The Evaluation and Management of Depression in Women Across the Life Span

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Depression is more common in women than in men, particularly during the childbearing years. Women may present with different depressive symptoms than men and may respond differently to antidepressant treatment. In addition, depression in women can surface in association with specific points in the reproductive cycle, such as during the premenstrual period, during pregnancy and the postpartum period, and during the perimenopausal years. Antidepressant medications may be used effectively at all stages in a woman's life. In the case of premenstrual dysphoric disorder, serotonergic agents have demonstrated efficacy in both full-cycle and luteal-phase dosing strategies. For depressed women who are pregnant or breastfeeding, the limited safety data available on antidepressants suggest minimal danger to the fetus or infant, and the risks and benefits to both mother and child must be weighed against the risks of untreated illness. Treatment of depression in middle-aged and elderly women should take into account the possible influence of both menopausal status and hormone replacement therapy on antidepressant response. This article will focus on special considerations in the evaluation and management of depression in women across the life span.

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Women show a greater prevalence of depressive disorders than men, especially during the childbearing years. For example, the National Comorbidity Survey (NCS)[1] found that the lifetime prevalence for major depression is 21.3% for females and 12.7% for males, a female-to-male ratio of 1.7. The lifetime prevalence of dysthymia was found to be 8.0% for females and 4.8% for males, again a ratio of 1.7. Other studies have confirmed that women are about twice as likely as men to experience depression.[2–5] Wu and Anthony[3] recently found the point prevalence of depressive episodes to be 1.9% in women, compared with 1.0% in men. In a study[4] of 1000 primary care patients, 31% of women were diagnosed with a depressive disorder versus 19% of men.

This difference is found in countries other than the United States as well. In a cross-national epidemiologic survey, including the United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand, Weissman et al.[5] found that the rate of major depression was higher in women than in men in all 10 countries. The female-to-male ratios varied from 1.6 (Lebanon, Taiwan) to 3.1 (West Germany). A World Health Organization study of psychological problems in primary care in 14 countries[6] found the female-to-male ratio for current, remitted, first episode, and lifetime major depression to be 2:1. Similar ratios have been reported in a wide variety of populations, including Korean immigrants to Canada,[7] southeast Asian refugees,[8] and residents of an Israeli kibbutz.[9]

According to the NCS[10] and other longitudinal studies,[11,12] this gender difference in prevalence begins in adolescence, around age 10 to 13 years, and continues at least through midlife, a period that roughly coincides with a woman's childbearing years. The 2:1 female-to-male ratio cited above seems to be the result of a dramatic increase in depression in girls during adolescence and early adulthood that is unmatched by the increase in boys.[13] Although some epidemiologic studies have found that the higher rates among women persist in older age,[14,15] others report a narrowing of the gender gap after menopause.[16,17]

Many theories have attempted to explain this difference (Figure 1).[18] Some theories have suggested that the difference is a result of artifact, for example, diagnostic and recall biases or women's tendency to seek help and report depression more often than men. The sex difference may be due to biological differences between men and women, such as brain structures or reproductive function; it may also be related to psychosocial factors, e.g., socialization, stress and coping mechanisms, or rates of victimization. For example, Nolen-Hoeksema and colleagues[19] hypothesized that women are more prone to depression because they are more likely to experience ongoing stress, they perceive themselves to

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have little control or mastery over their situations, and, once they are depressed, they cope by dwelling or ruminating. Nolen-Hoeksema[20] argues that men cope with depression by distracting themselves from it, a more active response that may shorten the depressive episode, whereas a more ruminative coping style may lengthen it.

In addition, gender differences in both presentation and treatment response have been documented. Depressive symptoms in women commonly occur in association with reproductive events, such as the premenstrual period, pregnancy and the postpartum period, and perimenopause. Misunderstanding has existed about reproductive-associated events—for example, pregnancy was long thought to protect women from depression, whereas menopause was believed to cause depression and despair as a result of the loss of reproductive capacity. A different approach is often needed when treating a depressed woman as opposed to a depressed man, one that considers the woman's reproductive status and social roles. This article reviews the gender differences in clinical features of depression and discusses the evaluation and treatment of depression in women across the life span.

GENDER DIFFERENCES IN CLINICAL PRESENTATION

The gender difference in the prevalence of depression is well established. However, the degree of gender difference in the clinical presentation of depression has yet to be clarified; whereas some studies have found no variation between men and women in symptoms, course, or comorbidity, others have found significant differences in all 3 areas.

Symptoms

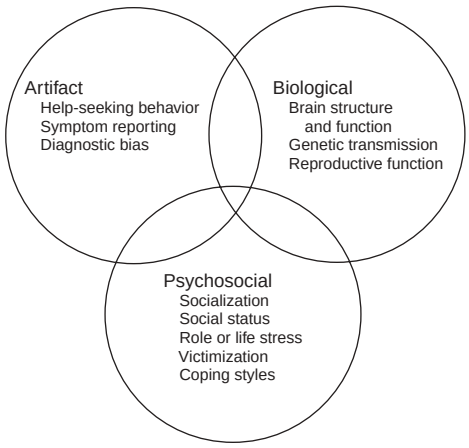
Atypical symptoms of depression are more common in women than in men. For example, women have been consistently shown to have increased appetite and weight gain as symptoms of depression.[21,22] In addition, women tend to endorse a greater number of symptoms and more severe distress on self-report measures than do men,[22–25] even though the severity is not always confirmed by clinician-rated measures.[22,24,25] Women may be more likely than men to report anger,[22] somatization and anxiety,[22,24,25] psychomotor retardation,[23,25] and greater functional impairment, especially in family and marital roles.[23,25] Possible reasons for these differences may include psychosocial factors, such as the male tendency to deny depressive symptoms[22] or the female tendency to ruminate and focus on symptoms.[24]

Course

Although some studies show no difference based on gender in course of depression,[10,22,24,26,27] others have shown that women may have a more chronic and recurrent course of depression with more frequent and longer episodes than men.[28–31] For example, during a 5-year follow-up study[31] of patients with unipolar and bipolar affective disorders, women diagnosed with unipolar depression were significantly more likely to have experienced further episodes of depression and to have been hospitalized than men with unipolar depression. No gender differences were found in bipolar patients. Keitner and colleagues[30] found that women with depression uncomplicated by comorbidity were less likely than men to have recovered at a 12-month follow-up: 100% of men had recovered at follow-up compared with 50% of women. Sargeant and coworkers[29] found that women over the age of 30 years had a significant increase in persistent depression (depression that was still present at 1-year follow-up) compared with younger women and men of all ages.

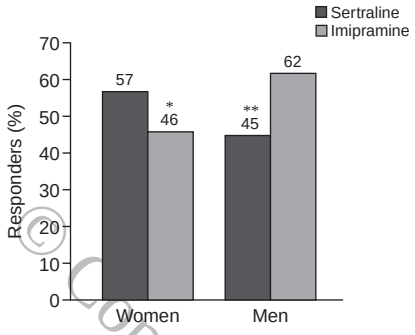
Although most studies have shown no gender difference in age at onset of depression,[10,32] some researchers have found that women have an earlier age at onset of depression than men.[25,33] For example, in a sample of 635 patients with chronic major depression or double depression, my colleagues and I[25] found a mean ± SD age at onset of 23.4 ± 11.6 years for women compared with 27.3 ± 12.5 years for men ($p < .05$). The tendency for early onset of depression in women can have a negative impact on a woman's educational and professional attainment. In a recent report[34] of 531 subjects with chronic depression, women with early-onset depression (before age 22 years) were less likely to finish college or attend graduate school than women with late-onset depression and men in both groups. In addition, based on 1995 U.S. Census Bureau data regarding earnings by age, gender, and level of education, a woman with early-onset depression could expect annual earnings 12% less than that of late-onset or nondepressed women at age 35 years and 18% less at age 55

Figure 1. Theories to Explain Gender Differences in Depression[a]



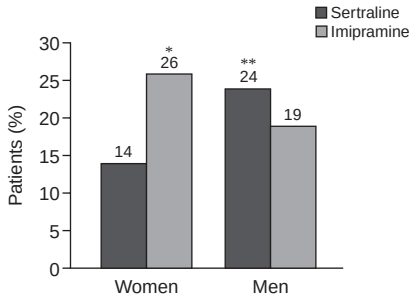
[a]Reprinted from Kornstein,[18] with permission.

Figure 2. Sertraline Versus Imipramine in the Treatment of Chronic Major Depressive Disorder: Response Rates by Gender[a]



[a]Adapted from Kornstein et al.,[42] with permission. Response is defined as a 50% decrease in Hamilton Rating Scale for Depression (HAM-D) score, a total HAM-D score ≤ 15, a Clinical Global Impressions (CGI)-Severity of Illness score ≤ 3, and a CGI-Global Improvement score of 1 or 2.
*p = .012.
**p = .043.

Figure 3. Sertraline Versus Imipramine in the Treatment of Chronic Major Depressive Disorder: Attrition Rates by Gender[a]



[a]Data from Kornstein et al.[42]
*p = .002.
**p = .377.

years.[34] Clearly, an earlier age of illness onset in women has far-reaching implications.

Comorbidity

The pattern of comorbidity with depression is also different for women than for men. In addition to having higher overall rates of comorbid psychiatric disorders than men, depressed women tend to experience comorbid anxiety disorders and eating disorders, whereas depressed men tend to have comorbid alcohol and substance abuse.[23,33,35] It appears that in women who do have comorbid depression and alcohol abuse or dependence, depressive symptoms usually precede the alcoholism,[36] perhaps revealing an attempt to self-medicate. According to a recent review,[37] pain and depression also co-occur more often in women than in men, although more investigation is needed to explore and explain this correlation.

GENDER DIFFERENCES IN PHARMACOLOGIC TREATMENT RESPONSE

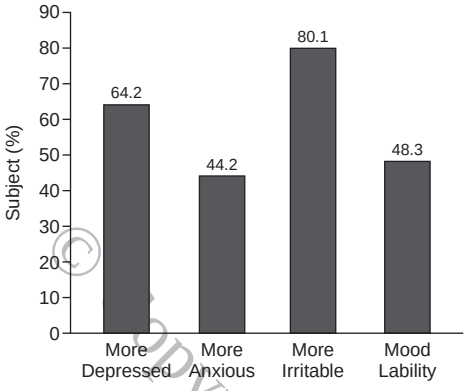
Men and women have also been shown to respond differently to pharmacologic treatment for depression. For example, in a database reanalysis of phenelzine and imipramine for the treatment of major depressive disorder, Raskin[38] found that men and older women had an equivalent response to imipramine, whereas younger women had a poor response to imipramine but responded better than young men to phenelzine. A meta-analysis of gender differences in treatment response to imipramine examined 35 studies and found that 62% of men were responders compared with 51% of women, a significant difference ($p < .001$).[39] In a study comparing paroxetine and imipramine for the treatment of major depressive disorder, Steiner and coworkers[40] found that paroxetine-treated women had a significantly greater decrease in Hamilton Rating Scale for Depression (HAM-D) scores compared with imipramine-treated women. In these studies, women clearly responded better to drugs other than the tricyclic antidepressant (TCA) imipramine.

My colleagues and I[41,42] studied 635 patients with DSM-III-R chronic major or double depression, 235 men and 400 women aged 21 to 65 years. Patients were randomly assigned to treatment with sertraline, 50–200 mg/day, or imipramine, 50–300 mg/day. Response was defined as a 50% decrease in HAM-D score, a total HAM-D score ≤ 15, a Clinical Global Impressions-Severity of Illness (CGI-S) score ≤ 3, and a CGI-Global Improvement score of 1 (very much improved) or 2 (much improved). The response rate was similar for both treatments for both completers and the intent-to-treat population.[41] However, significantly fewer women than men responded to imipramine, and significantly fewer men than women responded to sertraline (Figure 2).[42] In addition, significantly more imipramine-treated women dropped out of the study compared with sertraline-treated women (Figure 3).[42] Yonkers et al.[43] also found that women with dysthymia had a much more robust response to sertraline than did men. Again, it seems that the TCA imipramine is not as effective for the treatment of depression in women as drugs from other classes, in this case, the selective serotonin reuptake inhibitor (SSRI) sertraline.

PREMENSTRUAL MOOD CHANGES

A woman's menstrual cycle can have a profound impact on the course of her depression.[44,45] For example, in women with mood disorders, the premenstrual phase of the cycle is associated with an increased risk for the onset of a new episode as well as exacerbation of ongoing depression. Premenstrual exacerbation of depression may be characterized by increased severity of symptoms, the appearance of new symptoms, and decreased impulse con-

Figure 4. Premenstrual Mood Changes in 120 Women With Chronic Depression[a]



[a]Data from Kornstein et al.[46]

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 *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.[48]
[b]Mood symptom.

trol.[45] Consistent with this pattern, an increase in psychiatric hospital admissions and suicide attempts during the premenstrual phase has been found.[44,45] My colleagues and I[46] noted menstrual-cycle–related worsening of depression in women with chronic depression. Of 229 women, over half (52.4%) reported premenstrual exacerbation; another 9% reported mood worsening during menses, and 3% each, after menses and around ovulation. Of those women who reported premenstrual changes, the most common symptoms were increases in depressed mood, anxiety, irritability, and emotional lability (Figure 4).[46]

Worldwide, approximately 3% to 9% of women experience severe premenstrual symptoms.[47] The diagnosis of premenstrual dysphoric disorder (PMDD) specifically targets the most severe of those symptoms and is distinct from a diagnosis of depression or any other psychiatric disorder. The DSM-IV criteria for the disorder are shown in Table 1.[48] PMDD differs from premenstrual syndrome and other menstrual-cycle–related changes in that a diagnosis of PMDD requires the presence of severe mood symptoms and functional impairment. The cause of PMDD, and premenstrual mood changes in general, is still unknown, although recent studies have implicated serotonin and hypothalamic-pituitary-gonadal axis dysregulation.[49,50]

Given the possible serotonergic etiology of PMDD, it is not surprising that the SSRIs seem to be an effective treatment for PMDD.[51–53] In a double-blind, placebo-controlled trial of fluoxetine,[52] 313 women with PMDD were randomly assigned to 60 mg/day of fluoxetine, 20 mg/day of fluoxetine, or placebo. Fluoxetine was significantly more effective than placebo in alleviating symptoms of tension, irritability, and dysphoria, and the 20-mg dose was associated with fewer side effects than was the 60-mg dose. The authors concluded that 20 mg/day of fluoxetine is an effective strategy for the reduction of symptoms of PMDD. In another randomized controlled trial,[51] 189 women with severe premenstrual syndrome or PMDD were randomly assigned to treatment with sertraline, desipramine, or placebo. Sertraline was the most effective treatment—65% of sertraline-treated subjects were considered responders, whereas only 36% of desipramine-treated and 29% of placebo-treated subjects were responders, a significant difference.

Both of the studies discussed above used full-cycle dosing; however, some women may prefer not to take drugs during their symptom-free follicular phases to avoid possible side effects. Intermittent treatment during the luteal phase of the cycle, when the severe mood symptoms occur, may be a more attractive option for these women, one that has been shown to be similarly effective.[53–55] Sundblad and coworkers[54] found that women taking clomipramine, a (nonselective) serotonin reuptake inhibitor, during only the luteal phase experienced a 70% reduction in premenstrual irritability and depressed mood, compared with a 45% reduction of these symptoms in placebo-treated women. In a recent study, Halbreich and colleagues[55] reported on 281 women with PMDD randomly assigned to sertraline or placebo treatment during only the luteal phase for 3 menstrual cycles. They found that significantly more sertraline-treated women than placebo-treated women were considered responders across all 3 cycles of treatment.

Even in women with no other psychiatric disorder, the luteal phase can be associated with severe mental and physical distress. Both full-cycle and intermittent pharmacologic treatment can help alleviate that distress.

PREGNANCY

Contrary to popular belief, pregnancy does not protect a woman against depression. In fact, one study[56] found depressive symptoms in about 20% of pregnant women and a full-blown major depressive episode in about 10% of pregnant women. Risk factors for depression during pregnancy include a history of depression,[57] limited social support,[58] living alone or having a large number of children,[59] marital conflicts,[60] ambivalence about the pregnancy,[60] and young age.[61] Depressed women who discontinue antidepressant treatment because of pregnancy have over a

50% risk of relapse[62] during the course of the pregnancy. Since untreated depression during pregnancy may lead to poor prenatal care, substance use, suicide, obstetric complications, and postpartum depression, a compromise must be found that will alleviate the patient's depression without endangering the fetus.

No antidepressants are currently approved by the U.S. Food and Drug Administration for use during pregnancy. However, limited data show no evidence of teratogenesis or effects on infant development; the largest databases are on fluoxetine (N = 3000) and the TCAs.[62] Besides fluoxetine, other SSRIs have recently been reported to be safe in the treatment of depression in pregnant women. Kulin and colleagues[63] conducted a prospective, controlled multicenter study of 267 women exposed to an SSRI—sertraline, paroxetine, or fluvoxamine—during pregnancy. No differences were found between the treated women and the controls in pregnancy outcome; the 2 groups had similar risks for malformations, miscarriage, and stillbirth. Similar mean birth weight and gestational age were found in both groups. A recent review[64] of the use of antidepressants during pregnancy also concluded that exposure to TCAs and SSRIs did not increase the risk for miscarriage or major birth defects. Although nonpharmacologic treatment is preferable in milder cases, in a severely depressed pregnant woman, the risks of nontreatment versus possible risks to the fetus must be weighed carefully. Another option to pharmacologic treatment for severe or delusional depression is electroconvulsive therapy, which can be a safe and beneficial treatment for depressed, pregnant patients.[65]

POSTPARTUM DEPRESSION

A postpartum-onset specifier was included in DSM-IV to describe episodes of mood disorder that begin within 4 weeks after delivery. The symptoms of postpartum depression are those of a major depressive episode, such as depressed mood, lack of interest, weight and sleep changes, fatigue, psychomotor agitation or retardation, guilt, lack of concentration, and suicidal thoughts.[48] About 10% to 15% of new mothers experience postpartum depression, although some estimates are as high as 23%.[66,67] Past history of depression and depressive symptoms during pregnancy are major risk factors, especially previous episodes of postpartum depression.[67] Symptoms and management of postpartum depression are similar to those of nonpostpartum depression, except for considerations of infant safety during breastfeeding.

All antidepressants are excreted into breast milk, although levels in infants are usually undetectable.[68] The limited data currently available show no adverse effects on infants, and as in depression during pregnancy, the possible risks of treatment must be weighed against the risks of leaving the illness untreated, not only for the mother and infant but also for the patient's family. When treating a new mother who has postpartum depression and is breastfeeding, it is preferable to begin with an antidepressant to which she has responded in the past in order to maximize the likelihood of response and minimize the number of agents to which the infant is exposed. If she is medication naive, a drug with a short half-life and some demonstrated safety data during lactation should be used. Doses should be kept as low as possible to adequately treat the depression, and, if possible, the dosing and feeding schedules should be arranged so as to minimize the infant's exposure to the drug.

Stowe and coworkers[69] found that the highest concentrations of sertraline and its metabolite desmethylsertraline were in hind milk (the later part of a feeding) 7 to 10 hours after the mother's dose, and higher concentrations were found in the breast milk of women taking higher doses of the antidepressant. Sertraline and desmethylsertraline were present in all breast milk samples taken from the 12 participants, but serum sertraline levels were detectable in only 3 of 11 infants for whom serum samples were available. Although desmethylsertraline was detectable in 6 infants, no infants exhibited any adverse effects of drug exposure. In a study of paroxetine and lactation, Stowe et al.[70] reported that paroxetine was also found in all breast milk samples of the 16 participants, with greater concentrations in hind milk. Although no time course was evident, as with the sertraline study, maternal daily dose of paroxetine was a reliable predictor of paroxetine breast milk concentrations over a 24-hour period. No paroxetine was detected in serum samples from 16 infants, and no adverse effects were noted in any of the infants. A recent case series[71] of fluvoxamine in breastfed infants had similar results; each infant serum fluvoxamine level was too low to quantify, and neither of the participating infants was noted to experience adverse events. If pharmacologic treatment is necessary in a depressed, breastfeeding mother, the SSRIs seem to be a relatively safe option, although more research is clearly needed.

MENOPAUSE

Little evidence supports the notion of menopause as a high-risk period for the onset of affective disorders. However, in women with a history of affective illness, the perimenopausal and early menopausal periods are associated with an increased risk of recurrence of that illness.[10] A perimenopausal or postmenopausal woman may react differently to antidepressants than a woman who has not reached that stage; my colleagues and I[42] found in our study of sertraline versus imipramine that, unlike other women in the study, postmenopausal women had similar response rates to both sertraline and imipramine, and among those taking imipramine, postmenopausal women had significantly lower attrition rates than premenopausal women.

Estrogen has a role in the treatment of mood and cognitive symptoms in perimenopausal or postmenopausal women. The minor mood symptoms associated with perimenopause are often alleviated by estrogen therapy.[72] In a study of older, nondemented women, Maki et al.[73] found that women on estrogen replacement therapy scored significantly better on tests of verbal learning and memory than women who were not on hormone therapy. Some research suggests that estrogen replacement therapy may enhance antidepressant effects in depressed postmenopausal women. In a study of elderly depressed women receiving fluoxetine,[74] a significant interaction between estrogen therapy and treatment effect was found. A study[75] of the effect of estrogen replacement therapy on sertraline treatment showed that depressed women who received both sertraline and estrogen experienced a greater improvement than women who received sertraline only. More research is also needed in this area of the treatment of women with depression.

SUMMARY

Women have a high risk for depression, especially during the reproductive years. The treatment of depressive disorders in women requires attention not only to aspects of depression that are unique to women, but also to gender differences in symptoms, course, comorbidity, and/or treatment response. Treating a depressed woman may call for a different approach than that used to treat a depressed man. At the very least, the clinician should inquire into the female patient's reproductive status and history and take that information into account when devising a treatment strategy. The SSRIs should be considered first-line treatment for mood disorders in women, including major depressive disorder, dysthymia, and PMDD.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of her knowledge, clomipramine is not approved by the U.S. Food and Drug Administration for the treatment of premenstrual dysphoria; fluoxetine for use during pregnancy; fluvoxamine and paroxetine for use during pregnancy and lactation; and sertraline for PMDD or for use during pregnancy and lactation.

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