JANUARY 2005 / VOL. 27, NO. 1

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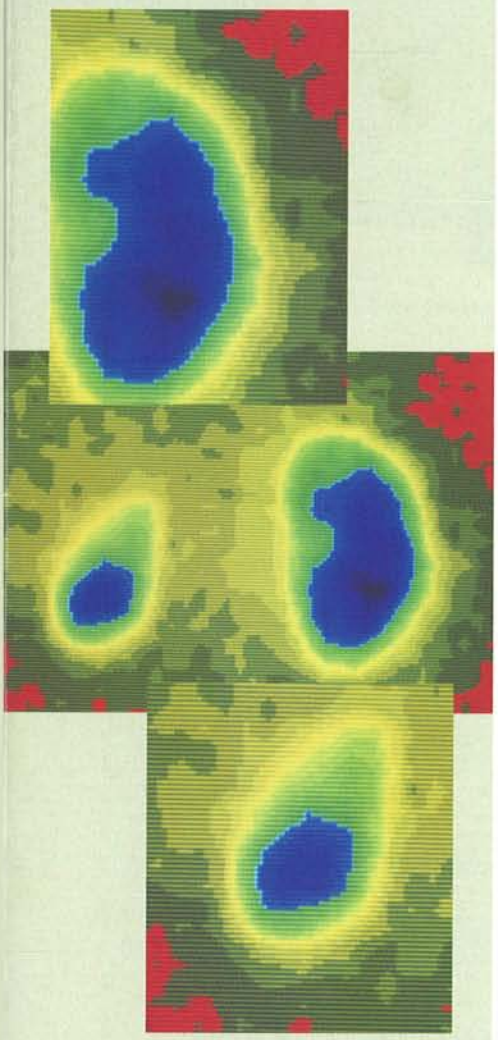

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Depression in women: Gender-related differences in occurrence and treatment

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ABSTRACT Depression is one of the most disabling of illnesses in women. Some symptoms and causes, as well as the response to treatment, are influenced by gender. Until recently, women of childbearing age were often excluded from clinical trials—and pregnant women are excluded from all drug trials for ethical reasons. For these reasons, our understanding of gender differences in depression and its management has been incomplete. Nevertheless, it is possible to predict times of increased risk and organize strategies to minimize recurrence and severity. Established depression is treated with pharmacotherapy and psychotherapy.

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Women are twice as likely as men to suffer from major depressive disorder (MDD),[1] which is a particular problem during the childbearing years. An ongoing study by the Centers for Disease Control and Prevention and the Harvard School of Public Health found that the leading cause of disability in all adults in the United States in 1966 was ischemic heart disease.[2] In women, the second most disabling condition was major depression, ranking ahead of cerebrovascular disease, respiratory tract cancers, osteoarthritis, and breast cancer.[2]

The approach to treating depression in a woman differs from that for a man and must take into account her reproductive status and social roles. This article reviews gender differences in the development and manifestations of depression and the evaluation and treatment of depression in women across the lifespan.

The extent of the problem

MDD can be diagnosed based on a single major depressive episode (Table 1)[3] or recurrent episodes. The lifetime prevalence of MDD is approximately 21% in women and 13% in men, for a 7:1 female-to-male ratio.[4] The corresponding figures for dysthymia (chronic mild depression) are 8% and 5%, again, a ratio of 7:1. The gender disparity persists regardless of country of residence and ethnicity. A World Health Organization study of psychological problems in primary care in 14 countries found a female-to-male ratio of 2:1 for current, remitted, first-episode, and lifetime major depression.[1] The trend starts in adolescence and continues through childbearing years. The gender gap tends to persist in older age,[5] although it may narrow in the very old.[6]

Table 1

***DSM-IV-TR* diagnostic criteria for major depressive episode**

A. Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (feels sad or empty, for example) or observation made by others (appears tearful, for example). **Note:** In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (change of > 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (such as a drug of abuse or medication) or a general medical condition (such as hypothyroidism).

E. The symptoms are not better accounted for by bereavement; the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Key: *DSM-IV-TR* = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.
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Why the gender differences?

The difference in rates of depression is not an artifact of how often men and women seek help. The reason for the higher prevalence in women is probably a combination of differences in cognitive styles, biological factors, and psychosocial and economic stresses.

Women—who may have more limitations and fewer choices than men—are more likely to have incomes below the poverty line, which has been associated with depressive symptoms, particularly in mothers with young children.[7] Poverty is a pathway to depression in part because of frequent and uncontrollable adverse events such as exposure to crime and violence. Partner violence,[8] the leading cause of injury in women requiring emergency treatment,[9] is a common cause of depression, and ongoing abuse maintains depressive symptoms. More than half of older women live alone compared with one fourth of older men,[10] and these women are likely to face financial strains and a loss of independence with declining health.

Men and women also react differently to depression. Men may use distraction to cope, an active response that can shorten the depressive episode, as opposed to a ruminative coping style that can lengthen it.[11] Women are more likely to experience ongoing stress, perceive themselves as

having little control over the situation, and dwell on their problems once they are depressed.[12] Among possible biological mechanisms are gender-related differences in brain structure and function, genetics, and behavioral- or mood-related effects of estrogen and progesterone secretion on neurotransmitters and enzyme functions.[13]

Because the difference in risk of depression emerges over a span of 5 years coinciding with the onset of puberty, it seems almost certain that psychosocial factors interact with neuroendocrine development. As an at-risk girl reaches puberty, a heightened affiliating need combined with a difficult adolescent transition (insecure parental attachment, anxious/inhibited temperament, lack of confidence in her ability to cope with stressful life events) may lead to a diathetic depression. During adolescence, depression may be triggered by concerns about personal appearance, safety, and self-worth. Parents have different expectations for girls and boys; girls are thought to be more nurturing, while boys are more independent. Such stereotypical gender socialization lowers a girl's sense of mastery and control, making her more concerned about the social estimation of others.

Gender disparity: Symptoms, course of illness, and comorbidity

The same diagnostic criteria are used for both men and women, but the presentation and course of depression often differ. Women are more susceptible to seasonal depression[14] and symptoms of atypical depression (increased appetite or weight gain, hypersomnia, a heavy feeling in the arms and legs, and sensitivity to perceived interpersonal rejection).[3] They more frequently experience anxiety, panic, and phobias and are more likely to report somatic symptoms such as back, joint, or limb pain, bowel complaints, dizziness, dyspnea, headache, fatigue, insomnia, palpitations, and nausea or indigestion.[15] Women also have a higher incidence of hypothyroidism, a cause of depression.

Men tend to respond more quickly to treatment and relapse less often,[16] partly because of differences in the pharmacokinetics of antidepressants.[17] Their absorption may be enhanced in women because they secrete less gastric acid. Further, in the late luteal phase of the menstrual cycle, gastric emptying and small intestinal transit times slow. The volume of distribution of many drugs is also increased in women because they have a higher ratio of body fat to muscle, which increases with age.

Finally, although there are more successful suicides in men, suicidal ideation is more common in women. Depressive symptoms are a strong risk factor in suicidal women, who tend to use less violent means such as drugs or carbon monoxide poisoning.[18]

Premenstrual dysphoric disorder (PMDD)

A woman's menstrual cycle can have a profound impact on the course of depression. In those with mood disorders, the premenstrual phase is associated with an increased risk for both new episodes and a worsening of established depression. Premenstrual exacerbation may be manifest as new symptoms, increased symptom severity, or reduced impulse control. Consistent with this pattern, more psychiatric hospital admissions and suicide attempts occur in the premenstrual phase.[19]

PMDD is characterized by recurrent physical and emotional symptoms that appear in the late luteal phase and dissipate by the first or second day after menses (Table 2, page 53).[3] Diagnosis requires having the woman record daily symptom ratings for at least two consecutive cycles. Mood and anxiety symptoms predominate over somatic complaints in PMDD, unlike premenstrual syndrome (PMS).

The exact role of the luteal phase and of estrogen and progesterone is unclear. Using the progesterone receptor antagonist mifepristone (Mifeprex) to truncate the luteal phase does not lessen symptoms,[20] although ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists usually does.[21] This is consistent with the idea that hormone-related events before the midluteal phase can trigger PMDD. In susceptible women, even normal plasma concentrations of gonadal steroids can cause an abnormal response (deterioration of mood).[13] A heightened central nervous system sensitivity to normal hormonal cycling can lead to reduced levels of serotonin and cause symptoms such as irritability, dysphoria, impulsivity, and carbohydrate craving. Acute depletion of tryptophan, the serotonin precursor, also aggravates symptoms.[22] The predictable, cycli-

Table 2

***DSM-IV-TR* diagnostic criteria for premenstrual dysphoric disorder**

A. In most menstrual cycles during the past year, five or more of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week post-menses. At least one of the first four symptoms must be present:

1. Depressed mood
2. Marked anxiety or tension
3. Marked affective lability
4. Persistent and marked anger or lability
5. Decreased interest in usual activities
6. Subjective sense of difficulty in concentrating
7. Lethargy or lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. Subjective sense of being overwhelmed or out of control
11. Other physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, bloating, weight gain

B. Symptoms must be present for most months for at least 1 year.

C. Symptoms must cause impairment in social and/or occupational functioning (such as increased social isolation, conflict with others, decreased productivity at work) in the week prior to onset of menses.

D. The disturbance cannot represent a worsening of symptoms of another Axis I disorder such as mood or anxiety disorders or a personality disorder.

E. Diagnostic criteria must be confirmed by daily ratings during at least 2 consecutive cycles.

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cal pattern of symptoms is further evidence of PMDD as a distinct, biologically driven syndrome.

A prospective, longitudinal community survey of more than 1,200 women found a lifetime incidence of PMDD of about 7%.[23] Age of onset is typically the mid-20s, but many women do not seek treatment until at least a decade later.[24] The mean duration of symptoms is 4.8 days per cycle, and some women have symptoms for as long as 2 weeks a month,[25] underscoring the significant impact of PMDD.

Nonpharmacologic treatments such as exercise and diet (reduced intake of caffeine, alcohol, and chocolate) have not shown consistent benefits,[26] but selective serotonin reuptake inhibitors (SSRIs) have.[27] In a double-blind, placebo-controlled trial, 313 women with PMDD were randomly assigned to fluoxetine HCl (Prozac, Sarafem), 60 or 20 mg/d, or placebo.[27] Fluoxetine was significantly more effective in alleviating tension, irritability, and dysphoria; women taking the 20-mg dose had fewer side effects. This study used full-cycle dosing, but treatment during the luteal phase has also been successful.[28] Even physical symptoms such as bloating and breast tenderness improve.[29] The efficacy of SSRIs clearly points to altered serotonin levels as a cause of PMDD.

In most studies, improvement has been seen within three menstrual cycles of SSRI therapy,[24] but moderate improvement can occur in the first treatment cycle.[27] It is worth noting that non–serotonin-enhancing antidepressants such as bupropion HCl (Wellbutrin),[30] maprotiline HCl,[31] and tricyclic antidepressants[32] have not been effective in relieving PMDD symptoms.

For women hesitant to take a psychotropic medication, calcium supplementation is an alternative first-line treatment. A 1998 trial showed that PMDD symptoms improved significantly in women randomized to calcium carbonate, 1,200 mg/d, compared with placebo.[33] GnRH agonists such as leuprolide acetate (Lupron, Eligard) have also shown efficacy,[13] but since these agents can cause menopausal symptoms, they should be reserved for patients resistant to other forms of therapy.

continued

Despite widespread use, there is no evidence that oral contraceptives (OCs) alleviate PMDD symptoms. In fact, they can cause depression, and women with a history of depression are at greater risk.[34] Studies have implicated both estrogen and progesterone, but recent research indicates that progesterone is the more likely culprit.[34] Switching to low-dose OCs appears to reduce fatigue, moodiness, anxiety, and anger.[35]

Depression in pregnancy

Despite a generally held belief that pregnancy is a period of happy anticipation and well-being, this may not be true for women with a history of depression. Typical depressive symptoms—sadness, impaired concentration, poor memory, irritability, disturbed appetite and sleep, and thoughts of death can make pregnancy a difficult experience for these women, their partners, other family members, and treating physicians. Such women are also at risk for recurrence during pregnancy.[36]

Treating depression during pregnancy requires a careful assessment of risks and benefits for both the mother and fetus. Potential risks to the fetus include organ malformation, neonatal toxicity, and postnatal behavioral sequelae.[37] In the mother, untreated or undertreated depression may lead to increased suicide risk, poor self-care, diminished productivity, and serious morbidity. It can also continue into the postpartum period and affect mother-child bonding and contribute to chronic depression. In addition, symptomatic depression during pregnancy has been associated with preterm labor and small-for-gestational-age babies.[38]

No psychotropic medication has been approved by the Food and Drug Administration (FDA) for use during pregnancy, but these drugs may be appropriate in many clinical situations. Most antidepressants are classified as FDA category C (demonstrated adverse effects in animals or studies in humans are lacking). A meta-analysis including more than 2,700 women taking antidepressants (fluoxetine, citalopram HBr [Celexa], sertraline HCl [Zoloft], paroxetine HCl [Paxil, Pexeva], and fluvoxamine maleate) during pregnancy found no increased risk of teratogenicity, which may be reassuring to many women.[37] Limited data on the use of psychotropic medications in later pregnancy suggest there is no increase in clinically significant adverse obstetrical outcomes.[39] Some prospective data indicate that in utero exposure to antidepressants does not affect children's global IQ, language development, or motor or behavioral development up to 7 years of age.[40] The number of children who have been studied thus far is small (approximately 200), and it is wise to remember that no medication can be viewed as completely safe.

Deciding on the best approach for a woman who is pregnant or wishing to conceive is complicated, and no decision is risk free. An expert consensus panel in 2001 determined that a combination of medication and psychotherapy is the treatment of choice for severe major depression, whether an initial or recurrent episode, during any trimester.[41] For women with a history of severe recurrences, most experts agree that it is appropriate to resume pharmacotherapy at the first sign of depression, without waiting for a full syndrome to develop. In severe depression, most prefer an open-ended course of psychotherapy rather than a short-term approach.[41]

Electroconvulsive therapy (ECT) has been used to treat depression in pregnancy for more than 50 years and is reportedly relatively safe in those with severe, refractory depression.[42] For those who have depression with psychosis during any trimester, the panel endorsed using either ECT or a combination of an antipsychotic and an antidepressant.[41]

Postpartum depression

Three distinct postpartum mood conditions have been recognized: postpartum blues, postpartum depression, and postpartum psychosis. Some 30%-75% of women experience mild postpartum blues (labile mood, tearfulness, irritability, and sleep disturbances) lasting 4-10 days.[43] Supportive care, empathy, and education about the condition are all that is needed.

DSM-IV-TR specifies that postpartum onset for mood disorder episodes starts within 4 weeks of delivery.[3] The incidence of postpartum depression peaks at 10 weeks postpartum, however, and some authors believe it can occur anytime during the first postpartum year.[44] Inconsistencies in the time frame (ranging from 4 weeks to 6 months after delivery) make epidemiologic estimates diffi-

cult to interpret. One study found that 10%-15% of new mothers experience postpartum depression.[45] Risk is higher in women with a history of depression (25% increase) or postpartum depression (50%-62% increase),[45] and in those with depressive symptoms during pregnancy, marital discord, and stressful life events.[43] In women with a history of postpartum depression, the risk of recurrence can be decreased from 60% to 6% simply by starting treatment within 24 hours after delivery.[46]

Women with postpartum depression have symptoms consistent with those of major depression, but they also tend to be particularly anxious and ruminative, often about the health and well-being of their babies. Despite being exhausted, they are often unable to sleep. Because the neurovegetative symptoms of depression may be difficult to detect in the new mother, a self-rating instrument such as the 10-item Edinburgh Postnatal Depression Scale can be useful for evaluation.

A small percentage of women with postpartum depression (1 in 500-1,000 births) experience psychotic symptoms,[47] such as auditory hallucinations and delusional guilt. This can put both mother and newborn at serious risk, with the possibility of suicide or infanticide. Psychotic symptoms in the postpartum period should be considered a medical emergency and warrant immediate psychiatry referral. ECT should be considered for rapid reversal.

Children of depressed mothers can have impaired social and cognitive development through 4 years of age.[48] In addition, the quality of mother-child interaction can suffer if the mother has a depressive disorder in the postnatal year.[48]

For women who are not nursing, treatment of postpartum depression is similar to that for MDD. Bipolar disorder is important to consider in the differential diagnosis when the mother has new-onset depression after delivery. Most experts advise including the spouse in psychotherapy sessions, and full-time or live-in help (either a relative or a professional) is recommended for severe depression if at all possible.[41]

Treating depression in breast-feeding women

When psychiatric medications are indicated during breast-feeding, a woman and her partner should be informed about the potential effects on the neonate before making a decision. Infant monitoring is strongly recommended during treatment. Before starting therapy, it is important to examine the infant thoroughly for physical and neurologic abnormalities. If concerns arise because of factors such as irritability or change in sleep patterns, discontinuing either the medication or the breast-feeding should be considered.

All antidepressants are excreted into breast milk, but levels in infants are usually undetectable.[49] No conclusive evidence has shown that exposure to trace amounts of antidepressants in breast milk produces long-term neurobehavioral deficits in infants. Moreover, no one agent is preferred, in part because of limited data.[49]

Infants exposed to antidepressants in breast milk have shown normal weight gain in the first 6 months of life.[50] In contrast, reduced weight gain has been associated with prolonged postpartum depression,[50] possibly because of changes in the mother's feeding behavior or cortisol levels in breast milk. Thus, maternal depression can have as large an impact as antidepressant exposure on infant growth. Data support a low incidence of toxicity in infants exposed to antidepressants through breast milk; but the number of cases reported is small, and concern for infant safety remains. It is also important to keep in mind that premature infants are at greater risk because of reduced drug metabolism.[51]

Depression in menopause

Menopause is probably not a high-risk time for the onset of affective disorders, women with a history of affective illness may be at risk for a recurrence during perimenopause.[52] No direct link between estrogen depletion and depression has been found, and treatment of perimenopausal depression with hormone replacement therapy (HRT) is controversial. Estrogen has a number of biochemical effects that should theoretically improve depression—an increased number of serotonergic receptors and enhanced serotonergic postsynaptic responsiveness and neurotransmitter uptake. In studies of perimenopausal women with MDD, improvement has been seen with estradiol monotherapy[53] and combined sertraline and estrogen therapy.[54] Depressed women using HRT who were

treated with SSRIs were also found to have higher remission rates than those not taking HRT.[55]

Conclusion

Clinicians need to consider gender when assessing a depressive illness and deciding on the best course of treatment. In women, the physician should identify any relationship between depression and menstruation, pregnancy, the perinatal period, or the perimenopausal period. Depression may appear or be exacerbated during puberty or menopause.

For some women, especially those with a personal or family history of affective illness, reproductive life events pose greater risk. Understanding the patterns of depression in women with mood disorders at times of reproductive transition makes it possible to plan clinical strategies to minimize or even prevent recurrences. Psychosocial therapies can address issues that are particularly relevant to women, such as competing roles and conflicts. SSRIs are the usual pharmacologic treatment. ■

Disclosure *The author has no relationship with any commercial entity that might represent a conflict of interest with the content of this article.*

SELF-EXAMINATION

1. Which of these statements about depression in women is false?
   a) Women are twice as likely as men to have major depressive disorder (MDD).
   b) Fewer women than men have dysthymia.
   c) The gender disparity in the incidence of depression begins at puberty.
   d) Depression is the second leading cause of disability in women.
   e) Suicidal ideation is more common in women than in men.

2. Which one of these symptoms is not common in depressed women?
   a) weight loss
   b) bulimia
   c) anxiety
   d) back pain
   e) dizziness

3. Which of these is not a diagnostic criterion for the stated condition?
   a) fatigue nearly every day in MDD
   b) difficulty concentrating in premenstrual dysphoric disorder (PMDD)
   c) change of more than 5% of body weight in a month in MDD
   d) feelings of worthlessness in PMDD
   e) diminished ability to concentrate in MDD

4. Which one of these statements about the treatment of PMDD is false?
   a) Aerobic exercise improves symptoms.
   b) Selective serotonin reuptake inhibitors (SSRIs) can be effective if used intermittently in each cycle.
   c) The beneficial effects of SSRIs are appreciated sooner in PMDD than in MDD.
   d) SSRIs have been shown to relieve breast tenderness.
   e) Calcium supplementation has shown efficacy.

5. Which one of these statements about treating depression in women of childbearing age is true?
   a) Symptomatic depression during pregnancy does not increase risk for preterm labor.
   b) Only fluoxetine has been approved for the treatment of depression during pregnancy.
   c) Electroconvulsive therapy is contraindicated for the treatment of severe refractory depression after 24 weeks' gestation.
   d) The incidence of postpartum depression peaks 10 weeks after delivery.
   e) If a mother takes an antidepressant while breast-feeding, her infant will have detectable levels of the drug in his serum.

Answers at end of reference list.

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Answers: 1)b, 2)a, 3)d, 4)a, 5)d