

Low-dose Transdermal Testosterone Augmentation Therapy Improves Depression Severity in Women

Karen K. Miller, MD, Roy H. Perlis, MD, MSc, George I. Papakostas, MD, David Mischoulon, MD, PhD, Dan V. Iosifescu, MD, MSc, Danielle J. Brick, BA, and Maurizio Fava, MD

ABSTRACT

Background: Inadequate response to antidepressant monotherapy in women with major depressive disorder is common. Testosterone administration has been shown to be an effective augmentation therapy in depressed hypogonadal men with selective serotonin reuptake inhibitor-resistant depression. However, the effects of low-dose testosterone as augmentation therapy in women with treatment-resistant depression have not been studied.

Methods: Low-dose transdermal testosterone (300 mcg/day, Intrinsa, Procter and Gamble Pharmaceuticals) was administered to nine women with treatment-resistant depression in an 8 week open-label pilot protocol.

Results: There was a statistically significant improvement in mean Montgomery-Asberg Depression Rating Scale (MADRS) scores at 2 weeks, sustained through the 8 week period. Two-thirds of subjects achieved a response to the treatment (decrease in MADRS score of $\geq 50\%$) and 33% achieved remission (final

FOCUS POINTS

- Inadequate response to antidepressant monotherapy in women with major depressive disorder is common and few effective augmentation therapies have been identified.
- Low-dose transdermal testosterone (300 mcg/day) was an effective augmentation therapy in women with resistant depression in an 8 week open-label pilot protocol; two-thirds of subjects achieved a response to the treatment and 33% achieved remission after 8 weeks of therapy.
- These preliminary pilot data suggest that low-dose transdermal testosterone may be an effective augmentation therapy in women with treatment-resistant depression.

MADRS score < 10) after 8 weeks of therapy. Mean levels of fatigue, as measured by the MADRS lassitude item, significantly decreased at all time points with a mean 38% decrease from baseline to 8 weeks.

Conclusion: These preliminary pilot data suggest that low-dose transdermal testosterone may be an effective augmentation therapy in women with treatment-resistant depression. Further studies are warranted.

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INTRODUCTION

Major depressive disorder (MDD) affects 16.6% of the population and is more prevalent in women.¹ However, a majority of patients will either fail to respond to standard therapy with selective serotonin reuptake inhibitors (SSRIs) or will achieve only a partial response, as confirmed by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which only 30% of patients with MDD achieved remission after 8–12 weeks of SSRI therapy despite adequate dosing.² In addition, the majority of patients with MDD experience fatigue,³ which persists despite treatment in ~one-third of patients.⁴ Therefore, there is a critical need for effective augmentation strategies for women with MDD that result in improvement of depression and associated symptoms, such as fatigue.

Augmentation therapy with testosterone has been demonstrated to be effective in hypogonadal depressed men⁵ but there are no published data in women with MDD who do not respond to standard antidepressants. However, there are data to suggest an anti-depressant effect in women. We have previously shown in randomized, placebo-controlled studies that low-dose transdermal testosterone improves mood in women with hypopituitarism,⁶ which is characterized by severe androgen deficiency. In a one-year randomized, placebo-controlled study, the mean Beck depression score decreased >50% in women receiving testosterone compared with ~25% in women receiving placebo.⁶ We have also demonstrated a decrease in depression severity, as measured by the Beck Depression Inventory, in women with anorexia nervosa and depression.⁷ In addition, Shifren and colleagues⁸ have shown improvements in mood in bilaterally oophorectomized women. A preliminary study of methyltestosterone as augmentation of venlafaxine in the treatment of postmenopausal women with depression showed promising results.⁹ However, this study did not investigate the effects of this therapy in women with refractory depression. We hypothesized that low-dose testosterone therapy would be an effective augmentation therapy in women with treatment-resistant depression and conducted an open-label pilot study to investigate this hypothesis.

METHODS

Nine women, 25–59 years of age, with MDD and a current major depressive episode despite

receiving an adequate dose of an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) for at least one year were studied in an 8 week open-label protocol. The study was approved by the Massachusetts General Hospital Institutional Review Board and all subjects gave informed, written consent before study participation.

Protocol

Study subjects were recruited through advertisements or clinical referral. At the screening visit, a medical history and physical examination were performed. The Structured Clinical Interview for *DSM-IV* (SCID),¹⁰ the SCID Mood Module, the Psychiatric Diagnostic Screening Questionnaire,¹¹ and the Montgomery-Asberg Depression Rating Scale (MADRS)¹² were performed to determine whether potential study subjects fit eligibility criteria. Blood was drawn for measurement of total testosterone, sex hormone-binding globulin (SHBG), estradiol, thyroid stimulating hormone (TSH), free thyroxine, alanine aminotransferase, and creatinine. Urine was collected for measurement of human chorionic gonadotropin. In order to be eligible for the study, subjects were required to meet SCID criteria for a current major depressive episode and to have a MADRS score ≥ 16 despite ongoing treatment with an SSRI or SNRI for at least one year and at an adequate dose for at least six weeks. This MADRS score was chosen as it is the equivalent of the STAR*D study depression severity entry criterion of a minimum score of 14 on the 17 item Hamilton Rating Scale for Depression.²

Eighteen potential study subjects were screened to obtain nine eligible study participants (reasons for exclusion were diagnosis of bipolar disorder, history of psychosis, recent history of alcoholism, change in psychopharmacologic medication or dose within the previous six weeks, and diagnosis of hypothyroidism at the screening visit.) Each eligible subject returned for a baseline visit during which the MADRS and Clinical Global Impressions–Improvement (CGI-I) (patient version)¹³ were performed. Baseline levels of facial hair and body hair were evaluated using the Lorenzo scale.¹⁴ After completion of the baseline visit, each participant received transdermal testosterone 300 mcg (Intrinsa, Procter & Gamble Pharmaceuticals, Cincinnati, OH), in the form of one 300 mcg patch placed on the abdomen and changed twice weekly. This dose is at

the higher end of the estimates of mean daily testosterone production for healthy non-hirsute women, ~100–300 mcg daily.^{15–17} Each subject returned for study visits at 2, 4, and 8 weeks after the baseline visit, during which the MADRS and CGI-I were administered. At these visits, patch sites were examined for patch adherence, compliance, and skin reaction assessment, and all study subjects were interviewed regarding side effects, including specifically the presence of acne or oily skin and whether there had been any change in depilation frequency. At the 8 week visit, the following tests were performed also: testosterone, SHBG, estradiol, and Lorenzo scale hirsutism evaluation.

Laboratory Methods

Total testosterone was measured by radioimmunoassay (Siemens Medical Solutions Diagnostics, Inc, Deerfield, IL) with a sensitivity of 4 ng/dl, and an interassay CV of 5.9% to 12%. The normal range for women of reproductive age is <82 ng/dl. SHBG was measured by a solid-phase two-site chemiluminescent immunometric assay (Immulin 2000, Siemens Medical Solutions Diagnostics, Inc., Deerfield, IL). The analytic sensitivity of this assay is 0.02 nmol/L. The within run CV is 2.3% to 5.3% with a total CV of 4.0% to 6.6% and a normal range in women of 18–114 nmol/L. Free testosterone concentrations were calculated from total testosterone and SHBG serum levels using an equation based on the laws of mass action, which we have shown to be valid and accurate in women.¹⁸

Estradiol was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN) with a normal range of 12.5–498.0 pg/ml in women of reproductive age and of <5.0–54.7 pg/ml in postmenopausal women. The lower detection limit of the assay is 5.0 pg/ml and the total percent CV <7%. TSH was measured by two-site sandwich chemiluminometric immunoassay (ADVIA Centaur, Siemens Medical Solutions Diagnostics, Tarrytown, NY), with a normal range of 0.35–5.50 mIU/L and an analytic sensitivity of 0.004 mIU/L, within run %CV of 2.67–8.95 and run-to-run %CV of 1.18–4.47 for a total of <13%. Free T4 was measured by competitive chemiluminescent immunoassay, with a normal range of 0.89–1.76 ng/dl, analytic sensitivity of 0.1 ng/dl, and a total CV of <7%. Free androgen index was calculated as total testosterone (ng/dl) x 3.47/SHBG (nmol/L).

Statistical Analysis

JMP Statistical Discoveries (Version 4.0.2, SAS Institute, Inc, Cary, NC) was used for statistical analysis. Paired t tests were used to assess the degree of change in scores between baseline and 8 weeks and other time points. Univariate regression analyses were performed using linear fits and Pearson coefficients were reported.

RESULTS

Clinical Characteristics and Endocrine Data

Clinical characteristics and hormone levels are presented in the Table. The mean age of participants was 48.1±12.2 (SD) (range 25–59) years. The mean body mass index was 26.4±6.0 kg/m² (range 21.7–40.7 kg/m²). Six subjects, ≥50 years of age, were post-menopausal (four had undergone natural menopause and two were status/post bilateral oophorectomies). The two subjects who were surgically menopausal were receiving estrogen replacement therapy (one was receiving estradiol 1.5 mg/day and the other conjugated equine estrogens 0.625 mg/day). Three women of reproductive age were also studied; two were experiencing regular menses and one was receiving etonogestrel 0.120 mg/ethinyl estradiol 0.015 mg daily by vaginal ring. No study subjects had adrenal or pituitary disease, and no one was receiving glucocorticoid therapy.

The mean baseline MADRS score was 25.9±4.6 (range 18–32). All study participants had been receiving an adequate and stable dose of an SSRI or SNRI for at least one year prior to study participation, as follows: citalopram 40 mg/day (n=2), paroxetine 20 mg/day (n=1), escitalopram 20 mg/day (n=1), escitalopram 30 mg/day (n=1), venlafaxine XR 150 mg/day (n=2), venlafaxine extended release 300 mg/day (n=1), and duloxetine 120 mg/day (n=1). At baseline, one subject had borderline diabetes mellitus, one had rheumatoid arthritis, one had a history of migraine headaches, one had chronically treated hypothyroidism, one had hypercholesterolemia, and one had hypertension. Study participants were chronically receiving the following prescription medications before the start of the study: benzodiazepines (n=4), dextroamphetamine (n=1), bupropion (n=3), trazodone HCL (n=1), gabapentin (n=1), levothyroxine (n=1), atorvastatin (n=1), sumatriptin (n=1), etanercept (n=1),

leflunomide (n=1), protonix (n=1), oxycodone (n=2), nifedipine (n=1), pantoprazole (n=1), and glyburide (n=1). The subject receiving gabapentin discontinued it prior to the week 4 visit. The patient receiving glyburide took it intermittently and reported both a subjective increase in appetite and increased usage of glyburide during the study. No other study subjects reported any change in any of the above medications or doses during the 8 week study period.

In no case were SSRI or SNRI doses increased during the study. In two cases, doses were decreased during the 8 week study; duloxetine was decreased from 120 to 60 mg/day in one study subject and escitalopram was decreased from 20 mg to 20 mg alternating with 10 mg/day in another subject; the latter dose reduction was instituted due to a side effect (grogginess). In the latter case, five days prior to the 8 week visit (study completion), bupropion slow release 150 mg/day was also added to the study subject's regimen.

The mean serum testosterone concentration at baseline was 14.7±6.5 ng/dl, with an increase to 69.7±57.3 ng/dl at 8 weeks ($P=.012$) (normal range <86 ng/dl). The mean serum free testosterone concentration at baseline was 1.5±0.9 pg/

ml and increased to 5.2±4.9 pg/ml at 8 weeks ($P=.029$). Mean estradiol did not change significantly with testosterone administration over the 8-week period [38.3±67.7 pg/ml (baseline) vs. 30.0±43.9 pg/ml (8-week visit), $P=.62$]. All subjects completed 8 weeks of treatment.

Depression and Fatigue

There was a significant improvement in mean MADRS scores at 2 weeks [25.9±4.6 SD (baseline) vs. 14.7±8.4 (2-week), $P=.002$] that was sustained through the 8-week period [25.9±4.6 (baseline) vs. 15.2±10.9 (8-week), $P=.004$] (Figure 1). Two-thirds of subjects achieved a response to treatment (decrease in MADRS score of ≥50%) and 33% achieved remission (final MADRS score <10) after 8 weeks of therapy. When excluding the data from the subject in whom bupropion was added shortly before the week 8 visit, the decrease in MADRS score from baseline to 8 weeks remained significant ($P=.021$). Five of nine (56%) participants reported a CGI-I (patient version) score of ≤2, indicating "much improved" or "very much improved."

Mean levels of fatigue, as measured by the MADRS lassitude item, decreased significantly by week 2 [3.44±0.88 (baseline) vs. 1.55±1.51 (week 2), $P=.003$] and remained significantly improved compared with baseline levels at week 8 [3.44±0.88 (baseline) vs. 2.33±1.87 (week 8), $P=.031$] (Figure 2). At 8 weeks, fatigue had improved in 56% of participants and 44% of

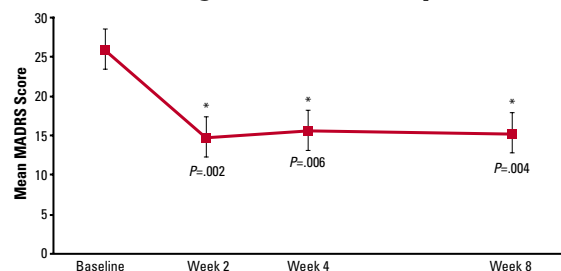
TABLE.
Baseline Clinical Characteristics

Characteristics	Mean	SD	Normal Ranges
Age (years)	48.1	12.2	—
BMI (kg/m ²)	26.4	6.0	18.5–24.9
Number of major depressive episodes	2.4	1.3	—
Onset of MDD (months since)	254	165	—
MADRS score	25.9	4.6	—
Total testosterone (ng/dl)	14.7	6.5	<82
Free testosterone (pg/ml)	1.5	0.9	1.1–6.3
SHBG (nmol/l)	90.2	49.9	12–139
Free T4 (ng/dl)	1.2	0.2	0.9–1.8
T3 (ng/dl)	134.9	31.8	60–181
Number of subjects menopausal/total subjects	6/9	—	—

SD=standard deviation; BMI=body mass index; MDD=major depressive disorder; MADRS=Montgomery-Asberg Depression Rating Scale; SHBG=sex hormone-binding globulin; T4=free thyroxine; T3=triiodothyronine.

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FIGURE 1.
Significant improvement in mean MADRS scores at week 2 was sustained through the 8 week period



* $P<.05$; two-thirds of subjects achieved a response to treatment (≥50% decrease in MADRS score) and 33% achieved remission (final MADRS score <10) after 8 weeks of therapy.

MADRS=Montgomery-Asberg Depression Rating Scale.

Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Iosifescu DV, Brick DJ, Fava M. *CNS Spectr.* Vol 14, No 12. 2009.

subjects had achieved a response to treatment, defined as a decrease in MADRS score of $\geq 50\%$.

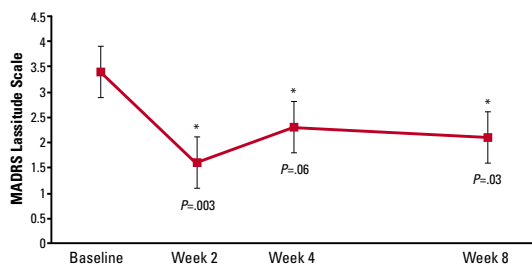
Baseline total testosterone ($R=.84$, $P=.005$) and free testosterone ($R=.68$, $P=.042$) were strong predictors of change in MADRS score; in general, women with lower pre-treatment total or free testosterone levels experienced greater responses in depression severity. Change in total testosterone predicted change in lassitude scale over the 8 week period ($R=-.70$, $P=.038$) but not in MADRS depression severity score. Menopause was a negative predictor of response to testosterone treatment of fatigue, ie women with menopause were less likely to respond ($P=.018$), but it did not predict response for overall depression severity. Change in free testosterone over the 8 week period, age, BMI, or whether study subjects were receiving SSRIs versus SNRIs did not predict the response to testosterone in depressive symptoms or fatigue.

Tolerability

All subjects completed the 8 week protocol. One subject experienced erythema at the patch site, which was not severe enough to cause her to discontinue the study medication. One subject reported a possible increase in oily skin or acne. No other side effects from the medication were noted on exam or reported by the study subjects, including no increase in depilation rate reported by any study subject. There was no significant increase in facial or body hair as measured by the Lorenzo scale ($P=.97$).

FIGURE 2.

Mean levels of fatigue decreased significantly by week 2 and remained significantly improved at week 8



* $P<.05$; 44% of subjects achieved a response to treatment ($\geq 50\%$ decrease in MADRS score) after 8 weeks of therapy.

MADRS=Montgomery-Asberg Depression Rating Scale.

Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Iosifescu DV, Brick DJ, Fava M. *CNS Spectr*. Vol 14, No 12. 2009.

DISCUSSION

In this pilot study, we demonstrate a statistically significant and sustained reduction in depression severity over an 8 week period with low-dose transdermal testosterone in women with treatment-resistant depression. The rate of response of 67% is more than double the response to placebo seen in other studies.^{19,20} However, the absence of a placebo comparison precludes us from drawing any firm conclusion, as randomized, placebo-controlled trials will be necessary to further investigate the efficacy of low-dose testosterone as augmentation therapy in women.

MDD is a highly prevalent disorder with significant morbidity and as many as 70% of patients do not respond to standard treatment despite adequate dosing and duration of therapy.² Therefore, the identification of a potentially effective antidepressant augmentation therapy that is well-tolerated, such as low-dose testosterone in this study, could have important clinical implications.

We also demonstrate that low-dose transdermal testosterone therapy may improve fatigue in women with treatment-resistant depression. Fatigue and loss of energy are very common residual symptoms^{3,4} in patients with MDD and may be more prevalent in depressed women than men.²¹ Although such symptoms may improve with SSRI treatment, fatigue remains a significant concern in one-third of patients in whom depressive symptoms respond.⁴ Psychostimulant augmentation has shown efficacy in some studies but can have significant side effects.^{3,22-25} Additional effective options to improve energy in such patients are needed. Higher dose testosterone therapy improves fatigue in hypogonadal²⁶ and HIV-infected men,^{27,28} and we have shown significant efficacy of low-dose transdermal testosterone therapy in women with hypopituitarism.⁶ Therefore, our findings in this study are consistent with data in these other populations.

Fifty percent of women with MDD report diminished libido and sexual function.²⁹ Although these symptoms may improve in concert with depressive symptoms, SSRIs appear to exert independent deleterious effects on sexual function.^{30,31} There are no established effective treatments for these effects in women, which may cause significant distress and affect compliance with antidepressants.³¹ Higher testosterone doses appropriated for treatment in men have

been shown to improve libido and sexual function in hypogonadal men,³² forming the basis of trials with lower doses in women. Trials of low-dose testosterone using the preparation we used in this study have been shown to improve libido and sexual function in women with surgical and natural menopause, with few side effects over periods of up to 12 months.^{8,33-38} We have demonstrated improvements in these areas in women with hypopituitarism.⁶ Therefore, studies are warranted to investigate whether low-dose testosterone is effective to improve libido and sexual function in women with treatment-resistant depression.

It is interesting to note that our data suggest that women with lower pre-treatment androgen levels may be more likely to experience beneficial effects of testosterone administration on depression than those with higher levels. In addition, mean pre-treatment androgen levels were in the lower end of the normal range for our small, but unselected, group of women with treatment-resistant depression. This raises the question of whether relative androgen deficiency could play a role in the etiology of treatment resistance. In addition, it would be important in future studies to investigate whether menopausal status, age, BMI, or concurrent administration of oral or transdermal estrogens influence the response to low-dose testosterone. For example, one could hypothesize that oral estrogens, by increasing SHBG and thereby decreasing circulating free testosterone levels, would diminish the effectiveness of testosterone therapy. Large, randomized, placebo-controlled studies have shown that the preparation used in this study is similarly effective at treating female sexual dysfunction in women of reproductive age with bilateral oophorectomies,^{8,34,37,38} naturally postmenopausal women receiving estrogens,³³ and naturally postmenopausal women not receiving concurrent estrogen therapy.³⁵ However, whether baseline demographic factors, hormone levels, or medications that affect testosterone metabolism or SHBG, and therefore free androgen levels, would modulate the effects of testosterone administration on depression symptomatology or residual symptoms in women with treatment-resistant depression is unknown and an important focus for future studies.

CONCLUSION

In conclusion, we have demonstrated significant efficacy of low-dose testosterone transdermal therapy in women in this preliminary, open-label

pilot study as an augmentation therapy to reduce depression severity and fatigue. Importantly, the treatment was well-tolerated without significant short-term side effects, resulting in 100% compliance and protocol completion over the 8 week study period. Randomized, placebo-controlled studies are warranted to confirm these findings, to determine the tolerability of this preparation when used for longer periods of time, and to determine whether low-dose transdermal testosterone therapy is effective for decreased libido and sexual function in women with treatment-resistant depression and associated symptoms. **CNS**

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
2. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163:28-40.
3. Fava M. Symptoms of fatigue and cognitive/executive dysfunction in major depressive disorder before and after antidepressant treatment. *J Clin Psychiatry*. 2003;64(Suppl 14):30-34.
4. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry*. 1999;60:221-225.
5. Pope HG, Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JL. Testosterone Gel Supplementation for Men With Refractory Depression: A Randomized, Placebo-Controlled Trial. *Am J Psychiatry*. 2003;160:105-111.
6. Miller KK, Biller BM, Beauregard C, et al. Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2006;91:1683-1690.
7. Miller KK, Grieco KA, Klibanski A. Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab*. 2005;90:1428-1433.
8. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med*. 2000;343:682-688.
9. Dias RS, Kerr-Correa F, Moreno RA, et al. Efficacy of hormone therapy with and without methyltestosterone augmentation of venlafaxine in the treatment of postmenopausal depression: a double-blind controlled pilot study. *Menopause*. 2006;13:202-211.
10. First M, Spitzer R, Gibbon M, Williams J. *Structured clinical interview for DSM-IV Axis I disorders -- patient edition* (SCID-I/P, version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1995.
11. Sheeran T, Zimmerman M. Factor structure of the Psychiatric Diagnostic Screening Questionnaire (PDSQ), a screening questionnaire for DSM-IV axis I disorders. *J Behav Ther Exp Psychiatry*. 2004;35:49-55.
12. Montgomery SM. Depressive symptoms in acute schizophrenia. *Prog Neuropsychopharmacol*. 1979;3:429-433.
13. Guy W. *ECDEU assessment manual for psychopharmacology, revised*. Rockville, MD: National Institute of Mental Health; 1976.
14. Moncada E. Familial study of hirsutism. *J Clin Endocrinol Metab*. 1970;31:556-564.
15. Bardin CW, Lipsett MB. Testosterone and androstenedione blood production rates in normal women and women with idiopathic hirsutism or polycystic ovaries. *J Clin Invest*. 1967;46:891-902.
16. Kirschner MA, Bardin CW. Androgen production and metabolism in normal and virilized women. *Metabolism*. 1972;21:667-688.
17. Longcope C, Jaffee W, Griffing G. Production rates of androgens and oestrogens in post-menopausal women. *Maturitas*. 1981;3:215-223.
18. Miller KK, Rosner W, Lee H, et al. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. *J Clin Endocrinol Metab*. 2004;89:525-533.
19. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28:156-165.
20. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007;68:826-831.
21. Khan AA, Gardner CO, Prescott CA, Kendler KS. Gender differences in the symptoms of major depression in opposite-sex dizygotic twin pairs. *Am J Psychiatry*. 2002;159:1427-1429.

22. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry*. 2005;66:85-93.
23. Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry*. 2007;19:153-159.
24. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry*. 2000;61:378-381.
25. Thase ME, Fava M, DeBattista C, Arora S, Hughes RJ. Modafinil augmentation of SSRI therapy in patients with major depressive disorder and excessive sleepiness and fatigue: a 12-week, open-label, extension study. *CNS Spectr*. 2006;11:93-102.
26. Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *J Clin Endocrinol Metab*. 1996;81:3578-3583.
27. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. *J Clin Psychopharmacol*. 2004;24:379-385.
28. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry*. 2000;57:141-147; discussion 155-146.
29. Kennedy SH, Dickens SE, Eisfeld BS, Bagby RM. Sexual dysfunction before antidepressant therapy in major depression. *J Affect Disord*. 1999;56:201-208.
30. Zajecka J, Mitchell S, Fawcett J. Treatment-emergent changes in sexual function with selective serotonin reuptake inhibitors as measured with the Rush Sexual Inventory. *Psychopharmacol Bull*. 1997;33:755-760.
31. Fava M, Rankin M. Sexual functioning and SSRIs. *J Clin Psychiatry*. 2002;63(Suppl 5):13-16; discussion 23-15.
32. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 2000;85:2839-2853.
33. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause*. 2006;13:770-779.
34. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med*. 2005;165:1582-1589.
35. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med*. 2008;359:2005-2017.
36. Davis SR, van der Mooren MJ, van Lunsen RH, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause*. 2006;13:387-396.
37. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol*. 2005;105(5 Pt 1):944-952.
38. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*. 2005;90:5226-5233.

Dr. Miller is Director of the Neuroendocrine Research Program in Women's Health in the Neuroendocrine Unit at Massachusetts General Hospital (MGH) in Boston, MA. Dr. Perlis is Medical Director of the Bipolar Clinic and Research Program at MGH. Dr. Papakostas is Director of Treatment-Resistant Depression Studies in the Depression Clinical and Research Center at MGH. Dr. Mischoulon is Director of Research in the Depression Clinical and Research Center at MGH. Dr. Iosifescu is Director of Translational Neuroscience in the Depression Clinical and Research Center at MGH. Ms. Brick is Clinical Research Coordinator in the Neuroendocrine Unit at MGH. Dr. Fava is Director of the Depression Clinical and Research Center at MGH.

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Please direct all correspondence to: Karen K. Miller, MD, Neuroendocrine Unit, BUL 457B, Massachusetts General Hospital, Boston, MA 02114; Phone: 617-724-7388, Fax: 617-726-5072; e-mail: kkmiller@partners.org.