

Special Issues Related to the Treatment of Depression in Women

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Depressive disorders in women are commonly associated with reproductive events. This association may be due in part to the changing balance between estrogen, progesterone, and other hormones that affect neurotransmitter function throughout a woman's lifecycle. Alternatively, they may be related to psychosocial events surrounding these pivotal times or to both sets of conditions. Some data suggest that depression in women tends to respond differently to antidepressant treatment than depression in men, underscoring the need to examine the risk and treatment of depressive disorders in males and females separately. Women have benefited considerably from serotonin reuptake inhibitor antidepressants that are currently available. These agents appear to be more effective than the older tricyclic antidepressants in treating various depressive disorders that occur commonly or exclusively in women. Additionally, serotonin reuptake inhibitors have increased tolerability in women, who generally experience more adverse effects from tricyclics and monoamine oxidase inhibitors than do men. Estrogen appears to enhance antidepressant response in postmenopausal women receiving estrogen replacement therapy. More research is needed, however, that examines how the balance between estrogen, progesterone, and other hormones affects neurotransmitter function.

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Not only are depressive disorders considerably more prevalent in women than in men, but depression is the leading cause of disease-related disability among women in the world today.¹ Depressive disorders in women are commonly associated with reproductive events and tend to respond differently to antidepressant treatment than depressive disorders in men. According to the National Comorbidity Survey,² the lifetime prevalence for major depression in women is 21.3% compared with 12.7% in men, and the lifetime prevalence of dysthymic disorder is 8.0% for women compared with 4.8% for men. In a review of 1000 primary care patients, Williams et al.³ reported that 31% of the female patients had been diagnosed with a depressive disorder versus only 19% of the male patients. Additional studies have also shown that depression in women may be more recurrent and chronic than in men and may have more frequent and longer episodes.⁴⁻⁶

DEPRESSION ASSOCIATED WITH REPRODUCTIVE PHYSIOLOGY

The relative risk of depression is equal in boys and girls, but that risk precipitously increases in both sexes as they age and eventually becomes twice as high in women as in men.² This increase in risk underscores the need to specifically study the risk and treatment of depressive disorders in men and women separately, and it suggests that both biology and psychosocial factors play a role in the pathophysiology of depressive disorders.

Depressive disorders frequently occur in association with reproductive events such as prior to menstruation, during pregnancy, following pregnancy, and during the perimenopausal years. Some of this correlation may be a product of the changing balance between estrogen, progesterone, and other hormones that likely affects neurotransmitter function throughout a woman's life. The sudden introduction of high levels of estrogen in puberty may alter the sensitivity of the neurotransmitter system, and continually fluctuating estrogen and progesterone levels throughout the reproductive years and declining estrogen afterward underlie continual modification of the neurotransmitter systems,⁷ which may contribute to depression in adult women.

Pre-menstrual depressive symptoms may be the result of this altered sensitivity or activity of neurotransmitter systems.⁷ According to the American College of Obstetricians and Gynecologists,⁸ as many as 20% to 40% of

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Table 1. Diagnostic Criteria for Premenstrual Dysphoric Disorder^a

Cyclical relationship to luteal phase of menstrual cycle
Minimum of 5 of the following symptoms; at least 1 must be a mood symptom: low mood, ^b irritability, ^b anxiety/tension, ^b mood swings, ^b fatigue, sleep changes, appetite changes, decreased interest, difficulty concentrating, feeling overwhelmed or out of control, physical symptoms (eg, bloating, breast tenderness)
Symptoms cause functional impairment
Not merely exacerbation of another disorder
Diagnosis confirmed by 2 cycles of prospective daily ratings
^a Adapted from the <i>Diagnostic and Statistical Manual of Mental Disorders</i> , Fourth Edition. ¹²
^b Mood symptom.

reproductive-age women experience difficulties with premenstrual changes. Women who experience premenstrual changes report increases in depressed mood, irritability, anxiety, and emotional lability.⁹ The premenstrual phase is also associated with an increased risk for the onset of a new episode or the exacerbation of acute depression in women with concurrent mood disorders.^{10,11} Research findings reveal an increase in hospital admissions and suicide attempts by women in the premenstrual phase of their cycles—a trend that is consistent with this pattern of premenstrual depressive onset or exacerbation.¹⁰

Approximately 2% to 10% of women report experiencing a severe disruption of work or relationships during the luteal phase of their menstrual cycle and meet the DSM-IV criteria¹² (Table 1) for premenstrual dysphoric disorder (PMDD).⁸ The diagnosis of PMDD specifically targets the most severe premenstrual symptoms, distinct from any other psychiatric disorder, and requires the presence of functional impairment and severe mood symptoms, distinguishing it from the less severe symptom profile of premenstrual syndrome. PMDD shares features with depression and anxiety that have been linked to serotonergic dysregulation, and although the etiology of PMDD has yet to be determined, studies have implicated serotonin and hypothalamic-pituitary-gonadal axis dysregulation.^{13,14}

Although most people primarily associate the period that immediately follows childbirth with depression, depression during pregnancy is also quite common, with one study reporting depressive symptoms occurring in approximately 20% of pregnant women and full-blown major depressive episodes occurring in about 10%.¹⁵ Pregnancy causes dramatic changes in estrogen and progesterone levels as well as in the hypophysial-pituitary axis, which could increase vulnerability to depression.⁷ Overall, risk factors for depression during pregnancy include limited social support,¹⁶ a history of depression,¹⁷ ambivalence about the pregnancy,¹⁸ young age,¹⁹ living alone or having a large number of children,²⁰ and persistent marital conflicts.¹⁸ A woman who discontinues antidepressant treatment because of pregnancy has a 50%

greater risk of experiencing a relapse of depression during her pregnancy than a woman who does not.¹⁷

Like pregnancy, delivery can produce dramatic changes in estrogen and progesterone, which can act as catalysts for depression.⁷ Postpartum depression affects about 10% of new mothers within 12 months of childbirth, having a peak incidence during the first 4 months.²¹⁻²³ Additionally, 30% to 40% of women who suffer from postpartum depression experience comorbid anxiety that can result in debilitating panic attacks as well as terrifying intrusive thoughts of harming their infants.²⁴ A few patients with postpartum depression even suffer from superimposed psychotic symptoms.²⁵ The serious consequences that can come from not treating postpartum depression are testament to the severity of symptoms associated with this disorder. One possible consequence is that children of depressed mothers are less often the focus of maternal attention, thus adversely influencing benefits that optimize a child's cognitive and emotional development. This lack of connection can subject these children to increased incidences of emotional disturbance and poor cognitive performance,²⁶ which can continue even after the maternal depression has subsided.²⁷

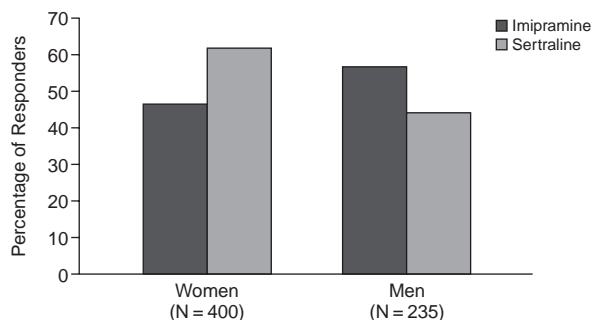
Although there is little evidence that the high risk of affective disorders increases post-menopausally, a woman with a history of affective illness is subject to a perimenopausal increased risk of experiencing a recurrence of that preexisting disorder.²⁸ At menopause, estrogen levels decline, and the modulating effects of estrogen and progesterone may bring about the development of postmenopausal mood disorders in vulnerable women.⁷

Patterns of neuroendocrine events relating to female reproduction are vulnerable to change and are sensitive to a variety of environmental, psychosocial, and physiologic influences. All of these influences can substantially heighten a woman's risk of developing or exacerbating depression or other affective disorders throughout her lifetime.⁷

TREATMENT OF DEPRESSION IN WOMEN

Women have been major beneficiaries of the numerous new serotonin reuptake inhibitor (SRI) antidepressants that are currently available, primarily because these agents appear to be more effective for women than tricyclic antidepressants (TCAs) in treating various depressive disorders. SRIs have expanded the efficacy domain to include a number of disorders that either exclusively or predominantly affect women,²⁹⁻³¹ and the newer agents increase tolerability for women,²⁹ who frequently experience more adverse effects from older antidepressants than men. Older agents, such as TCAs and monoamine oxidase inhibitors (MAOIs), also appear to be more effective in men than in women.^{32,33} Some of this difference may be because these antidepressants can generally be admin-

Figure 1. Rates of Response to Sertraline and Imipramine at Endpoint Among Men and Women With Chronic Depression in a 12-Week Double-Blind Treatment Study^a



^aReprinted with permission from Kornstein et al.²⁹

istered in higher doses for men, while dosages for women are frequently limited due to side effects or potential side effects. Postmenopausal women appear to respond more like men to antidepressant treatments, however, suggesting that estrogen plays a role in priming the brain and enhancing response for some women.²⁹

Although only a few studies have evaluated sex differences in antidepressant treatment response among patients with chronic depression, results fairly consistently favor SRIs for the treatment of depressive disorders in women. Sex differences in treatment response to the SRI sertraline and the TCA imipramine were found in a treatment study²⁹ of chronic depression. In this double-blind, randomized, parallel-group comparison, 235 male and 400 female outpatients with DSM-III-R chronic depression were randomly assigned to receive 12 weeks of treatment with sertraline or imipramine with a starting dose for both drugs of 50 mg/day. The mean sertraline dose at endpoint was 139.6 mg/day for women and 143.2 mg/day for men, and the mean imipramine dose at endpoint was 196.3 mg/day for women and 207.5 mg/day for men. As demonstrated in Figure 1, women responded significantly better to sertraline than to imipramine (62% vs. 46%, $p = .02$), while men responded significantly more favorably to imipramine than to sertraline (57% vs. 45%, $p = .04$). Sex differences in discontinuation rates were found as well, revealing that women were much more likely to drop out of the study during treatment with imipramine than were men. Additionally, differences between premenopausal and postmenopausal women were reported, suggesting that estrogen might play a role in antidepressant response. Premenopausal women responded better to sertraline than to imipramine (57% vs. 43%, $p = .01$), whereas there was essentially no difference in response rates among postmenopausal women (57% vs. 56%).

Sex differences in treatment response were also explored in a 12-week study³⁰ of sertraline, imipramine, and placebo in 410 patients who had "pure" dysthymic dis-

order for at least 5 years. Although the findings revealed no differences in overall efficacy between antidepressant agents (each was more efficacious than placebo), differences by gender were found, with significantly more women than men responding to sertraline (64% vs. 42%; $p = .02$).

These findings are consistent with the results of a database reanalysis by Steiner et al.³¹ that compared the SRI paroxetine to the TCA imipramine. In this study, which comprised 347 men and 370 women, the pooled results of 6 multicenter, placebo- and imipramine-controlled, 6-week trials assessing the efficacy of paroxetine in the treatment of major depression were analyzed to explore the potential for gender-based variability in treatment response. Examining mean HAM-D changes from baseline, researchers found an 8-point change from baseline in paroxetine treatment in men and a 12-point change in women. For imipramine, the decrease from baseline was about 8.5 in both men and women. Men and women receiving either drug improved, but women receiving the SRI improved the most. This study further demonstrated the difference between men and women in their responses to antidepressant pharmacotherapies.

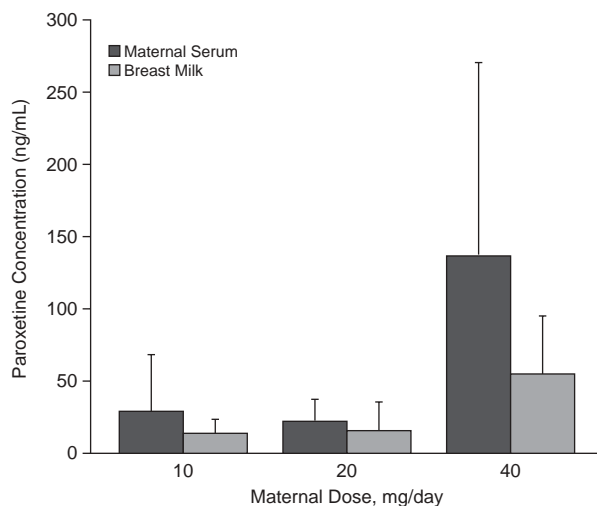
Treatment of PMDD

In addition to treating chronic depressive disorders, SRIs have been successfully used to treat a mood disorder occurring during the luteal phase of the menstrual cycle. Despite the fact that agents such as TCAs can be effective for major depressive disorder, they are no more effective than placebo in the treatment of PMDD.³⁴ Agents that block the serotonin transporter, however, do appear efficacious in treating PMDD as well as other mood conditions.^{34,35}

A classically designed study³⁵ was conducted in Canada to evaluate the efficacy of fluoxetine compared with placebo in the treatment of PMDD. In this study, 313 women suffering from PMDD participated in a single-blind washout period that lasted 2 menstrual cycles and a subsequent randomized, double-blind, placebo-controlled trial in which they received either 20 mg/day or 60 mg/day of fluoxetine for 6 menstrual cycles. In the 180 patients who completed the study, both 20 mg/day of fluoxetine and 60 mg/day of fluoxetine were superior to placebo in reducing the symptoms of irritability, tension, and dysphoria ($p < .0001$) that were associated with PMDD. Participants who received 60 mg/day of fluoxetine, however, experienced substantially more side effects than those who received 20 mg/day of fluoxetine. Researchers concluded that fluoxetine is useful in the treatment of PMDD and added that 20 mg/day of fluoxetine reduces the potential for side effects while simultaneously maximizing therapeutic effects.

In a study³⁴ supported by the National Institute of Mental Health, the SRI sertraline was compared with the TCA desipramine and placebo in 189 women to determine

Figure 2. Mean \pm SD Paroxetine Concentration in Maternal Serum and Breast Milk at Each Dosing Level: 10 mg/day (N = 12), 20 mg/day (N = 10), and 40 mg/day (N = 3)^a



^aReprinted with permission from Misri et al.⁴¹

whether efficacy in PMDD is a result of a predominantly serotonergic effect of antidepressants. Participants were randomly assigned to receive 50 to 150 mg/day of sertraline or desipramine. Of the 189 subjects, 167 participants completed the study, and at endpoint, sertraline therapy was determined to be more effective than desipramine therapy and placebo. Desipramine was no more effective than placebo treatment. HAM-D scores decreased by 65% (N = 40) in the sertraline group, 36% (N = 18) in the desipramine group, and 29% (N = 16) in the placebo group ($p < .001$). The serotonergic agent effectively reduced symptoms and improved functioning. Researchers added that a history of depression did not affect treatment results. Overall, SRI agents have benefited women by both improving efficacy in major depressive disorder and expanding the therapeutic areas of treatment.

Treatment of Depression Associated With Childbearing

Postpartum depression and depression that occurs during pregnancy are 2 other depressive disorders besides PMDD that affect only women, and they can have substantial consequences if left untreated. The symptomatology and management of these disorders are similar to those of other depressive disorders not associated with childbearing; however, there are considerations regarding infant safety.

Although no antidepressant is currently approved by the U.S. Food and Drug Administration for use during pregnancy, the limited available data show no evidence of teratogenesis or effects on infant development¹⁷ resulting from the use of antidepressants during pregnancy. The largest databases examine fluoxetine (N = 3000) and

TCAs¹⁷ and, along with other research,³⁶ indicate that exposure to SRIs or TCAs does not appear to increase the risk for miscarriage or major birth defects. One prospective, multicenter, controlled cohort study³⁷ documented the fetal safety of fluoxetine, paroxetine, and sertraline when taken during pregnancy. Using rates of major congenital malformations as the primary outcome measure, 267 women exposed to an SRI and 267 controls were studied. Results revealed no differences between the treated women and the controls regarding pregnancy outcome. Both groups had similar risks for miscarriage, malformation, and stillbirth, as well as similar mean birth rates and gestational ages. In milder cases of depression, non-pharmacologic treatments are preferable, but in severely depressed pregnant women, the risks of nontreatment versus possible treatment risks must be weighed carefully. For some of these patients, electroconvulsive therapy may be a safe and beneficial alternative to psychopharmacologic treatment.³⁸

Antidepressants are excreted into breastmilk; however, levels are generally undetectable,³⁹ and currently available limited data show no adverse effects on infants.^{40,41} Precautions should be taken, nonetheless, when treating a mother who is breastfeeding her infant, and pharmacotherapy should be employed only if other nonpharmacologic treatments have failed. The number of agents to which the infant is exposed should be kept to a minimum, doses should be kept as low as possible, and feeding schedules should be arranged that minimize the infant's exposure to the drug.

In a study⁴¹ conducted to determine the concentrations of paroxetine in maternal serum, breast milk, and infant serum and to estimate infant exposure through breastfeeding, minimal exposure to the infant was found. Mothers who were recruited for the trial had already begun treatment for postpartum depression and were taking a stable daily dose of paroxetine. Trial doses of paroxetine were fixed at 10 mg/day (N = 12), 20 mg/day (N = 10), or 40 mg/day (N = 3) for a minimum of 30 days. Samples were then collected 6 hours after dose intake and the concentration of paroxetine was determined. Researchers found detectable concentrations of > 0.1 ng/mL of paroxetine in all maternal serum samples and in 24 of 25 breast milk samples (Figure 2). Paroxetine was detected in all of the infant serum samples at a mean of 1.1% of the maternal dose; however, concentrations were below the lower limit of quantification, and no adverse effects were reported in any of the infants. It appears that SRIs are a relatively safe option for breastfeeding mothers suffering from depression, but more research is needed.

Treatment of Depression After Menopause

Postmenopausal women appear to respond more favorably to antidepressants than other women. For example, in a study conducted by Kornstein et al.²⁹ comparing sertraline with imipramine, researchers found that post-

menopausal women had similar response rates to both sertraline and imipramine, while other women did not. They also found that postmenopausal women taking imipramine had significantly lower attrition rates than the other participants.⁴²

Data suggest that estrogen primes the system for antidepressant therapy and thereby may enhance antidepressant response in women receiving estrogen replacement therapy (ERT). Schneider et al.⁴³ conducted a study to determine the effect of ERT on antidepressant response to sertraline in 127 women over the age of 60 who met DSM-III-R criteria for major depression. They analyzed pooled data from two 12-week, double-blind, multicenter trials^{44,45} and determined that women who were treated with sertraline and were taking ERT had substantially greater global improvement and quality of life scores than those not receiving ERT. They also noted that modest improvements were evident in anxiety symptoms and cognitive functioning in women receiving both sertraline and ERT.

CONCLUSIONS

SRI appears to be an efficacious treatment for women suffering from various depressive disorders throughout the life cycle. These agents have expanded treatment options for many women, especially women who experience intermittent symptoms such as with PMDD, and side effects of SRIs are typically less severe than those of TCAs. SRIs appear to improve depressive symptoms in pregnant women and women suffering from postpartum depression, and they are a relatively safe option for breastfeeding mothers. Additionally, their effectiveness appears to be enhanced by estrogen, making them a favorable treatment option for older women suffering from postmenopausal depression. More research is needed, however, that examines how the balance between estrogen, progesterone, and other hormones affects neurotransmitter function, and future long-term studies should comprehensively examine the effects of antidepressant treatment on the developing fetus and on breastfeeding infants.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of her knowledge, sertraline, imipramine, paroxetine, and fluoxetine are not approved by the U.S. Food and Drug Administration for the treatment of postpartum depression, and desipramine is not approved for the treatment of premenstrual dysphoric disorder.

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