Testosterone Antidepressant Augmentation in Women

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Study Endpoints and Data Analysis

Specific Aim 1: We will investigate in women with partial/nonresponse to antidepressant therapy whether low-dose testosterone augmentation leads to a significantly greater reduction in depressive symptoms compared to a placebo group over an 8-week period.

Experimental Strategy and Endpoints: To investigate the effects of physiologic testosterone augmentation on antidepressant therapy partial/nonresponse, 50 women with partial/nonresponse to antidepressant therapy randomized to testosterone augmentation and 50 to placebo in the 8-week randomized, double-blind placebo controlled study delineated in the "Overall Protocol", will be compared. Depressive symptom endpoints will be measured at baseline and weeks 2, 4, 6 and 8. **The primary endpoint will be MADRS score in weeks 2-8.**

- **These data will determine the effects of low-dose testosterone augmentation on depressive symptoms in women with partial/nonresponse to antidepressant therapy.**

Data Analysis: For Aim 1, the data will be analyzed using a mixed-effect linear regression model. The randomization will be stratified by site, estrogen use, and one vs. more than one adequate antidepressant therapy trial. The model will specify a baseline MADRS score and baseline non-responder vs. partial responder as covariates and then an "on treatment score," which is the score from weeks 2 through 8. The following will be entered into the model as covariates: baseline non-responder vs. partial responder, one vs. more than one adequate antidepressant therapy trial, baseline free testosterone level, baseline age and site (MGH or Butler Hospital). The on treatment score will have a fixed treatment effect and a random patient effect. We will examine interactions between menopausal status and effect to determine whether menopausal status moderates the treatment effect. This model is the same as in a repeated measures analysis of (co)variance with the assumption of compound symmetry. Our pilot data shown in Figure 2 fits this model. Specifically, based on our preliminary data, we expect a rapid improvement in depression severity by 2 weeks followed by maintenance of the effect of the subsequent 6 weeks. One advantage of this method is that it allows us to use data from patients who drop out early despite our plans to obtain follow-up data on all patients randomized and analyze all data obtained. A subject who drops out in the middle of the study will add data to the analysis. The drop-out rate should be low due to the relatively short duration of the study and the anticipated low side effect profile, the latter as confirmed in our pilot study in this population in which we had no drop-outs over the 8-week period. This model assumes that the drop-outs are missing at random. We will attempt to obtain 8-week observations on all patients, including drop-outs. Sensitivity analysis will be performed to determine whether our conclusions are sensitive to this assumption (185). **Secondary analyses** will determine whether the response of depressive symptoms to testosterone is affected by baseline androgens and neuroactive metabolites (including free testosterone level, DHEAS, and 3α-diol), estradiol, blood cortisol, late night cortisol and 8 a.m. salivary cortisol, and changes in the same variables over the 8-week period. Pre-treatment free testosterone level will be entered into the model as a covariate along with a treatment baseline interaction. Other covariates that will be explored will be age, menopausal status, baseline MADRS score, change in estradiol levels, change in free testosterone levels and BMI. As a secondary

endpoint, we will determine the 8-week remission rate in an exploratory analysis. Remission will be defined as MADRS score<10. Comparison of ratios of remitters to the total number of study participants in the testosterone and placebo groups will be compared using a Fisher Exact test. Another secondary endpoint will be effects of testosterone on functional measures. The same methods as described for MADRS score analyses will be used to analyze functional measures, including the SF-36.

For Aim 1B, the primary analysis will be to determine whether the neuroactive metabolite of testosterone, 3α-diol, is an important determinant of the effects of testosterone on our primary endpoint, MADRS score. We expect to be able to distinguish the effect of 3α-diol from the effect of an increase in serum free testosterone levels because we expect the relative levels of the two hormones will differ, i.e. we expect that some study subjects will convert a greater proportion of testosterone to the 3α-diol metabolite than other study subjects. Analyzing the effect of both free testosterone and 3α-diol on the outcome (MADRS score) by linear regression, we hope to determine the relative importance of each hormone as a determinant of outcome. It is conceivable that both will correlate with the MADRS score, simply reflecting absorption of testosterone, and it is also possible that one will correlate with MADRS score, and the other will not. For instance, if the coefficient of the metabolite 3α-diol in a regression of outcome on 3α-diol and free testosterone is large while that of free testosterone is small, then we would conclude that the active factor is 3α-diol rather than free testosterone. If the correlation coefficient between the two of these is large, we would not have data to make a determination of which is active.

Specific Aim 2: We will investigate in women with partial/nonresponse to antidepressant therapy whether adjunctive low-dose testosterone is safe and well-tolerated in women with partial/nonresponse to antidepressant therapy.
Experimental Strategy and Endpoints: To investigate whether adjunctive physiologic testosterone is safe and well-tolerated over the 8-week protocol, we will compare rates of adverse events in subjects randomized to testosterone augmentation to those receiving placebo using the SAFTEE-SI. These endpoints will also include increases in ALT and hirsutism and skin assessment scores and decreases in HDL cholesterol. **The primary endpoint will be adverse effect rate.**

- **These data will determine whether adjunctive physiologic testosterone is safe and well-tolerated in women with relative partial/nonresponse to antidepressant therapy**.

Data Analysis: Rates for each adverse effect will be computed by group. Differences between treatment groups in dropout rates will be examined using a Fisher's Exact test, though every effort will be made to retain subjects through the 8-week course. If a trend ($p < .10$) indicative of differential dropout is detected, a more detailed survival analysis will be completed to illustrate the timing and magnitude of these differences.

Specific Aim 3: Low-dose testosterone augmentation improves persistent/residual symptoms in women with antidepressant-resistant depression.
Experimental Strategy and Endpoints: To investigate the effects of low-dose testosterone augmentation on fatigue and energy in women with antidepressant-resistant depression, the 50 women with antidepressant-resistant depression

randomized to testosterone augmentation and 50 to the placebo arm of the 8-week randomized, double-blind placebo controlled study delineated in the “Overall Protocol”, will be compared. Energy/fatigue and sexual function/libido endpoints will be measured at baseline and weeks 2, 4, 6 and 8. **The primary endpoint will be BFI score weeks 2-8.**

- **These data will determine the effects of low-dose testosterone augmentation on fatigue and sexual function in women with antidepressant-resistant depression.**

Data Analysis: The data will be analyzed using a mixed-effect linear regression model, using methods and assumptions as in Specific Aim 1 Data Analysis, above.