REVIEW

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Recognizing and managing depression in women throughout the stages of life

ABSTRACT

Depression is twice as common in women as in men, and women often experience different symptoms, a different course, and a different response to treatment. Furthermore, the menses, oral contraceptive use, parturition, menopause, and old age may cause or exacerbate depression. This paper discusses the diagnosis and management of depression in women throughout the stages of life.

KEY POINTS

Rule out depression induced by steroids, oral contraceptives, or antihypertensive medications.

Treat concurrent conditions that may exacerbate depression such as premenstrual syndrome and thyroid dysfunction.

Consider any comorbid conditions when choosing treatment for depression and select a medication that may help with both.

Consider selective serotonin reuptake inhibitors as first-line therapy.

Women may take longer to respond to antidepressant therapy, require lower dosages, and experience more side effects and drug interactions than men.

DEPRESSION IS DIFFERENT in women. Not only is it much more common in women than in men, but it often has a very different cause, presentation, course, and response to treatment. Furthermore, depression is often associated with events of the female life cycle.

To treat depression in women effectively, one needs to appreciate the differences.

GENDER DIFFERENCES IN DEPRESSION

Compared with men, women are:

- Approximately twice as likely to suffer from depression (as many as 20% of women have depression at some point in their lives[1])
- More prone to develop depression at a younger age, often during adolescence[2]
- More likely to have recurrent bouts of depression[2]
- More likely, if depressed, to report somatic symptoms such as back pain, bowel complaints, dizziness, dyspnea, headache, fatigue, insomnia, joint or limb pain, palpitations, nausea, or indigestion[3]
- More likely, if depressed, to have reverse vegetative symptoms (eg, weight gain rather than weight loss)[4]
- Three times more likely to experience seasonal affective disorder[5]
- More likely, if depressed, to have a coexisting psychiatric disorder such as anxiety or an eating disorder, making treatment more difficult[6]
- More likely to attempt suicide (although men who attempt suicide are more likely to succeed).[7]

WHY IS DEPRESSION MORE COMMON IN WOMEN?

Kornstein[8] outlined three general theories to account for why women seem to develop depression more often than men, and suggested that the real reason is an interaction among the three theories:

Women have biological differences in brain structure and function (eg, neuroendocrine and circadian systems), genetic transmission, and hormones.

Women more often seek help when they are depressed. (Therefore, the apparent difference in prevalence may partly be an artifact of reporting.)

Women have more psychosocial reasons to be depressed, ie, they are socialized differently, often have a lower social status, are more likely to be victimized, cope differently with stress, and—of special note—face greater stress due to juggling the demands of job and home. Even though most women work outside the home, often in positions as demanding as those of men, they still carry the primary responsibility for the household and child-rearing. Although married people of either sex are less likely to be depressed than single people, this finding is more consistent in men than in women.[9] Finally, women are more likely than men to have a specific trigger (eg, a stressful life event) in the 6 months preceding the onset of depression.

Depression is more likely to recur in women than in men

DEPRESSION AND THE MENSTRUAL CYCLE

The menstrual cycle can exacerbate mental disorders such as depression, anxiety, panic disorder, and dysthymia. At the same time, the menstrual cycle itself can cause mood changes severe enough to seriously affect function.

Premenstrual syndrome vs premenstrual dysphoric disorder

An estimated 75% of women experience physical, cognitive, and emotional symptoms in the late luteal phase of the menstrual cycle, including mood alteration, irritability, nervousness, depression, and fatigue.[10] Commonly called **premenstrual syndrome** or **PMS**, these symptoms usually do not interfere with daily function, do not constitute a mood disorder, and do not require antidepressant treatment.[11]

Premenstrual dysphoric disorder (PMDD), in contrast, is much less common and more severe. Fewer than 5% of women have PMDD, with symptoms severe enough to interfere with school, work, social activities, or relationships and which may require drug therapy or psychotherapy or both.[10]

PMDD is much less common than depression, anxiety, panic disorder, or dysthymia. It differs from true depressive disorders in that the symptoms do not persist throughout the menstrual cycle, but rather occur only during the luteal phase.

Diagnosing premenstrual dysphoric disorder

To confirm the diagnosis of premenstrual dysphoric disorder and to differentiate it from PMS and mental disorders such as major depression, patients should keep a daily chart of their moods, feelings, and basal body temperatures for at least two consecutive menstrual cycles.[11] According to the definition of PMDD in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM IV),[12] five or more of the following symptoms must be present most of the time during the last week of the luteal phase of the menstrual cycle, and during most menstrual cycles for 1 year:

- Depressed mood
- Anxiety
- Affective lability
- Anger, irritability, or increased interpersonal conflicts
- Decreased interest in usual activities
- Difficulty concentrating
- Lack of energy
- Marked change in appetite
- Hypersomnia or insomnia
- Feeling of being out of control
- Physical signs and symptoms such as breast swelling or tenderness, headaches, joint or muscle pain, a sensation of bloating, and weight gain.

The signs and symptoms begin to remit within a few days after the onset of menses and are always absent in the week following the menses.[12] If the woman is not menstruating, it

may be necessary to measure her reproductive hormone levels to accurately distinguish the luteal and the follicular phases of the cycle.[10]

Organic syndromes that mimic PMDD include thyroid disorder, menopause, and perimenopause. Therefore, measurements of thyrotropin (formerly TSH) and follicle-stimulating hormone may help in the differential diagnosis.[11]

Treating premenstrual dysphoric disorder

TABLE 1 lists treatments for PMDD.[11] First-line treatments (education and lifestyle modifications, vitamins, and mild analgesics) can be used for milder cases and for PMS. Second-line and third-line treatments include the following.

Oral contraceptives have varying effects on PMDD, helping with some symptoms but sometimes exacerbating others. Those having more estrogen than progesterone are recommended (eg, Demulen 1/35, Ortho-Cept, others).[11]

Selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine, sertraline) have been effective in controlled trials.[13–15] The starting dose of fluoxetine is 20 mg daily, and the starting dose of sertraline is 50 to 150 mg daily. Side effects include headache, nausea, changes in appetite, changes in bowel frequency, and sexual dysfunction.

Anxiolytics also proved effective in double-blind studies.[16–19] Commonly used are buspirone (5 to 10 mg three times a day, which can be increased to 15 mg four times a day), alprazolam (0.25 mg four times a day), and others. The primary side effect of this drug class is sedation, and they are not recommended for patients with a personal or family history of substance abuse or alcoholism. Some patients need only to take an anxiolytic for the 7 to 10 days before the menses.

TABLE 1

General management of premenstrual dysphoric disorder

First-line treatments
- Education and lifestyle modifications
  - Diet modifications such as reducing caffeine, salt, chocolate, and carbohydrate
  - Vitamin supplements, particularly B complex (one capsule or tablet; avoid excessive dosing)[51]
  - Mild analgesics

Second-line treatments
- Hormonal therapy
  - Oral contraceptives with more estrogen than progestin
  - Gonadotropin-releasing hormone analogs or danazol for severe or refractory symptoms

Third-line treatments
- Psychotropic drugs
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Tricyclic antidepressants
  - Anxiolytics

Adjunctive treatment
- Psychotherapy

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ORAL CONTRACEPTIVES AND DEPRESSION

Oral contraceptive pills are an easily overlooked cause of depression in women and may be considered a precipitant after a thorough history and physical examination rule out other causes.

Studies[20] have implicated both the estrogen and the progesterone in oral contraceptives, but recent research indicates progesterone is more likely to affect mood adversely.[21] Women who have had depression in the past are at greater risk for depression while taking oral contraceptives.

The clinician should involve the patient in any decision about changing or stopping her oral contraceptive. For some women, stopping may not be an option. In these cases, discuss changing to a low-dose preparation. Symptoms such as depression, fatigue, moodiness, anxiety, and anger have been found to decrease in women who switched to low-dose contraceptives.[22]

Oral contraceptives may alter drug levels of antidepressants; for example, they may increase levels of the tricyclic antidepressant imipramine.[23] Unfortunately, gender-specific data about the effects of antidepressants are limited, because until recently clinical trials included few women.

TABLE 2

Antidepressant medications considered safe in nursing mothers

MEDICATION	BRAND NAME	FOUND IN INFANT SERUM	ADVERSE EFFECTS DOCUMENTED IN THE INFANT
Tricyclic antidepressants			
Amitriptyline	Elavil	No	None
Nortriptyline	Aventyl, Pamelor	No	None
Desipramine	Norpramin	No	None
Clomipramine	Anafranil	No	None
Doxepin	Sinequan	Yes	Sedation
Selective serotonin reuptake inhibitors			
Fluoxetine	Prozac	Yes	Colicky behavior
Sertraline	Zoloft	No	None
Other			
Bupropion	Wellbutrin	No	None (but is concentrated in breast milk)

POSTPARTUM DEPRESSION

One third of women experience mild dysphoria (tearfulness, irritability, depressed mood) beginning 5 to 14 days after delivery[24] and lasting 5 to 7 days. While this postpartum "blues" is not serious, women who develop these symptoms need to be carefully monitored, because 25% develop postpartum depression, a serious disorder.[25] Interestingly, the incidence is approximately the same in various cultures.

Diagnosing postpartum depression

The diagnostic criteria for postpartum depression are the same as the DSM IV criteria for major depression. Its peak prevalence is at 10 weeks postpartum, but it can occur anytime in the first postpartum year.[25]

Risk factors for postpartum depression[25,26] are:

- Past history of an affective disorder
- Family history of an affective disorder
- Severe life event or loss
- Thyroid antibodies.

A recent study[27] found that 43% of postpartum women who were thyroid antibody-positive had symptoms of depression, compared with 28% of antibody-negative mothers ($P < .005$), regardless of whether they had thyroid dysfunction. Thyroid disease is more common in the postpartum period than is postpartum depression but is probably a separate disorder and is not necessarily causing the depression.

Potential impact on mother and child

Postpartum depression can severely affect both the mother and child. Possible risks for the mother: suicide or homicide (especially if she is a teenager, unwed, or pregnant for the first time, or if the infant is stillborn), hallucinations, delusions, and inability to care for herself and the infant. Psychosis occurs in 0.1% to 0.2% of postpartum mothers.[28]

Moreover, children of depressed mothers display impaired social and cognitive development through the age of at least 4 years.[29] Stein et al[30] found a "reduced quality of interaction" between children and mothers at 19 months if the mother had had a depressive disorder in the postnatal year, compared with a control group.

In nursing mothers, use the lowest antidepressant dose needed to achieve remission

Treating postpartum depression

If postpartum depression is suspected, treatment must begin immediately, following a careful assessment of treatment options.

Psychiatric evaluation is recommended.

Hospitalization is mandatory if the patient has severe homicidal or suicidal ideation with a plan that she can carry out or is psychotic, manic, or unable to take medications as an outpatient.[26]

Drugs for postpartum depression include SSRIs and tricyclic antidepressants. Women with postpartum depression may take 2 to 6 weeks to respond to antidepressant therapy. If a woman has had a previous episode of postpartum depression, the risk of a recurrence can be decreased from 60% to 6% if treatment is started within 24 hours after delivery.[26] Approximately 60% to 70% of women improve with antidepressant therapy. However, 40% to 60% have another episode of major depression later in life. Of these cases, 10% will occur only in the postpartum period.[26]

Psychotherapy should be offered and should include the patient's partner.

Electroconvulsion therapy may be considered if rapid reversal is desired.

Treating the nursing mother

For nursing mothers with postpartum depression, careful questioning and individualized management are in order. Rapid weaning of the infant may worsen depression and add to the mother's already threatened self-image.[29] On the other hand, she may be relieved to stop nursing, particularly if she and the baby can sleep better as a result.[29]

Hospitalization is mandatory for postpartum depression if the patient has a homicidal or suicidal plan

Little is known about the safety of antidepressant drugs during breast-feeding. The drugs shown in **TABLE 2** are generally regarded as safe in full-term infants.[29,31] Premature infants are at greater risk because of decreased drug metabolism.[29]

In general, a mother's choice to continue breast-feeding should not discourage the clinician from treating postpartum depression. If an antidepressant is used, give the minimal dose needed to achieve remission. If the mother is taking a tricyclic antidepressant, check the serum level of the drug in the infant when the mother begins taking a maintenance dose.[31]

Lithium and carbamazepine should be avoided in women who are breast-feeding, but valproate may be used in women with bipolar affective disorder if levels are monitored.

PERIMENOPAUSAL DEPRESSION

Distinguishing common symptoms of menopause from true major depression can be a challenge.

Does estrogen deficiency cause perimenopausal depression?

A direct link between estrogen depletion and depression has not yet been found, and treatment of perimenopausal depression with hormone replacement therapy is controversial.

Estrogen has, however, a number of biochemical effects that should in theory improve depression: it increases the number of serotonergic receptors, serotonergic postsynaptic responsiveness, and neurotransmitter uptake. It also increases serotonin synthesis and levels of serotonin's metabolite 5HIAA. Furthermore, it increases acetylcholine transferase and decreases monoamine oxidase activity, leading to increased serotonin concentrations in the brain.[32,33]

Diagnosing perimenopausal depression

Psychosocial and hormonal changes surrounding the menopause can lead to psychiatric morbidity.[34] Diagnostic criteria are the same as those for major depression.

Treating perimenopausal depression

Estrogen replacement therapy for perimenopausal depression is controversial, but several lines of evidence support its use. Many women already take estrogen for its well-documented benefits of preventing osteoporosis, genitourinary atrophy, and vasomotor symptoms. Increasing evidence indicates that it helps preserve memory.[35,36] It has shown benefit in women who underwent surgical menopause and subsequently had mood disorder symptoms,[34] and studies[37–39] found it beneficial in improving mood in the perimenopause. Estrogen replacement has also been used as an adjunct to antidepressants to shorten time to response and counter treatment-resistant depression in postmenopausal women.[39]

On the other hand, estrogen replacement therapy often causes unacceptable side effects such as bloating, breast tenderness, and bleeding. In addition, the long-standing controversy about whether it causes breast cancer is still unresolved.

FIGURE 1 presents our approach to treating perimenopausal depression.

LATE-LIFE DEPRESSION

Depression is the most common mood disorder in the elderly, with a prevalence approaching 27%.[40] Functional impairment increases the risk of depression, while exercise reduces it.[41] Approximately half of patients newly diagnosed with Alzheimer disease have had at least one bout of major depression in the previous 2 years.[42] The elderly have the highest risk of suicide of any population age group. The prevalence of depression is highest in elderly patients in nursing facilities.[43]

Since living alone can have a major effect on mood, and since 50% of women over age 75 live alone, compared with 25% of men,[40] screening for depression is especially important in women.

Diagnosing late-life depression

The presentation of depression in the elderly is similar to that of depression in younger persons, but older adults are more likely to report physical complaints such as insomnia, fatigue, constipation, and repeated minor aches and pains.[44,45] They also are more likely to have vegetative symptoms, cognitive dysfunction, signs of social withdrawal, and increased dependency.[46]

Treating late life depression

Because elderly women tend to have more adipose tissue than elderly men, they generally have a higher volume of distribution for drugs, and therefore may not experience an adequate response to drug treatment for up to 12 weeks.[47]

SSRIs are recommended as a first-line treatment for depression in elderly women. Side effects of SSRIs more frequently seen in the elderly are akathisia, restlessness, anorexia, nausea, and other gastrointestinal symptoms. For severely depressed patients who respond to antidepressants, continuing treatment for at least 2 years may have benefit.[48]

Of the tricyclic antidepressants, only nortriptyline or desipramine are recommended in the elderly. Tricyclic side effects occur more often in women than men due to differences in the P450-2D6 system.[49] Before giving a tricyclic antidepressant, monitor for cardiac conduction disturbances (eg, prolonged QT interval syndrome on electrocardiography) and check hepatic and renal function. After a maintenance level is achieved, recheck the electrocardiogram and assess the plasma drug level before the morning dose.

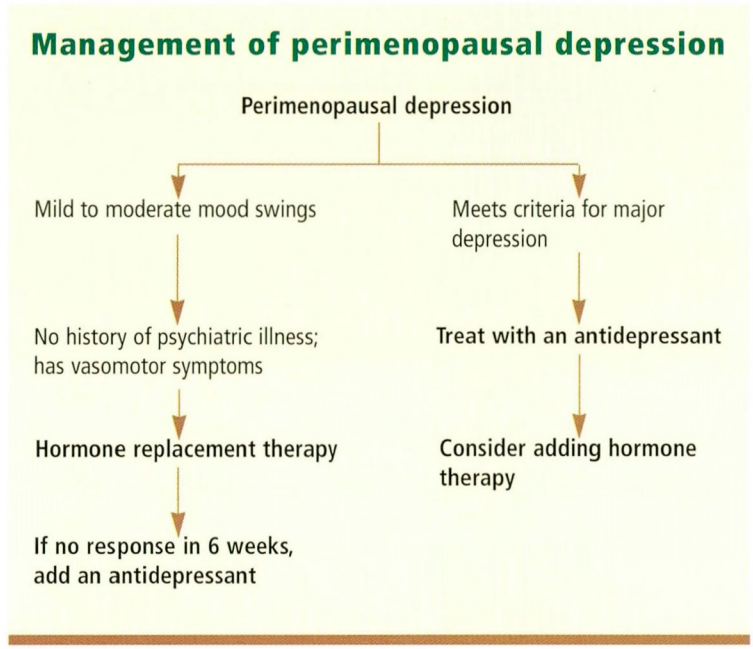

FIGURE 1

About 60% of elderly women treated for depression have a recurrence within 2 years, more than 90% of these during the first 12 months. Because the risk of recurrence is so high, many experts now recommend lifelong maintenance therapy for patients 50 years or older with a first episode of depression, or 40 years and older with two or more previous episodes.[50]

Many experts recommend lifelong antidepressant therapy for a first episode after age 50

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CME ANSWERS

Answers to the CREDIT TEST on page 383 of this issue

1 **D** 2 **D** 3 **D** 4 **E** 5 **D** 6 **C** 7 **B** 8 **A** 9 **C** 10 **C**
11 **C** 12 **B** 13 **B** 14 **A**