Gender-Specific Considerations in the Treatment of Mood Disorders in Women Across the Life Cycle

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Major depressive disorder in women is a significant health concern. Rates of depression in women are approximately twice those seen in men. Observations of gender-based differences in prevalence, presentation, and treatment response in depression raise questions about the underlying causes of such differences. In addition, the specific factors that predict vulnerability to reproductive-associated mood disturbance, including premenstrual dysphoric disorder, postpartum depression, and perimenopausal mood disturbance, remain to be delineated. While a growing amount of controlled data is emerging that describes response to treatment in women who suffer from these disorders, further investigation is needed to identify subgroups of women who are most at risk for depression and to define the most effective treatments for these patients. *(J Clin Psychiatry 2003;64[suppl 15]:18–29)*

Depression occurs more often in women than in men, with differences between men and women also observed in the clinical features of depression and in response to treatment.[1] Women may also experience depressive symptoms in the context of the shifting reproductive hormonal environment. For example, women who suffer from premenstrual dysphoric disorder note that the severity of their symptoms changes across the menstrual cycle. Although pregnancy was once thought to be a time of emotional well-being, recent studies suggest that depression during pregnancy is common.[2,3] Similarly, depression during the postpartum period remains one of the most frequently observed complications in modern obstetrics and is particularly prevalent in women with histories of mood disturbance. The extent to which the transition to menopause, another time of change in respect to female reproduction biology, is associated with risk for depression remains unclear.[4]

The biochemical mechanisms underlying observed gender-based differences in risk for depression and those underlying reproductive-associated mood disturbance, including postpartum depression and perimenopausal depression, remain to be elucidated. Nevertheless, a growing number of clinical trials are being conducted to evaluate treatment options for these disorders. Data from these studies will be discussed in this article. Treatment choices for depressed women who are pregnant or lactating will also be addressed.

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Supported by an unrestricted educational grant from Wyeth Pharmaceuticals, Collegeville, Pa.

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PREVALENCE, RISK FACTORS, AND COURSE OF ILLNESS

Major depressive disorder (MDD) is highly prevalent in the general population and is associated with significant morbidity and functional impairment.[5–8] Epidemiologic studies have consistently demonstrated higher rates of depressive illness in women than in men. In fact, rates of depression in women are approximately double those of depression in men.[9,10] In the National Comorbidity Survey, lifetime prevalence rates for major depression were 21.3% for women and 12.7% for men.[10] In the National Comorbidity Survey, lifetime prevalence rates for major depression were widely variable, ranging from 1.5 to 19.0 cases per 100 adults, with rates consistently higher among women than among men; the female-to-male ratio ranged from 1.6 to 3.1.[11]

Despite the higher prevalence of depression in women, enhanced interest in the issue of diagnosis and treatment of mood disorders in women has occurred only recently. Prior to the last decade, the inclusion of women of childbearing age in clinical trials was often limited or prohibited during the early stages of drug testing.[12] Later-phase trials that included women often did not evaluate subgroups by gender interactions. Thus gender differences in presentation, course, and/or response to treatment were rarely addressed in early studies. Emerging analyses are now beginning to address these issues.

Risk factors for depression also differ by gender. Known risk factors for both sexes include stressful life events,[13,14] family history of a mood disorder,[15] and per-

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sistent psychosocial stressors. Certain risk factors, such as childhood abuse or a previous mood disorder during the early reproductive years, are associated with a greater risk of a depressive disorder developing in women than in men.[16]

Gender differences appear to have a role in the clinical features of depression, specifically in presenting symptoms, course of illness, and comorbidities. For example, premenopausal women are more likely to present with "atypical" or reverse androgenous symptoms (e.g., hypersomnia, carbohydrate craving, hyperphagia, or weight gain).[17,18] Women tend to report a greater number of symptoms and a greater degree of distress associated with these symptoms.[19,20] Women are also more likely than men to report such symptoms as anxiety or functional impairment, particularly as related to family and marital roles,[19,20] and are more likely to experience seasonal depression and depression associated with stressful life events.[13,18] However, although women attempt suicide more often, men have a higher rate of completed suicides.[21]

Available data on gender differences in age at onset of depression are mixed.[1,17,19,20] Some studies suggest that depression in women is more likely to be chronic and recurrent,[19,22–24] whereas other studies have reported no difference in the incidence of depression between men and women.[1] Women are more likely to experience comorbid anxiety disorders or eating disorders, but alcoholism and other substance abuse disorders are more commonly observed in men.[10,15]

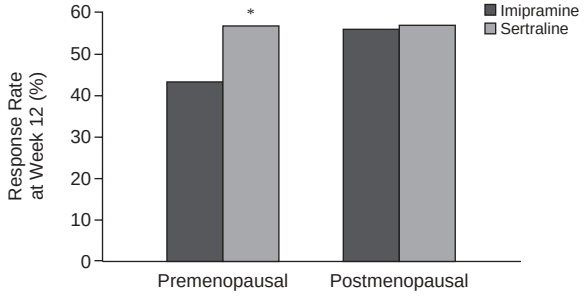
RESPONSE TO ANTIDEPRESSANT TREATMENT

Gender-Specific Differences in Treatment Response

Gender-related differences in response to treatment have recently begun to be addressed. Response to treatment with imipramine, a tricyclic antidepressant (TCA), was assessed in a meta-analysis of 35 studies comprising 711 women and 342 men.[25] The data demonstrated a significantly greater response to imipramine in men than in women (62% and 51%, respectively). These results are similar to earlier findings showing that men and older women had a better response to TCAs than did younger women, who responded better to monoamine oxidase inhibitors (MAOIs).[26]

A recent study comparing patient response to imipramine with response to sertraline found that men were more likely to respond to imipramine but women were more likely to respond to sertraline.[27] A subgroup analysis showed that premenopausal women had a significantly greater response rate to sertraline than to imipramine (57% vs. 43%; p = .01). Postmenopausal women, however, had similar response rates for sertraline and imipramine (57% vs. 56%; p = .88) (Figure 1). The differences in response rates might be attributed to the different subtypes of depression endorsed by men compared with women (i.e., neurovegetative and atypical symptoms, respectively). Alternatively, differences in the reproductive hormonal environment noted between older and younger women may also play a role in response to treatment.

Figure 1. Response to Imipramine and to Sertraline in Chronic Depression by Menopausal Status[a,b]



[a]Data from Kornstein et al.[27]
[b]Last observation carried forward; intention to treat. Response defined as a decrease in Hamilton Rating Scale for Depression (HAM-D) score of 50% or more from baseline to endpoint, and a HAM-D score of 15 or less, and a Clinical Global Impressions Scale–Severity score of 3 or less, and a Clinical Global Impressions Scale–Improvement score of 1 or 2.
*p = .01, response rate for the sertraline-treated group vs. response rate for the imipramine-treated group.

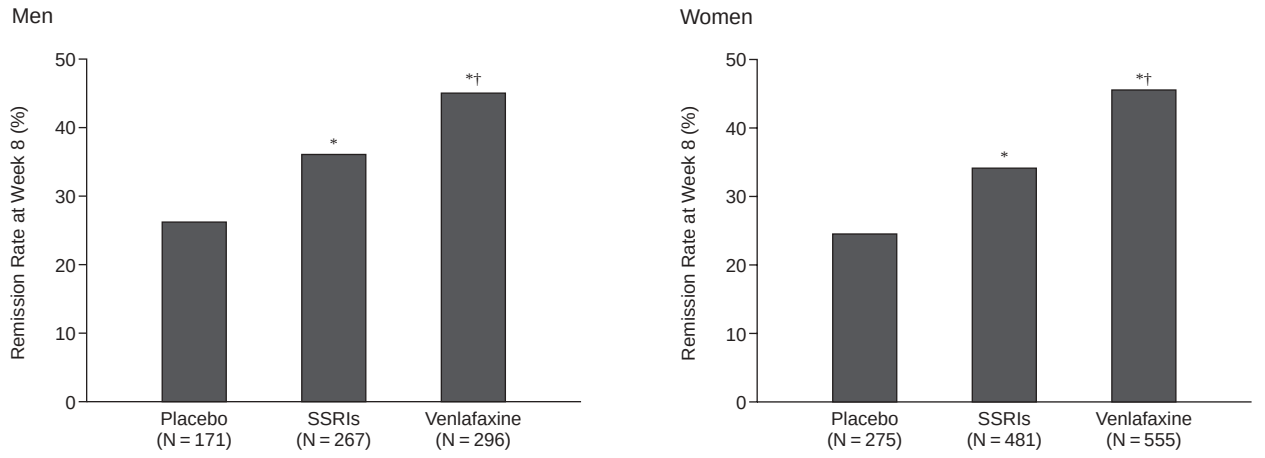
Treatment Response and Hormonal Status

When examining the issue of gender-based differences in response to antidepressant therapy, the effects of the menstrual cycle or exogenous hormones are important considerations. Currently, limited data are available. Clinical trials typically have failed to consider whether the phase of a woman's menstrual cycle at the time of assessment or the use of oral contraceptives or estrogen replacement therapy (ERT) might affect treatment response. Recent analyses have demonstrated, however, that menopausal status, the menstrual cycle, oral contraceptives, and ERT may influence response to antidepressant treatment. For example, analysis of response to imipramine and to sertraline by menopausal status found that premenopausal women were more likely to respond to sertraline than to imipramine, but this difference in response was not observed in postmenopausal women.[27]

In another investigation, the effects of age and gender on treatment response to fluoxetine and to maprotiline, a TCA, were compared.[28] Women younger than 44 years responded significantly better to fluoxetine than to maprotiline, as assessed by the change from baseline in scores on the Hamilton Rating Scale for Depression (HAM-D) (fluoxetine, –18.4 vs. maprotiline, –12.9; p = .023). However, in men and in women older than 44 years, no difference in treatment response was observed.

The role of exogenous estrogen in the treatment of depression in postmenopausal women remains unclear. A

Figure 2. Remission Rates by Gender After Venlafaxine or SSRI Treatment[a,b]



[a]Data from Entsuah et al.[32]
[b]Pooled analysis of 8 studies, last observation carried forward; intention to treat. Remission defined as Hamilton Rating Scale for Depression score of 7 or less. Selective serotonin reuptake inhibitors (SSRIs) included fluoxetine, fluvoxamine, and paroxetine.
*p < .05, treatment vs. placebo.
†p < .05, venlafaxine vs. SSRIs.

retrospective study of fluoxetine in depression found no difference in response among older women using ERT, older women not using ERT, younger women, and men.[29] This study is consistent with another study that failed to determine a difference in response to fluoxetine in older and younger women.[30] These results contrast, however, with a study of fluoxetine with or without ERT in depressed women aged 60 years and older.[31] This study found that women on ERT who received fluoxetine showed significantly greater improvement compared with those receiving placebo, as assessed by the percentage change from baseline in HAM-D scores (40.1% vs. 17.0%; p = .015); those women not on ERT who received fluoxetine did not show a significant improvement compared with placebo (36.1% vs. 30.4%, respectively).

Another recent analysis of pooled data[32] comparing treatment with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine and with selective serotonin reuptake inhibitors (SSRIs) in relation to age and gender consisted of data from 2045 patients from 8 controlled studies who received either venlafaxine immediate release, venlafaxine extended release, an SSRI (fluoxetine, paroxetine, or fluvoxamine), or placebo for 8 weeks. The analysis suggested that venlafaxine treatment consistently resulted in remission for a greater percentage of patients than did the SSRIs; the SSRIs, in turn, were superior to placebo, regardless of patient gender (Figure 2).[32] A further analysis of female patients treated with venlafaxine, an SSRI, or placebo showed that in both older (at least 50 years of age) and younger (less than 50 years of age) women, venlafaxine treatment was significantly better than placebo (Figure 3).[33]

Results of these analyses suggest the need for adequately designed studies that can demonstrate potential variability in response to different classes of antidepressants among premenopausal women, postmenopausal women using ERT, and postmenopausal women not using ERT. Such research may identify subgroups of depressed women who respond preferentially to one type of antidepressant compared with another.

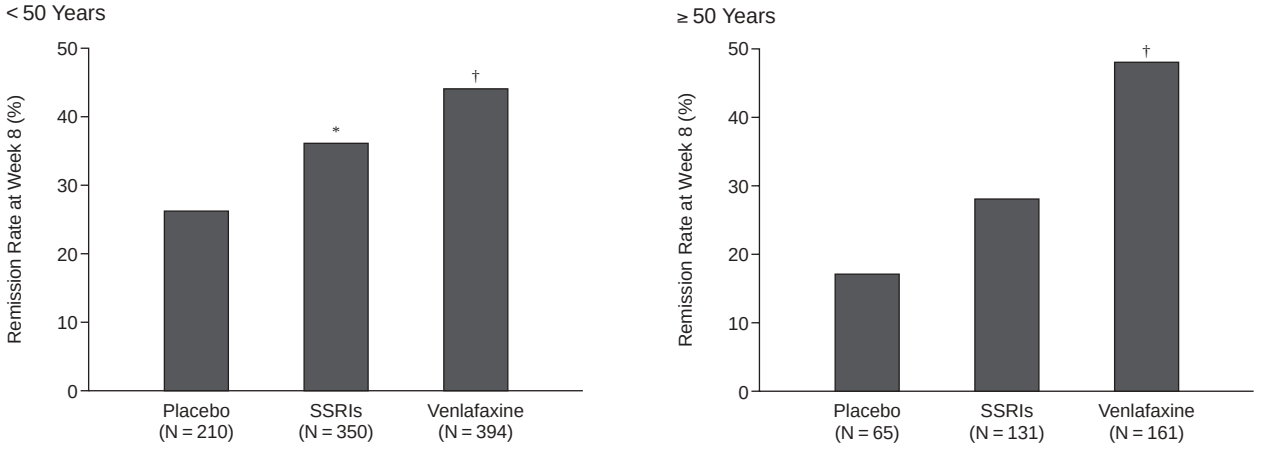
REPRODUCTIVE-ASSOCIATED MOOD DISTURBANCE

Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder (PMDD) is a mood disturbance that affects women of childbearing age. Like premenstrual syndrome (PMS), symptoms occur in the late luteal phase of the menstrual cycle and end shortly after the beginning of menses.[34] Previously referred to as late luteal-phase dysphoric disorder, PMDD has not been extensively investigated until recently. It has only been officially recognized as a distinct mood disorder with specific diagnostic criteria with the release of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[35] PMDD differs from mood disorders in that its symptoms are cyclic and closely linked with phases of the menstrual cycle.[34] PMDD is more severe than PMS and more strictly defined, with an emphasis on mood, behavioral symptoms, the cyclic nature of the symptoms, and functional impairment.[34,36]

Core symptoms of PMDD include depressed mood or dysphoria, anxiety or tension, affective lability, and irritability.[37] Other symptoms include decreased interest in usual activities, difficulty concentrating, food cravings,

Figure 3. Remission Rates After Venlafaxine or SSRI Treatment in Women Younger Than 50 Years and in Women 50 Years and Older[a,b]



[a]Data from Thase et al.[33]
[b]Pooled analysis of 8 studies, last observation carried forward; intention to treat. Remission defined as a Hamilton Rating Scale for Depression score of 7 or less. Selective serotonin reuptake inhibitors included fluoxetine, fluvoxamine, and paroxetine.
*p < .05, SSRI vs. placebo.
†p < .05, venlafaxine vs. SSRI; p < .05, venlafaxine vs. placebo.

hypersomnia or insomnia, feeling overwhelmed, and physical symptoms such as headache, muscle pain, bloating, and fatigue. To confirm a diagnosis of PMDD, at least 5 symptoms (including 1 core symptom) must be present the week before menses and remit a few days after menses begins, must interfere with school, work, or other functioning, and must not be an exacerbation of a preexisting disorder.[37] Finally, these symptoms must be confirmed by prospective daily ratings for at least 2 cycles.

The average age at onset of PMDD is in the mid-20s, although PMDD may begin any time after menarche.[38] Women with fewer pregnancies seem to be at greater risk. Prevalence rates for PMDD have recently been demonstrated to be as high as 6.4%.[39] Although the symptoms of the disorder are cyclic in nature, women with PMDD have functional impairment in work, family life, and social and leisure activities equal to that experienced by people with major depression.[40] Functional impairment in women with premenstrual symptoms was also demonstrated in a recent study in which a survey was administered to 1045 menstruating women aged 18 through 49 years.[41] More than 50% of working women reported that their ability to work was at least somewhat affected by their premenstrual symptoms. Additionally, 8% to 16% of working women reported missing at least 1 day of work due to symptoms.[41]

The etiology of PMDD is still unclear. There is no evidence to support hormonal dysregulation as a specific cause of this disorder. However, evidence does suggest that premenstrual symptoms (PMS, PMDD, or both) may be associated with an abnormal response to typical hormonal fluctuations.[42] One investigation of the response to leuprolide, a gonadotropin-releasing hormone agonist, in women with PMDD demonstrated a significant decrease in premenstrual symptoms.[42] The study also demonstrated that women who had previously suffered from premenstrual symptoms remained asymptomatic when challenged with hormonal treatment. The study results suggest that women who experience severe premenstrual symptoms have an altered response to normal hormonal fluctuations.

A number of treatment approaches have been suggested for PMDD, including treating with oral contraceptives, dietary supplements, anxiolytic drugs, and antidepressants (in both continuous and premenstrual dosing schedules). To date, the largest amount of data available from randomized controlled trials is for antidepressant drugs.

Oral contraceptives and progesterone, although widely believed to be useful in treating PMDD, have not been extensively evaluated in controlled clinical trials. One trial of a triphasic oral contraceptive in women with "moderate to severe premenstrual symptoms" was done prior to the development of diagnostic criteria for PMDD. Results of this trial failed to demonstrate a significant improvement in premenstrual mood symptoms with oral contraceptives compared with placebo, although there was a significant reduction in breast pain and bloating.[43,44] At this time, the American College of Obstetricians and Gynecologists clinical guidelines do not recommend the use of oral contraceptives for the treatment of PMS.[45]

Antidepressants that have been shown to be effective in the treatment of PMDD include the SSRIs citalopram,[46] fluoxetine,[47–52] paroxetine,[53] and sertraline,[40,54–58] as well as venlafaxine[59] and clomipramine.[60,61] Although early

studies of antidepressants for treating PMDD used continuous (daily) treatment, recent studies have used intermittent (premenstrual) treatment.

In one study, the efficacy of continuous dosing with fluoxetine treatment for PMDD was evaluated.[50] Following a single-blind, placebo washout period for 2 menstrual cycles, 313 women with PMDD were randomized to double-blind treatment with 20 mg/day of fluoxetine, 60 mg/day of fluoxetine, or placebo for 6 menstrual cycles. The mean percent improvement in the luteal-phase score from baseline was 4 to 6 times greater in the fluoxetine groups than in the placebo group, as measured by the total visual analog scale. The significant difference in the scores between women receiving fluoxetine and women receiving placebo was maintained during the 6 cycles of the trial in the 180 women who completed the protocol (cycle 1, 46% vs. 16%; cycle 2, 54% vs. 16%; cycle 3, 52% vs. 16%; cycle 4, 38% vs. 24%; cycle 5, 36% vs. 16%; cycle 6, 40% vs. 23%; $p < .001$).

In another study, the efficacy of sertraline was compared with that of desipramine in the treatment of PMDD.[55] After 3 screening months, 189 subjects were randomized to 3 months of double-blind treatment with flexible doses of sertraline (50 – 150 mg/day), desipramine (150 mg/day), or placebo. Results showed that sertraline was more effective than placebo or desipramine ($p < .001$), but desipramine was not significantly more effective than placebo. At study endpoint, 65% of patients in the sertraline group, 36% in the desipramine group, and 29% in the placebo group ($p < .001$) experienced a greater than 50% reduction in baseline Daily Symptom Report (DSR) scores.

The efficacy of venlafaxine in the treatment of PMDD has been evaluated in a double-blind, placebo-controlled study.[59] One hundred fifty-seven women aged 21 to 45 years were randomly assigned to double-blind treatment with venlafaxine (50 – 200 mg/day) or with placebo for 4 menstrual cycles. Venlafaxine was significantly more effective than placebo at the end of the first cycle (42% vs. 14%; $p < .001$); improvement increased slightly in the second cycle and was maintained for the remaining 2 cycles (57% vs. 31%; $p < .001$), as assessed by decreases in mean DSR total scores. More patients achieved remission in the venlafaxine group compared with the placebo group, as defined by DSR score reduction to the postmenstrual level (43% vs. 25%; $p = .034$) at endpoint (fourth cycle). Analysis of DSR factor scores showed that there was significantly greater improvement in the venlafaxine group compared with the placebo group ($p < .05$) at endpoint (fourth cycle) in the primary factors of emotion, function, physical symptoms, and pain.

Antidepressant treatment limited to the luteal phase (intermittent) for women suffering from PMDD appears promising. Use of the drug during the luteal phase only (as opposed to daily continuous treatment throughout the menstrual cycle) may be an attractive option to many patients with PMDD because such a dosing schedule may reduce risk for certain treatment-emergent side effects. However, it is particularly critical to guarantee that patients who elect luteal phase versus continuous treatment are not experiencing an episode of depressive illness for which intermittent therapy would be inappropriate.

A multicenter, placebo-controlled, randomized study evaluated the efficacy of intermittent luteal-phase treatment with sertraline for PMDD.[62] Following a single-blind placebo lead-in period for 1 cycle, 245 female outpatients aged 24 to 45 years who met DSM-IV criteria for PMDD were randomized to sertraline (50 – 100 mg/day) or to placebo during the luteal phase (approximately 14 days prior to next menses) of 3 menstrual cycles. Patients remained medication-free during the follicular phase of each cycle. The mean dose of sertraline was 47.7 mg/day, 64.5 mg/day, and 73.7 mg/day for cycles 1, 2, and 3, respectively. Intermittent sertraline treatment was more effective than placebo, as measured by the response rates, defined as a Clinical Global Impressions Scale-Improvement (CGI-I) score of 1 or 2, i.e., much or very much improved (63% vs. 47%; $p < .05$), and by all other outcome measures, i.e., improvement in daily symptom scores and CGI-I/Clinical Global Impressions Scale-Severity (CGI-S) change from baseline.

In another study of luteal-phase antidepressant therapy for PMDD, fluoxetine treatment was administered at 20 U.S. study sites in a double-blind, randomized, placebo-controlled, parallel investigation.[63] Following 2 screening cycles, 260 women aged 18 to 45 years with a DSM-IV diagnosis of PMDD were randomized to 3 cycles of luteal-phase treatment with either fluoxetine (10 mg/day; $N = 86$), fluoxetine (20 mg/day; $N = 86$), or placebo ($N = 88$). Each patient was dosed for 14 days prior to the next expected menses through the first full day of menses.

Both fluoxetine groups showed significantly improved total scores on the Daily Record of Severity of Problems (DRSP) scale by the first treatment cycle (48.0, 47.8, 55.0 for fluoxetine 10 mg, fluoxetine 20 mg, and placebo, respectively; $p < .05$); however, only the group taking the higher dose of fluoxetine demonstrated significant improvement throughout the remainder of the study period. Compared with women taking placebo, patients treated daily with 20 mg of fluoxetine had greater mean changes from baseline in DRSP mood, physical, and functional impairment subtotals ($p < .05$). Patients treated with 10 mg/day of fluoxetine showed less improvement than those treated with 20 mg/day. The results of this study suggest that luteal-phase dosing of fluoxetine is effective for the treatment of PMDD and that 20 mg daily appears to be more effective than 10 mg daily in relieving physical symptoms and in overall measures of PMDD.

These studies demonstrate that PMDD may be successfully treated with antidepressants, including SSRIs and the SNRI venlafaxine. Both continuous treatment and luteal-

Table 1. Newer Antidepressants and Pregnancy

Medication	Design	N	References	Outcome
Fluvoxamine	Survey	50	McElhatton 1996[64]	No increase in major or minor malformations
	Cohort controlled	26	Kulin 1998[65]	No increase in major malformations; similar birth weight and gestational ages
Paroxetine	Cohort controlled	97	Kulin 1998[65]	No increase in major malformations; similar birth weight and gestational ages
	Danish registry	118	Ericson 1999[66]	No increase in congenital abnormalities
Sertraline	Cohort controlled	147	Kulin 1998[65]	No increase in major malformations; similar birth weight and gestational age
	Danish registry	32	Ericson 1999[66]	No increase in congenital abnormalities
Venlafaxine	Cohort controlled	150	Einarson 2001[67]	No increase in major malformations
Citalopram	Danish registry	364	Ericson 1999[66]	No increase in congenital abnormalities
Fluoxetine	Survey	64	Cohen 2000[68]	No increased risk in perinatal complications with early vs late trimester exposure
	Cohort controlled	128	Pastuszak 1999[69]	No increase in major malformations
	Danish registry	15	Ericson 1999[66]	No increase in congenital abnormalities
	Survey	686	Goldstein 1997[70]	No increase in fetal malformations with 1st trimester exposure
	Cohort controlled	174	Chambers 1996[71]	No increase in major malformations; increased risk of perinatal complications with 3rd trimester exposure
	Survey	67	McElhatton 1996[64]	No increase in major or minor malformations
	Survey	112	Goldstein 1995[72]	No increase in postnatal complications with 3rd trimester exposure

phase treatment appear to be effective, but further investigation is warranted to identify subgroups who may benefit from one dosing schedule versus the other.

Depression During Pregnancy

Although pregnancy may be a time of emotional well-being for some women, there is no "protection" during pregnancy from new-onset depression or relapse of depression. Evidence from the few systematic studies of depression during pregnancy demonstrates rates of mood disturbance in pregnant women that are comparable to those seen in nonpregnant women.[2,3] In addition, a recent prospective study observed a relapse rate of 75% in euthymic pregnant women with a history of depression who reduced or discontinued antidepressant medication during pregnancy.[73]

Several factors are associated with a greater risk of depression in pregnant women. The strongest risk factor is a history of MDD.[2] Other factors that seem to play a role are younger age,[74] limited social support,[75] greater number of children,[75] marital conflict,[76] and ambivalence about pregnancy.[76]

Due to a common misconception that women are protected from depression during pregnancy, the disorder may be underdiagnosed and undertreated. Depression that remains untreated during pregnancy is associated with a risk of substance abuse and poor self-care,[77] including failure to follow prenatal guidelines. The precise impact of maternal depression on fetal development is not known, though several studies describe an association between depression during pregnancy and low birth weight and preterm delivery.[78,79] It is important that clinicians be aware of the risk of depression in their pregnant patients and take advantage of the opportunity for screening provided by the frequency of health care visits during this time. Detection of severe depression during pregnancy is an opportunity for the clinician to intervene with pharmacologic treatment, nonpharmacologic therapies, or both. Detection of depression during pregnancy becomes an opportunity to identify women at risk for postpartum mood disturbance and provides an opportunity for early intervention during the acute puerperal period.

The decision to treat depression during pregnancy must be based on consideration of the risks associated with untreated depression as well as the possible risks associated with fetal exposure to medication. No antidepressant is currently approved by the U.S. Food and Drug Administration (FDA) for use during pregnancy. It is known, however, that all psychotropic medications cross the placenta to some degree and enter fetal circulation.[80] The FDA category labeling system for safety during pregnancy is not helpful in making the treatment decision; indeed, it may be somewhat misleading. Antidepressants that have been associated with adverse events in animal studies are classified as category C, which means that risk cannot be ruled out. But the category labeling system does not take into account other postmarketing teratovigilance data that may be available regarding the reproductive safety of the medication.[81] Therefore clinicians should consult additional sources of information other than the *Physicians' Desk Reference* when considering the use of antidepressant medications during pregnancy (Table 1).

Varying amounts of reproductive safety data are available regarding antidepressants. Considerable data are available for older agents, such as the TCAs. These data reveal no increased risk of major congenital malformations following first trimester exposure[82,83]; limited data regarding these compounds also suggest no evidence of behavioral teratogenicity.[69,77,84,85]

Of the newer antidepressants, information regarding outcomes following prenatal exposure to SSRIs is most available. The greatest amount of information supporting reproductive safety exists for fluoxetine and citalopram. However, accumulated studies of fetal exposure to SSRIs as a class do not demonstrate increased evidence of teratogenicity or spontaneous pregnancy loss.[65,69] An evaluation

of data from studies of pregnant women receiving SSRIs, venlafaxine, or nonteratogenic agents has also found no significant differences among the groups, suggesting no increased rate of malformations with venlafaxine or SSRIs compared with baseline rates.[67]

When making treatment decisions for depressed pregnant women, it is important to consider nonpharmacologic as well as pharmacologic interventions. Psychotherapy or electroconvulsive therapy (ECT) might be considered as alternatives to pharmacologic therapy for some patients. Pharmacotherapy or ECT is indicated in more severe depression when typically the risk to the mother and the fetus due to the mother's depression outweighs the potential risks to the fetus associated with the use of antidepressants.[83]

One clinical scenario frequently prompts the question of whether to change antidepressant medications for a newly pregnant patient (i.e., first trimester) who has been stabilized on one agent prior to pregnancy. Switching to an antidepressant for which more reproductive safety data are available would seem like a worthwhile consideration. However, making this transition may put the patient at higher risk for relapse absent a history of response to the new medication. Thus the decision to remain with an antidepressant with fewer safety data may be appropriate if it affords the patient a greater likelihood of remaining euthymic.

Postpartum Depression

Depressive illness in the postpartum period can be divided into 3 levels of severity: postpartum blues, nonpsychotic postpartum depression, and puerperal psychosis.[86] Postpartum blues is the most commonly observed and least severe, with symptoms beginning within a few days of delivery. By definition, this disorder is relatively benign, with symptoms remitting by about the 10th postpartum day. Nonpsychotic postpartum depression is less common than postpartum blues, with signs and symptoms similar to those seen in other depressed patients, e.g., depressed mood, anhedonia, low energy, guilty ruminations, and suicidal ideation.[86]

Postpartum psychosis is a rare disorder and is considered a psychiatric emergency. It is associated with the most severe symptoms and generally requires inpatient treatment. The onset of postpartum psychosis can be as early as the first 48 to 72 hours postpartum, with the majority of women developing symptoms within the first 2 weeks after delivery.[86] Symptoms may include restlessness, irritability, depressed or elated mood, disorganized behavior, delusions, and hallucinations.[86] Puerperal psychosis has been associated with bipolar disorder[87] and is often treated similarly to manic psychosis,[88] with mood stabilizers, antipsychotic medications, or ECT. Untreated puerperal psychosis has been associated with infanticide and considerable maternal morbidity.[89] Therefore aggressive treatment is necessary to ensure maternal and neonatal well-being.

Depression during the postpartum period occurs at a rate similar to that in nonpuerperal women, with estimates ranging from 5% to 10%.[2,76,87,90]

Although depression may present from 24 hours to several months after delivery, DSM-IV–defined postpartum depression is limited to that which manifests within 4 weeks of delivery.[86] While postpartum depression is well-known to the public as well as to the medical community, it is often overlooked or ignored by patients and caregivers. Many of the symptoms characteristic of depression, e.g., loss of sexual interest, change in appetite, or fatigue, are often observed during the postpartum period and thus may not be reported or recognized as clinically significant.[90]

Left untreated, depression is associated with health risks to the mother as well as to the child in terms of cognitive, emotional, and social development.[91] There also is evidence that maternal depression in the postpartum period may have adverse effects on maternal infant attachment and long-term infant cognitive development.[92,93]

A number of factors increase the risk of postpartum depression. Depressive symptoms during pregnancy, marital discord, inadequate social support, and stressful life events are associated with a greater risk of developing postpartum depression.[2,75,90] A history of psychiatric illness is also associated with an increased risk for developing postpartum depression, with an even greater risk associated with a previous history of postpartum illness.[86,94] It is important for clinicians to identify patients who are at risk for postpartum illness so that such patients can be closely monitored during the acute puerperium.

Treatment of postpartum depression may consist of psychotherapy or pharmacotherapy. Although postpartum depression is as common as many other obstetric complications, limited treatment data are available. Treatment strategies that have been evaluated include interpersonal psychotherapy,[95,96] cognitive-behavioral therapy,[97] counseling,[97] and treatment with fluoxetine,[97] sertraline,[98] and venlafaxine.[99]

Interpersonal psychotherapy was evaluated in 2 prospective studies and has been shown to significantly reduce depressive symptoms in patients with postpartum depression.[95,96] Counseling as a treatment strategy was examined in a small, prospective, controlled study. In this study, 6 counseling sessions with a health nurse led to recovery in 12 (80%) of 15 postpartum women with DSM-III-R MDD compared with 4 (25%) of 16 controls.[100] In a study of cognitive-behavioral therapy, Appleby and colleagues[97] demonstrated that 6 sessions were as effective as fluoxetine in the treatment of patients diagnosed with major or minor depression in the postpartum period.

Although limited, studies of antidepressants in the treatment of postpartum depressive disorders have demonstrated their efficacy. In addition to the fluoxetine data, results are available from studies of sertraline and of venlafaxine. A prospective, open-label, flexible-dose (50–200

mg/day) study of sertraline was conducted in 21 women meeting the DSM-III-R criteria for MDD within the first 24 weeks postpartum.[98] A response was noted in 20 of 21 women, with 14 (67%) of 21 women achieving total remission by 8 weeks.

An 8-week, open-label, flexible-dose (75–225 mg/day) study of venlafaxine was conducted in 15 women who met the DSM-III-R criteria for MDD within the first 3 months postpartum.[99] Statistically significant changes from baseline were observed in symptoms of depression, and 10 patients (67%) exhibited symptomatic remission at endpoint.

A secondary analysis using the Social Adjustment Scale was performed to determine differences in functional recovery from baseline to endpoint. Statistically significant improvement was observed in overall scores and in marital adjustment, family unit, and housework subscale scores.[101] The results of this analysis are of particular interest because functioning across psychosocial domains is important for mothers and their families.

Hormonal therapies have also been proposed for the treatment of postpartum depression. At this time, however, data on their usefulness in this population are sparse.[102,103] The potential role for hormonal interventions for the treatment of postpartum depression is an interesting possibility. However, since it is crucial for patients to achieve remission, pending more controlled data with hormonal therapy, these interventions should not be routinely pursued.

Given the significant risk of developing postpartum depression among those women with a history of previous puerperal mood disorder, prophylactic treatment has been considered in several investigations. Two studies have evaluated the use of antidepressants for preventing the recurrence of postpartum depression. In the first open-label study, women received either monitoring or monitoring plus nortriptyline or an antidepressant that had previously been effective. Those who received postpartum monitoring only were significantly more likely to experience a recurrence than were those women who received monitoring plus an antidepressant.[94] A second double-blind study comparing the effectiveness of monitoring with that of nortriptyline found no significant benefit with nortriptyline[104]; thus the available data are not conclusive. However, though not evidence-based, postpartum prophylaxis is frequently recommended for patients who experience depression during pregnancy, who have a past history of postpartum depression, or who have a history of severe recurrent depressive illness.

The appropriate use of psychotropic medications during lactation remains a matter of debate. Although data from controlled studies are not available, there is an evolving body of literature on this subject. It is known that all psychotropic medications are excreted into the breast milk in varying concentrations.[105] Several recent reports have estimated the extent of exposure of nursing infants to antidepressants by measuring infant serum concentrations.[106–113] Of the newer antidepressants, data are available for fluoxetine,[106,107] paroxetine,[106,111] sertraline,[108–110] and venlafaxine,[112,113] with the most data available for the SSRIs. These reports demonstrated varying levels of antidepressants and/or metabolites in breastfed infants.

Many women defer pharmacologic treatment during the postpartum period because of concerns about using these medications while breast-feeding. These women may then be at risk for the sequelae of untreated depression. While data on the maternal use of antidepressants during lactation are limited, reports of adverse events in nursing infants are particularly sparse. In addition, more data are available for antidepressants than for most other nonpsychiatric medications that have been used in the postpartum period, such as antibiotics or analgesics. An alternative to consider is the use of infant formula instead of breast-feeding for patients who are particularly concerned about the possibility of detrimental effects caused by the trace amounts of psychiatric medication evident in the serum of infants whose mothers use these compounds.

No antidepressant is known to be the safest for use by breast-feeding mothers. When selecting an antidepressant, consider the following[105]: (1) use medication to which the patient has previously responded; (2) use medication with the most data supporting safe use during breast-feeding and efficacy in treating postpartum illness; (3) try monotherapy first; (4) limit invasive monitoring of the infant; (5) use medication with flexible dosage forms to promote careful dose titration.

Depression in Perimenopause

Menopause is frequently associated with physical symptoms (e.g., hot flashes, night sweats) and with substantial psychosocial transition in a woman's life, e.g., the experience of children leaving home or altered family roles.[114–116] It was traditionally believed that this transitional time was associated with an increased risk of new-onset MDD but recent investigations have suggested that this is not the case.[9,24,117–124] An increased rate of recurrence, mood fluctuations, and the emergence of depressive symptoms, however, have been associated with perimenopause.[1,4,125–128]

The link between depression and the transition to menopause is somewhat unclear, although a number of cross-sectional and longitudinal studies have investigated the association between depressive symptoms and menopausal status.[4,117,118,120,125–131] The cross-sectional investigations reported an increase in depressive symptoms associated with the perimenopausal period.[4,117,120,126,127,129–131] The longitudinal studies, however, were unable to establish a clear association between depressive symptoms and the transition to menopause, due in part to a lack of distinction of menopausal status.[117,118,132] The etiology of depression or depressive symptoms around the time of menopause has not been clearly established.

Management of depressive symptoms in perimenopausal women may be similar to the management of depression at other times of life. However, in this population, women frequently present with somatic complaints unique to this age group, such as hot flashes, weight gain, vaginal dryness, and loss of libido.[114,116,133] Studies evaluating efficacy of treatment options for depression during perimenopause and menopause have included the use of: (1) estrogen replacement therapy, (2) antidepressant therapy, or (3) a combination of both of these treatments.

Results of studies of estrogen monotherapy have been mixed.[47,134–137] Earlier investigations, frequently utilizing oral ERT, did not demonstrate a significant improvement of menopausal depression.[31,134,135] More recent studies, with well-defined populations and transdermal estrogen therapy, have demonstrated positive results.[47,136,137]

In a recent investigation, the efficacy of short-term use of transdermal estrogen in treating depression in perimenopausal and postmenopausal women was evaluated.[47] In this open trial, 20 perimenopausal and postmenopausal women received transdermal 17-β estradiol for 4 weeks. Analysis of the results revealed that perimenopausal women tended to experience a rapid and significant improvement in depression. Postmenopausal women, however, did not seem to respond as rapidly. In addition, a significantly greater proportion of perimenopausal women achieved remission compared with postmenopausal women (66.7% vs. 9.1%; $p = .017$). The improvement of depressive symptoms seemed to be independent of any changes in menopause-related symptoms.

A double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy of estradiol in treating depressed perimenopausal women.[137] Fifty perimenopausal women aged 40 to 55 years who had been diagnosed with major depressive disorder, minor depressive disorder, or dysthymic disorder were randomized to receive either transdermal 17-β estradiol (100 μg) or placebo for 12 weeks. Remission, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) score of 10 or less, was observed in a significantly greater proportion of patients receiving estradiol compared with those receiving placebo (68% vs. 20%; $p = .001$).[137] Additionally, the antidepressant response to estrogen did not seem to be related to improvement in somatic symptoms. These data are similar to data observed by Schmidt et al.[136] in a study of transdermal estradiol administered to a similar population of women.

Despite the evolving data supporting an antidepressant effect of certain forms of estrogen, the role of the hormone as a therapeutic intervention will be scrutinized that much more following recent reports from the Women's Health Initiative.[138–142] These data indicate that postmenopausal women treated with estrogen and progestin may face a higher risk of serious health effects. The Women's Health Initiative was designed to evaluate the effects of treatment with estrogen or with estrogen and progestin on a range of health outcomes. The estrogen plus progestin arm of the trial was halted after 5.6 years, about 3 years earlier than planned, because women in this treatment group were found to have a greater risk of stroke, heart attack, venous thromboembolism, total cardiovascular disease, and breast cancer. Although there were also reductions in colorectal cancer and hip fractures, the risks were greater than the benefits.[138] More recent data from this study also demonstrated a higher rate of dementia[139] and confirmed the finding of a higher rate of stroke[140] in this treatment group. The estrogen-only arm of the trial is still in progress, however, so the overall health effects of estrogen treatment in this large-scale trial are still unknown.

Despite the rigor of these 2 studies and the small but quantifiable risk for the noted outcomes of concern, there remains some confusion regarding the generalizability of the findings to the spectrum of women who may be candidates for the use of hormone replacement therapy. It should be noted that the majority of the study population was postmenopausal and the extent to which the treatment poses comparable risk to the majority of perimenopausal patients who use hormonal interventions for their primary indication, i.e., treatment of vasomotor symptoms, has yet to be clarified. Moreover, though not stated in the results published to date, some concern must be given to the clinically observed risk for recurrent mood and anxiety symptoms as well as recrudescing vasomotor symptoms observed in the setting of abrupt discontinuation of hormone replacement therapy, a scenario that has been noted in at least some patients following the publication of the Women's Health Initiative data.

CONCLUSION

The successful diagnosis and treatment of depression in women require the consideration of differences between men and women in both presentation and treatment response. In addition, disturbance in mood may be seen coincident with critical times of change in female reproductive biology, such as during the time prior to menses and during pregnancy, the postpartum period, and the perimenopause.

Though the majority of rigorously done studies with these subpopulations of women is finite, there is a growing number of systematic studies that document the efficacy of antidepressants to treat these women. Further study of these groups of patients will minimize the morbidity associated with untreated depression.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), leuprolide (Viadur, Lupron, and others), maprotiline (Ludiomil and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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