months
- Abnormal alanine aminotransferase (ALT) or creatinine
- Women who are breastfeeding
- Pregnant women, women who desire to become pregnant, or women of child bearing potential who are not using a medically accepted means of contraception (to include condom, diaphragm, spermicide, intrauterine device, tubal ligation, or partner with vasectomy)
- Additional Routine MRI exclusion criteria as listed below:
    - Cardiac pacemaker
    - Surgical aneurysm clips
    - Neurostimulator
    - Implanted pumps
    - Metal fragments in body / eyes
    - Nitroglycerin patch (if non-removable)
    - Weight >250
    - Severe claustrophobia

Inclusion Criteria for Healthy Controls:

1. Female, age 50-75, who provide written informed consent
2. Free of lifetime psychiatric medication use
3. Postmenopausal, defined as amenorrhea for greater than one year and/or elevated FSH for women with prior hysterectomy

Exclusion Criteria for Healthy Controls:

1. Unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic
2. Current or past Axis I psychiatric or substance use disorder (non-prescribed medications, recreational drugs, or alcohol)
3. Use of androgens, including testosterone, DHEA and methyltestosterone, within the prior three months

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 for randomized subjects

Screening Visit: 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. It is estimated that after review of detailed source documents describing past treatment details, 60 women will be confirmed to have partial/nonresponse to antidepressant therapy and be eligible for the randomized, placebo-controlled phase. Screening visit testing will include:

- complete medical history
- physical examination, including height and weight
- 0800h Blood draw for ALT, creatinine, CBC, thyroid stimulating hormone (TSH), free testosterone, FSH, urine pregnancy and toxicology
- 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.

Baseline Visit for the Randomized, Placebo-Controlled, Augmentation Study: Eligible subjects will undergo baseline testing immediately before the augmentation phase of the protocol. Baseline visit testing will include the following. However, the blood draw will not be repeated if the Baseline visit occurs within 2 weeks of the screening visit.

- Weight, vital signs, waist-to-hip ratio, and consumptive habits (alcohol, caffeinated beverages) will be recorded
- Urine pregnancy test (for premenopausal women only). Postmenopausal is defined as at least one year since last menses and FSH in the postmenopausal range
- Baseline endocrine blood testing: free testosterone, estradiol, neuroactive steroid panel, DHEAS, blood cortisol, late night salivary cortisol and 8 a.m. salivary cortisol
- Baseline safety blood testing: ALT, creatinine, CBC
- Depression: MADRS, IDS-SR, CGI-I, S
- Cognitive Functioning: CPFQ
- Persistent/residual symptom assessment: SF-36, BFI, ESS, FSS, DISF
- Safety assessments: SAFTEE-SI, CHRT, and hirsutism and skin assessments
- We will distribute the Study Drug Compliance and Hot Flash Diary or Menopausal Symptom Diary

- We will also collect DNA to be banked for a future exploratory study into whether androgen receptor CAG repeat length moderates androgen-behavior relationships (based on data by Seidmanet *et al.*).

Follow-up Visits (Placebo-Controlled Augmentation Phase): Subjects will then be randomized to receive low-dose testosterone or placebo. Follow-up visits will take place at weeks 2, 4, 6 and 8 post-baseline. Follow up visits will include:

- Urine pregnancy test (for premenopausal women only). Postmenopausal is defined as at least one year since last menses and FSH in the postmenopausal range (weeks 2, 4, 6 and 8)
- Free testosterone levels (weeks 2, 4, 6 and 8)
- Skin evaluations to monitor for side effects (weeks 4 and 8)
- Weight and vital signs will be recorded (weeks 4 and 8)
- Waist-to-hip ratio (week 8)
- Depression: MADRS, IDS-SR, CGI-I, S (weeks 2, 4, 6 and 8)
- Cognitive Functioning: CPFQ (weeks 2, 4, 6 and 8)
- Persistent/residual symptom assessment: SF-36, BFI, ESS, FSS, DISF (weeks 2, 4, 6 and 8)
- Safety: SAFTEE-SI, CHRT (weeks 2, 4, 6 and 8)
- Estradiol levels (weeks 2, 4, 6 and 8)
- Salivary cortisol (week 8)
- Medication management sessions (weeks 2, 4, 6 and 8)
- Neuroactive steroid panel (week 8)
- We will distribute the Study Drug Compliance and Hot Flash Diary or Menopausal Symptom Diary (weeks 2, 4, 6, and 8)

fMRI Substudy Visits for Randomized Subjects

- fMRI substudy participants will be further evaluated at the screening visit for suitability to undergo MRI using the Martinos Center Patient/Volunteer Screening Form.
- Subjects will undergo urine pregnancy tests throughout the study as noted above.
- One hour fMRI sessions will be scheduled at baseline before intervention occurs and at 8 weeks (weeks 0,8)
- Subjects will be administered the IDS-SR, FSS and BFI before each scan (weeks 0, 8)
- A blood draw to measure blood hormone levels on the day of the fMRI scan will occur at both the baseline and 8 week scanning visit.

<u>fMRI Healthy Control Substudy Visits</u>

Screening visit: A screening visit will take place to determine eligibility for enrollment and ensure that subjects meet inclusion and exclusion criteria. Twenty women with no history of depression or other psychiatric illness will be eligible for the baseline fMRI scan. Screening visit testing will include:

- Complete medical history
- Diagnostic interview with SCID
- Physical examination, including height and weight
- Morning blood draw for ALT, creatinine, CBC, thyroid stimulating hormone (TSH),

free testosterone, FSH, and urine pregnancy test

If a subject is found to be eligible following screening procedures, the subject will be scheduled for the baseline fMRI visit in approximately 1-2 weeks.

Baseline fMRI Healthy Control Visit:

Healthy control subjects will receive one fMRI scan at this visit. Other study procedures include:

- Urine pregnancy test
- Study questionnaires: IDS-SR, FSS and BFI
- A blood draw to measure blood hormone levels on the day of the fMRI scan will occur at both the baseline and 8 week scanning visit.

Healthy control Visits

Screening Visit (n=60): A "Screening Visit" will be conducted to determine eligibility. It is estimated that 60 women will need to be screened to obtain 30 eligible study subjects.

The screening visit will include:

- Abbreviated SCID
- Medical and psychiatric history including past psychiatric medication use

Baseline Visit (n=30): The baseline visit will occur if subjects are found eligible.

Baseline visit will include:

- Psychiatric assessments: MADRS, IDS-SR, CGI-I, S, CPFQ, SF-36, BFI, ESS, FSS, DISF, SAFTEE-SI, CHRT
- Height, weight, vital signs, waist-to-hip ratio, and consumptive habits (alcohol, caffeinated beverages) will be recorded
- Salivary cortisol
- Blood for androgens including total testosterone, free testosterone, neuroactive steroid levels, including allopregnanolone, and cortisol, and other hormones

[redacted]

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: We will measure free testosterone levels every two weeks and decrease the dose to 5 mg (0.5 ml) in any subject with a free testosterone level of more than 2x the upper limit of normal for females at one visit or 1.5x the upper limit of normal at two visits. If the free testosterone level remains above the same limits listed above after the initial dose decrease, the dose will be decreased to 2.5mg (0.25ml). In order to ensure success at raising levels during the

trial, dose increases by 5 mg increments (0.5 ml) daily will be made in subjects in whom the free testosterone level is less than the mean for age at any visit.

Safety: Patients will be carefully monitored by clinicians for side effects and potential toxicities with hirsutism and skin assessments. The blood draws will be performed by trained staff who have certificates documenting their ability to draw blood. We are performing a physical examination and routine laboratory tests prior to allowing anyone to enter the randomized phase of the protocol to ensure that subjects are medically stable. 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 following study discontinuation. 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 and the Patient Assessment Services (PAS) at Butler Hospital, which provide emergent psychiatric care on a 24h/day basis.

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, 6) pregnancy.

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

[redacted]

Close skin contact with the area of application within an hour of application by a partner or child should be avoided.

AndroFeme contains almond oil. Therefore, individuals with almond allergies may be allergic to this preparation.

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.

[redacted]