Enhancing Pharmacologic Effects in the Treatment of Depression in Women

Susan G. Kornstein, M.D., and Geoffry McEnany, R.N., Ph.D., C.S.

The prevalence of depressive disorders in women is twice that in men. This gender difference emerges around the time of puberty and persists through the childbearing years. Reproductive events and psychosocial factors are important influences on depression in women. Women often present with atypical depressive symptoms and comorbid disorders that can complicate both diagnosis and treatment. Sex differences in pharmacokinetics have been noted, as well as differences in antidepressant treatment response. While sleep disturbances, sexual dysfunction, and weight gain may be part of the constellation of depressive symptoms, they are also important considerations in selecting a treatment option for depressed women. *(J Clin Psychiatry 2000;61[suppl 11]:18–27)*

As interest in women's health has grown over the past decade, an increasing knowledge base has developed concerning gender differences in the prevalence, presentation, and treatment response of various medical and psychiatric disorders. Such differences suggest the need for a gender-specific approach to clinical decision making. This article focuses on special considerations in the evaluation and treatment of depression in women.

EPIDEMIOLOGY

With the exception of bipolar disorder, women exhibit greater prevalence of all mood disorders compared with men (Figure 1). The lifetime prevalence of both major depressive disorder and dysthymia is about twice as high in women as in men. This finding has been a consistent observation in several epidemiologic studies, both in the United States and in cross-national studies.[1,2] In the National Comorbidity Survey,[1] the lifetime prevalence of major depressive disorder was 21% in women versus 13% in men; for dysthymia, the rates were 8% in women versus 5% in men. Women are also far more likely than men to experience seasonal affective disorder during their lifetime, with a rate of 4% in women compared with 1% in men.[3] Premenstrual dysphoric disorder occurs only in women, with reported prevalence of about 5%.[4] Men and women show approximately the same lifetime prevalence for bipolar disorder; however, women are more likely to experience depressive episodes of bipolar illness than men, again suggesting the greater propensity for depression in women.[5]

Rates of depression vary across the life span, and gender differences in these rates also fluctuate throughout life. During childhood, boys and girls show similar rates of depression. If any differences do emerge during this period, a slight preponderance in males is typically noted. Data from the National Comorbidity Survey[1] show that the gender difference in rates of depression begins around the age of 10 years and persists until midlife, which corresponds roughly to the reproductive years in women. After midlife, the gender gap decreases, and among the elderly, few differences have emerged in the rates of depression.

Theories Regarding Gender Differences in Depression

Many theories have been proposed to account for the gender differences in rates of depression.[6–9] Some have questioned whether the differences could be due to artifact, meaning that the methods used to estimate the prevalence of depression may overreport depression among women. For instance, diagnostic biases, more help-seeking behavior among women, and women's greater tendency to report emotional distress could lead to false gender differences in rates of depression. However, the consistency of findings across social classes and cultures, and in community samples as well as clinical samples, argues that the difference in prevalence rates is not artifactual.

Biological differences between the sexes are presumed to play a role in women's increased vulnerability to depression. Differences in brain structure and function, genetic factors, and hormonal fluctuations across the reproductive cycle have all been linked to higher rates of depression in women. The contribution of psychosocial factors is undoubtedly significant as well; in particular, gender differences in socialization, role stress, victimization, coping styles, and social status may all differentially predispose women to depression.

From the Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, Richmond (Dr. Kornstein) and the Medical Neuroscience Division, Bristol-Myers Squibb, Inc., Plainsboro, N.J. (Dr. McEnany).

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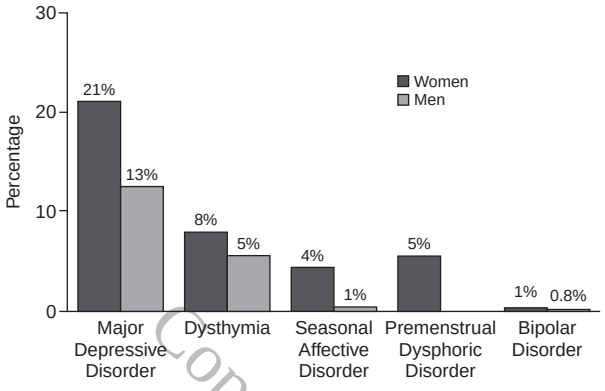
Reprint requests to: Susan G. Kornstein, M.D., Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, P.O. Box 980710, Richmond, VA 23298-0710.

Figure 1. Prevalence of Mood Disorders by Gender[a]



[a]Data from references 1 and 3–5.

ASSESSMENT OF DEPRESSION IN WOMEN

Symptoms and Course

There are a number of gender-related considerations in the assessment of depression. First, whereas men typically exhibit classic neurovegetative features of depression, women are more likely to present with atypical or reverse neurovegetative features, such as increased appetite and weight gain, as well as more anxiety and somatic symptoms.[10–13] Some of the instruments that are commonly used to measure depression, including both the 17-item and 24-item Hamilton Depression Rating Scale (HAM-D),[14] the Montgomery-Asberg Depression Rating Scale,[15] and the Beck Depression Inventory,[16] do not even assess reverse vegetative symptoms. Studies of depressed women should employ instruments that include atypical items, such as the 28-item HAM-D. Women also tend to report a greater number of depressive symptoms than men[17] and greater distress on self-report measures.[10,13] Although women are more likely to attempt suicide, the rate of completed suicide is higher in men and warrants careful assessment and monitoring.[18] In terms of course features, some evidence suggests that women may have longer episodes of depression,[19] as well as an increased likelihood of developing a chronic and recurrent course of illness.[20–22]

Comorbidity

Depressed women have higher rates of comorbid disorders than depressed men as well as different patterns of comorbidity.[23,24] Anxiety disorders and eating disorders are most frequently comorbid with depression in women, whereas alcohol and substance abuse and dependence are common in depressed men.[12,24,25] Depressed patients with comorbid anxiety tend to show a greater severity of illness and a worse prognosis, with increased rates of chronicity, relapse, and recurrence and a greater risk of suicide.[26,27] In addition, they may show a slower response to antidepressant medication, an incomplete remission of symptoms, and greater susceptibility to side effects.[26] Antidepressant choice in such patients should provide relief of anxiety as well as depressive symptoms and minimize activating side effects. A lower starting dose is also recommended.

Despite the higher prevalence of comorbid alcoholism in depressed men, women are more likely than men to develop alcoholism once they are depressed; in contrast, alcoholism in men usually precedes the onset of depression.[28,29] Differences in medical comorbidity are also important to consider, such as the greater frequency of thyroid disease, migraine headaches, chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome among women.[30–32] Thyroid screening is recommended for a woman presenting with depression if she is 45 years of age or older or if she has a personal or family history of thyroid disease.[33]

Precipitating Factors

Depressive episodes in women may be precipitated by various factors. Women appear to be more vulnerable than men to developing a depressive episode following stressful life events.[34] The type of psychosocial stressor may also be important; an unhappy marriage is more likely to lead to a depressive episode in women,[35] whereas men may be more sensitive to stressors related to employment.[36] The presence of young children at home is also a risk factor for depression in women, particularly if the woman is employed and has difficulty with child care needs.[37] In addition, a history of abuse or victimization has been strongly linked to depression in women.[38]

Women are also much more likely than men to develop a seasonal pattern to their depression; nearly 80% of those with seasonal affective disorder are women.[3] In addition, depressive symptoms in women often occur in association with the reproductive cycle, such as during the premenstrual time, the postpartum period, and perimenopause.[9] Other reproductive experiences, including miscarriage and infertility, as well as various hormonal therapies may also be associated with depressive symptoms in women.[9] A thorough reproductive history is essential in the assessment of women presenting with depression.

Influence of Reproductive Events

Menstrual cycle. It is important to consider the influence of the menstrual cycle on the course of depression in women. The premenstrual phase of the cycle is a time of increased vulnerability for both the onset of a depressive episode and the worsening of an ongoing depression.[39,40] Premenstrual exacerbation of depression may result in greater severity of ongoing depressive symptoms, the appearance of new symptoms (such as anxiety or irritability), and reduced control of suicidal and aggressive impulses during the late luteal phase of the cycle.[39] If the depression is occurring only during the premenstrual period, the diagnosis may actually be premenstrual dysphoric disorder. Menstrual cycle day should be noted in women at the time of assessment and at subsequent visits, since there may be fluctuations in symptoms, suicide risk, and treatment response related to cycle phase. Prospective charting of symptoms for several cycles may be useful

to clarify the diagnosis and delineate the exact pattern and timing of symptoms.

Pregnancy. Despite popular beliefs to the contrary, pregnancy is not protective against depression. About 20% of women experience depressive symptoms during pregnancy, and about 10% develop a major depressive episode.[41] One of the most important risk factors for depression during pregnancy is a prior history of depression. Data from the Harvard group[42] show that over 50% of women who discontinue an antidepressant proximate to conception may experience a recurrence of illness during the course of the pregnancy requiring treatment. Depression during pregnancy can have a serious impact on both mother and fetus; it can lead to poor prenatal care, smoking and substance abuse, suicide, obstetric complications (e.g., low birth weight, preterm deliveries), and increased risk of postpartum depression.[42–44] It is important to keep these issues in mind when weighing the risks versus benefits of treatment.

No antidepressants have been approved by the U.S. Food and Drug Administration for use during pregnancy. The limited data available show no evidence of teratogenesis or effects on infant development.[42] The largest database on reproductive safety is of fluoxetine, followed by the tricyclics. Mild-to-moderate symptoms may be addressed first with psychotherapy, such as cognitive or interpersonal therapy. However, when the illness is severe or poses a risk to mother or fetus, treatment with antidepressant medications or electroconvulsive therapy should strongly be considered.[42] If possible, first trimester exposure to antidepressants should be avoided.

Postpartum period. The postpartum period is an extremely vulnerable time for the onset of depressive symptoms. Three primary conditions have been described: postpartum blues, postpartum depression, and postpartum psychosis. The postpartum blues occur in 50% to 80% of new mothers during the first 2 weeks postpartum.[45] The symptoms are time limited, and therefore, management consists primarily of education, support, and close monitoring. At the other extreme is postpartum psychosis, which is a rare condition with an incidence of 0.1% to 0.2% of new mothers.[45] Episodes of postpartum psychosis typically begin within 2 weeks after childbirth and are affective in nature, usually bipolar. Hospitalization and aggressive treatment are generally indicated, since these patients may pose a danger to themselves and to their infants. The risk of subsequent postpartum psychosis is as high as 50% or greater.[42]

Postpartum depression affects 10% to 15% of new mothers, although the risk increases to 25% to 35% in women with a previous history of major depressive disorder and to over 50% in women with a previous postpartum episode.[46,47] The presence of depressive symptoms during the pregnancy is also a strong predictor of postpartum depression. A postpartum specifier for major depressive disorder is included in DSM-IV,[48] referring to episodes beginning within 4 weeks after childbirth. Pharmacologic management is generally similar to nonpostpartum depression, except for considerations of breastfeeding.[47]

All antidepressants are excreted into breast milk, although levels in infants are usually undetectable.[49] The data on specific drugs are very limited, but no significant adverse effects on infants have been described.[50] As in the case of depression during pregnancy, the risks of treatment must be weighed against the risks of untreated illness on the infant, mother, and family. Because so few data are available to guide medication choice, one should choose a drug on the basis of the patient's previous treatment response and side effects. Doses should be kept as low as possible to fully treat the depression. Feeding schedules may be adjusted to minimize exposure; for example, portions of breast milk with higher drug concentrations can be discarded.[49]

Menopause. Menopause was once thought to cause "involutional melancholia" and despair due to the loss of reproductive capacity. The menopausal years are now recognized as a positive and important developmental stage of life. National Comorbidity Survey data[1] indicate that the menopausal period is not associated with an increase in first-onset depression. However, women with a history of major depressive disorder do show an increased risk of recurrence during the perimenopausal years.[1] In addition, the perimenopause is commonly associated with minor mood symptoms, along with insomnia, concentration difficulties, and vasomotor symptoms.[51] Studies have shown that women who seek help from a menopause clinic are more likely to be those who suffer from depressive symptoms.[52] A history of premenstrual or postpartum depression appears to increase the likelihood of depressive symptoms during the perimenopause, suggesting that there is a subgroup of women who are especially vulnerable to mood disturbances at times of hormonal fluctuation.[53] Women who experience a protracted perimenopause or surgically induced menopause are also at greater risk for depressive symptoms.[54]

As with the menstrual cycle, a woman's menopausal status must also be considered in evaluating her depression. If her insomnia is actually related to perimenopausal hot flashes, an antidepressant would not be the treatment of choice. Minor depressive symptoms during the perimenopausal period are usually alleviated with estrogen replacement therapy (ERT).[55] However, estrogen alone will not treat a major depressive episode; if criteria for major depression are met, antidepressants and/or psychotherapy are required. Recent studies do suggest a potential role for estrogen in augmenting antidepressant response in postmenopausal women.[56,57]

PHARMACOLOGIC TREATMENT OF DEPRESSION IN WOMEN

Pharmacologic treatment of depression also requires special considerations with regard to gender.[9,58] Sex differences in pharmacokinetics and treatment response have been noted, as well as differences related to tolerability and adverse

effects. Choosing the most appropriate treatment requires careful assessment of underlying causes, precipitating factors, and comorbid illnesses as well as consideration of the woman's reproductive stage of life.

Pharmacokinetics

A growing body of evidence demonstrates sex differences in pharmacokinetics, including differences in drug absorption and bioavailability, drug distribution, and drug metabolism and elimination. For example, women have a slower gastric emptying time, lower gastric acid secretion, higher percentage of body fat, decreased hepatic metabolism, and lower renal clearance compared with men.[59] As a result of these differences, women may experience higher plasma levels and longer half-lives of drugs as well as a greater sensitivity to side effects. In addition, hormonal factors related to the menstrual cycle, pregnancy, or exogenous hormone use may affect medication levels in women.[59]

Treatment Response

Sex differences in treatment response to antidepressant medications have also been described.[58–60] Several studies have noted that women may respond more poorly than men to tricyclic antidepressants and appear to respond more favorably to selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs).[61–67] Hamilton and colleagues[61] performed a meta-analysis of all studies between 1957 and 1991 that had reported imipramine response rates separately for men and women. Across the 35 studies, there was an 11% difference in imipramine response rates favoring men (62% in men vs. 51% in women), which was a highly significant difference. Davidson and Pelton[62] noted that in patients with atypical depression and panic attacks, men responded preferentially to tricyclics and women to MAOIs. Steiner and colleagues[63] presented data comparing paroxetine with imipramine and placebo in patients with major depression and found that women responded significantly better to paroxetine than imipramine. Data from Yonkers et al.,[64] using a sample of dysthymic patients, showed that women were significantly more responsive to sertraline than men.

A recent meta-analysis used pooled data from 5 clinical trials of nefazodone, imipramine, and placebo for the treatment of major depression.[65] A total of 371 men and 647 women were studied, each of whom was randomly assigned to 6 to 8 weeks of treatment. No sex difference in nefazodone efficacy was found, whereas differences in imipramine response were consistent with other studies. In men, imipramine response was comparable to that with nefazodone, while the response rate with imipramine in women was no greater than that with placebo.

Kornstein and colleagues[66] examined gender differences in a 12-week study comparing sertraline and imipramine in the treatment of chronic depression. The results showed a significant gender-by-treatment interaction, with women responding more favorably to sertraline and men to imipramine. The overall response rates for sertraline and imipramine in the study were similar,[68] demonstrating the importance of data analysis by gender. Differences in tolerability were also noted, with women taking imipramine discontinuing from the study more frequently than those taking sertraline. In addition, an interaction was found between treatment response and menopausal status; premenopausal women responded significantly better to sertraline than imipramine, whereas response rates in postmenopausal women were similar.[66] Thus, the poor response to tricyclics appears to be seen predominantly in premenopausal women. Results from an early study by Raskin[67] support these findings.

Augmentation

In 2 studies, 1 with fluoxetine[56] and 1 with sertraline,[57] Schneider et al. have found that estrogen may enhance response to SSRIs in postmenopausal women. Both of these were post hoc analyses of data from late-life depression studies comparing response rates in women who were taking ERT with those who were not receiving ERT. Further investigation with studies designed more specifically to address this issue are needed. Other augmentation strategies have also shown possible advantages in women. For example, several studies suggest that triiodothyronine (T_3) augmentation is more beneficial in women than in men.[69–71] In addition, both lithium and stimulants may be more effective augmenting agents in women, whereas testosterone augmentation may be a useful strategy in men.[58]

ADDITIONAL CONSIDERATIONS IN THE ASSESSMENT AND TREATMENT OF DEPRESSION IN WOMEN

Several additional areas that merit attention when selecting an antidepressant for a depressed female patient are sleep disturbances, sexual dysfunction, and weight gain. Although all of these variables can represent dimensions of depressive illness itself, they are as likely to illustrate iatrogenic phenomena caused by antidepressant side effects. Importantly, they potentially influence treatment outcome if they compromise the patient's quality of life or her adherence to the prescribed treatment regimen. Therefore, they require consideration in choosing a treatment option for women with depression.

Sleep Disturbances in Women

Overview of sleep regulation. Sleep has both homeostatic and biorhythmic properties, and the relationship shared between these variables is reciprocal. Mechanisms driving sleep-wake patterns are complex and exquisitely sensitive to both internal and environmental shifts. For example, sleep and wakefulness are regulated by brain mechanisms, chemical mechanisms, and circadian regulation while also influenced by environmental factors.

Temperature plays an important role in sleep-wake periods. It has long been documented that humans have a daily

variance in temperature that spans approximately 1.5°F, with a peak in the latter part of the day and a nadir at some point during the night.[72] Shifts in the placement of the peak and nadir of this rhythm may result in difficulty getting to sleep (phase delay) or difficulty staying awake until the usual bedtime with subsequent awakening at a very early hour (phase advance).

Given that temperature is such a reliable indicator of circadian rhythm strength and phase, it is an excellent index of circadian system functioning in an illness such as depression. Core temperature dysregulation has been documented in major depression by Avery.[73] Phase advances and phase delays in sleep pattern are common in depression, as is fatigue, and all of these phenomena have a direct relationship to circadian variables such as temperature. McEnany and Lee[74] found a strong negative correlation (r = –.751) between mean temperature and sleep efficiency in a sample of 29 unmedicated women with major depression. To control for hormonally related temperature variation, the data were collected in women who were either in the follicular phase of the menstrual cycle or who were clearly postmenopausal. Their finding suggests an inverse relationship between temperature and wakefulness, i.e., the lower the mean temperature, the greater the sleep efficiency. This issue of circadian regulation of temperature and its effect on sleep-wake cycles holds potentially significant implications for understanding sleep-related phenomena in women, particularly those with depressive disorders.

Sleep and sleep regulation share an integral and fundamental relationship to the course of depressive illness. Sleep pattern disturbances often precede and may be driving factors in the onset of a new episode of depression. Similarly, deterioration in sleep pattern may be a sensitive indicator of relapse or recurrence.[75]

Sleep patterns in women. Women may be at increased risk for sleep disturbances. Results from the 1998 Women and Sleep Poll, conducted by the National Sleep Foundation,[76] show that 74% of women between the ages of 30 and 60 years get less than 8 hours of sleep per night. Of the 1012 women polled, 41% indicated that they had insomnia, and 53% endorsed at least one symptom of insomnia—either difficulty falling asleep, waking during the night, early-morning awakening, or not feeling refreshed upon awakening. Although these data were derived from self-reports, research by Armitage et al.[77] has shown that women are extremely accurate in estimating their sleep patterns. In both depressed patients and controls, they found that women's subjective reports of sleep disturbances accurately matched objective measures of their sleep patterns, and women's ability to judge their sleep characteristics exceeded that of men.

Armitage and colleagues[78] have also demonstrated that depressed women show greater electroencephalogram (EEG) dysregulation than men during sleep. Specifically, depressed women show a higher incidence and amplitude of fast frequency beta activity than men, particularly in the right hemisphere, which reflects hyperarousal. These findings may explain why women appear to be more sensitive to the arousing effects of antidepressants than men.[77,79] Their sleep is more easily disturbed, using objective measures, and they are more aware of sleep disturbances; therefore, they may be more likely to require hypnotics in addition to an antidepressant. For this reason, depressed women with insomnia may fare better with a less arousing antidepressant that addresses both their depressive symptoms and their sleep disturbance.

Causes of sleep disturbances in depressed women. Sleep disturbance in depressed women can arise from a variety of conditions. It may be a symptom of the depression itself; 50% to 80% of depressed patients experience sleep disturbances, predominantly insomnia.[80] Sleep disturbances may also occur as a side effect of medication; many antidepressants have been shown to either cause or worsen insomnia. Other causes include a comorbid psychiatric or general medical condition, such as posttraumatic stress disorder or chronic fatigue syndrome, as well as substance abuse, psychosocial stressors, or a primary sleep disorder. In women, sleep may also be disrupted by hormonal factors, such as those related to the menstrual cycle, pregnancy, postpartum, or menopause. In the recent National Sleep Foundation survey,[76] 71% of women reported sleep disturbances associated with the menstrual cycle; 79% of pregnant women and 56% of perimenopausal women reported disturbed sleep.

Hormonal factors and sleep. In a recent review of the interplay between gender, gonadal steroids, and sleep, Manber and Armitage[81] discuss the role of gonadal steroids in the physiologic processes driving sleep and sleep regulation in women. The authors note that hormonal patterns related to the menstrual cycle directly influence sleep variables, such as core body temperature. Specifically, progesterone raises body temperature, whereas estrogen lowers body temperature but does not block the effects of progesterone. As discussed earlier, higher core body temperatures during sleep are hypothesized to be a source of intermittent awakening and consequent reduction in sleep efficiency.

In women who ovulate, shifts in brain stem–driven mechanisms of thermoregulation may create changes in sleep between the follicular and luteal phases of the menstrual cycle. Lee[82] has demonstrated an increase in core body temperature mesor (mean) along with a dampening of the temperature amplitude postovulation. This pattern results in a deterioration in sleep quality during the luteal phase compared with the follicular phase. Such decline in sleep quality is reflected in reduced sleep efficiency.

In addition to the shifts in sleep architecture and other dimensions of biological rhythm dysregulation common to depression, normative variables in the reproductive cycle of women may worsen depressive symptoms through a sleep-driven mechanism. For example, an increase in mean temperature at ovulation and its subsequent deteriorating ef-

fects on sleep efficiency are likely to worsen mood symptoms in a depressed woman during the luteal phase of the menstrual cycle. Such a pattern offers one possible explanation as to why some women experience a premenstrual exacerbation of depression.

The impact of thermoregulation on sleep is also evident during the perimenopausal period. Several investigators[83–85] have demonstrated that core body temperature elevations precede a majority of menopausal hot flushes and serve as a trigger for the heat-loss phenomenon. Shaver and colleagues[86] documented the effects of hot flushes on sleep in perimenopausal women; specifically, they found a reduction in sleep efficiency and longer rapid eye movement (REM) latency in symptomatic women. Woodward and Freedman[87] also noted significant changes in sleep architecture related to menopausal hot flushes, including an increase in stage 4 sleep and a shortened first REM period. Hot flushes occurring during the 2 hours prior to sleep onset were positively correlated with the amount of slow-wave sleep. Consistent with the findings of Shaver and colleagues,[86] sleep efficiency was significantly lower in those women who experienced hot flushes during the study period.

Deteriorations in sleep efficiency with sleep deprivation may be one dimension of a common pathway leading to mania in those with bipolar propensities,[88] while potentially lowering the threshold for the onset of depressive symptoms in those with unipolar illness. Fundamental shifts in biological rhythms that influence thermoregulation and sleep may provide the stressor in vulnerable individuals that then creates the sequence of events leading to symptom emergence. Thus, the connection between thermoregulation, sleep efficiency, and mood regulation in women may influence depressive course of illness. Normative events related to the menstrual cycle or the perimenopause in women with depressive disorders may act as triggers for sleep deterioration and subsequent emergence of mood symptoms.

Antidepressant effects on sleep. Because hormonal fluctuations tend to have an alerting effect on sleep, antidepressant treatment for women should be selected to minimize these sleep disturbances. Most of the antidepressants available for the treatment of depression have been shown to negatively affect sleep. Objective data based on sleep EEG recordings show that fluoxetine, sertraline, paroxetine, and venlafaxine all tend to have disruptive effects on sleep physiology.[89,90] Specifically, they may cause increased sleep latency (time to fall asleep), increased wakefulness and arousals, increased stage 1 sleep (light sleep), and decreased sleep efficiency. MAOIs have also been shown to negatively impact sleep by suppressing REM sleep and reducing sleep time and efficiency. Tricyclics also inhibit REM sleep, but generally do not have an alerting effect like the SSRIs. Hypothetically, a sustained level of sleep discontinuity across a medication trial could mimic the same set of physiologic circumstances that women experience with sleep after ovulation, i.e., an increase in awakenings with a decrease in sleep efficiency, and for some, a loss of therapeutic effect from the antidepressant.

Some antidepressants actually promote sleep in patients with depression. The compounds with the most beneficial effects on sleep quality are those that exert serotonin-2 (5-HT_2) antagonism as a dimension of their pharmacologic profiles, as is the case with nefazodone, mirtazapine, amitriptyline, and trazodone.[89,90] The most sedating medication is trazodone, which increases sleep time, increases slow-wave sleep, and decreases awakenings. The sedating effect, however, is extreme at antidepressant dosages and can interfere with daily functioning and compliance.

Three studies[91–93] utilizing identical protocols compared nefazodone and fluoxetine regarding effects on sleep during 8 weeks of double-blind treatment, and the data were pooled for analyses. Several significant differences emerged concerning the effects of the 2 compounds on sleep architecture. Specifically, nefazodone was found to have beneficial effects on 4 key sleep parameters—number of awakenings, percentage of awake time, percentage of stage 1 sleep, and sleep efficiency—all of which were adversely affected by fluoxetine. Of note, sleep latency was similar for the 2 drugs, indicating that there was no difference in sedating effects. Thus, the beneficial effects of nefazodone on sleep are not due to sedating properties of the drug, but rather to positive intrinsic effects on sleep physiology in depressed patients, probably due to its 5-HT_2 receptor blockade.

These findings are of particular importance in selecting an antidepressant for women with depression. If a depressed patient is already experiencing significant arousal and awakenings in sleep as a dimension of the depression, this trend may be worsened with the addition of an antidepressant that stimulates 5-HT_2 receptors, such as the SSRIs or venlafaxine. In women who ovulate or who are perimenopausal, arousal and awakening in sleep will be even greater as a consequence of thermoregulatory shifts impacting sleep. Given the direct and strong relationship between sleep and mood regulation, any factor that perpetuates sleep disruption in the form of reduced sleep efficiency may negatively impact not only the course of the depression, but also the outcome of an intervention aimed at symptom reduction. Hence, one should consider treatment choices for depressed women that are the least assailing to sleep architecture.

Sexual Function

Another important area to consider in evaluating and treating depressed female patients is their sexual functioning. Sexual dysfunction in depressed women may be a symptom of the depression itself; about 70% to 80% of depressed patients report decreased libido as part of their depression.[94] It may also be a side effect of medication, such as an antidepressant, antihypertensive, or antiulcer medication. Hormonal factors may play a role in sexual dysfunction; sexual desire in women may fluctuate with the menstrual cycle, and changes in sexual functioning are commonly seen

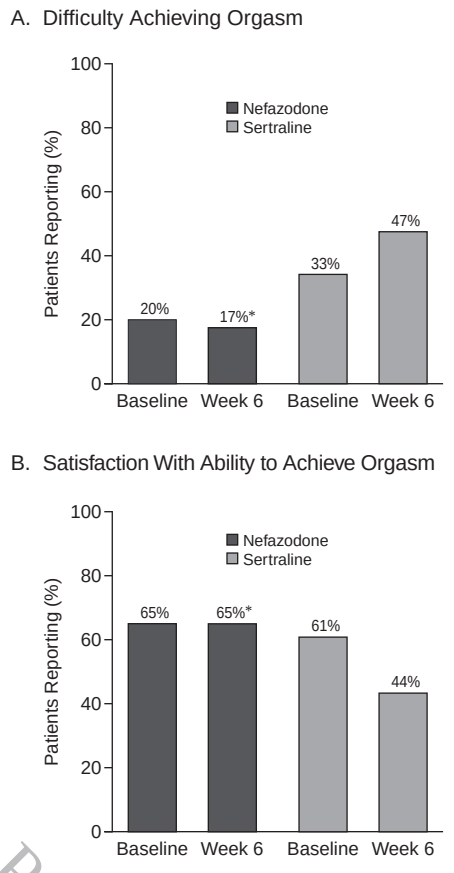
in perimenopausal and postmenopausal women.[51] Other causes include alcohol or substance abuse; a comorbid illness, such as an endocrine disorder; a primary sexual dysfunction, such as hypoactive sexual desire, dyspareunia, or vaginismus; or psychosocial factors, such as relationship difficulties or a history of sexual abuse.

Evaluating sexual function. Since many antidepressants can cause or worsen sexual dysfunction, sexual functioning should be assessed at baseline prior to starting medication as well as periodically during the course of treatment. Patients often do not spontaneously report sexual dysfunction, so the physician must inquire directly about it.[95] Questions in this area should assess the patient's overall satisfaction with her sex life and the type of dysfunction experienced (e.g., decreased desire, problems with lubrication, problems achieving orgasm). In addition, one should ask if the dysfunction occurs in all situations and with all partners, or if it is situation specific. Finally, one should assess the onset and course of the dysfunction relative to both the depressive illness and the initiation, change in dosage, or discontinuation of antidepressant medication. The responses to these questions will help shape clinical logic in making decisions regarding antidepressant treatment.

Antidepressant effects on sexual function. Many antidepressants have been shown to negatively affect sexual function, including the tricyclics, the MAOIs, and some of the newer agents.[95–97] Recent research indicates that sexual dysfunction is a common side effect of the SSRIs, although early estimates based on spontaneous reports in clinical trials were low. Shen and Hsu[98] studied the effects of SSRIs on sexual functioning in women and found that SSRI-associated sexual dysfunction in women occurs at a much higher rate than had previously been documented. In a study by Montejo-Gonzales and colleagues[99] of 344 outpatients taking SSRIs, 200 reported a sexual side effect on a sexual dysfunction questionnaire. Those reporting sexual dysfunction included 65% of patients taking paroxetine, 59% of patients taking fluvoxamine, 56% of patients taking sertraline, and 54% of patients taking fluoxetine. Men in the study reported a higher incidence of sexual dysfunction than women; however, women tended to report more severe dysfunction. Patients on venlafaxine treatment have shown rates of sexual dysfunction comparable to those with the SSRIs.[95]

Some antidepressants have shown little to no effect on sexual functioning. In particular, nefazodone, bupropion, and mirtazapine appear to have a very low incidence of sexual side effects on the basis of comparison studies with the SSRIs.[100–102] A 6-week double-blind study by Feiger and colleagues[100] compared nefazodone and sertraline with regard to depression and sexual functioning. Both compounds were well tolerated overall, and no differences in their antidepressant effect were noted. However, the results demonstrate markedly different effects on libido. Patients taking nefazodone showed significantly greater improvement in sexual desire compared with patients taking sertraline, and this difference was evident beginning as early as the second week of treatment. In contrast, no improvement in libido was noted in patients taking sertraline. Examining the data in women from this study who were sexually active at baseline, significant differences between the 2 drugs were found on measures of both difficulty of achieving orgasm and satisfaction with ability to achieve orgasm (Figure 2). The mean endpoint score for the sertraline group was worse than baseline for each of these measures, while nefazodone showed no adverse effect on orgasmic function.

Figure 2. Comparison of Nefazodone (N = 23) and Sertraline (N = 23) on Sexual Function in Women[a]

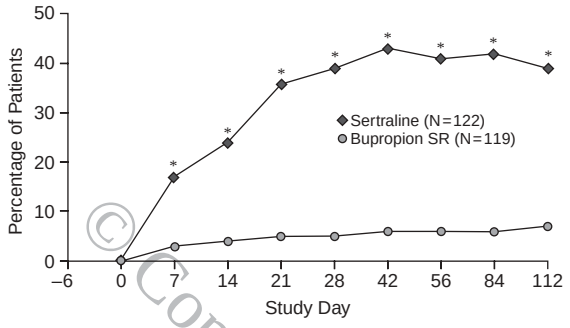


[a]Data from Feiger et al.[100]
*$p \leq .05$ vs. sertraline at week 6.

Bupropion sustained release and sertraline also differed in their effects on sexual function in a 16-week, randomized, double-blind, parallel group study.[101] Orgasm dysfunction was significantly ($p < .001$) more common in the sertraline-treated patients than in the bupropion-treated patients (Figure 3). Gender-specific analyses demonstrated that the incidence of orgasm dysfunction in women during the study was 7% for bupropion and 41% for sertraline ($p < .001$).

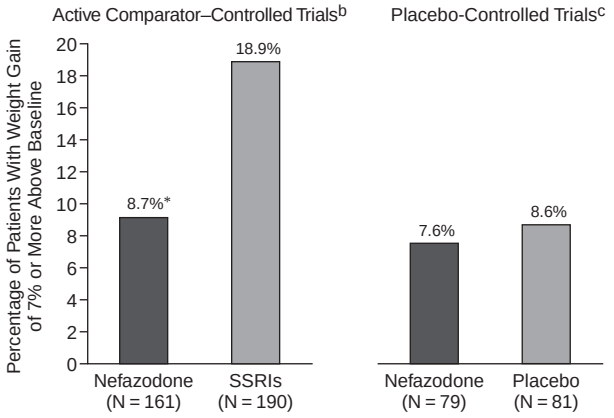
Selecting an antidepressant with minimal effect on sexual functioning increases the likelihood of compliance and, therefore, successful resolution of the patient's depression. Additionally, since antidepressant therapy is likely to con-

Figure 3. Percentage of Patients Experiencing Orgasm Failure and/or Delay During Treatment With Bupropion SR or Sertraline for 16 Weeks[a]



[a]Kavoussi et al.,[101] with permission.
*p < .001.

Figure 4. Impact of Long-Term Nefazodone Treatment on Weight in Depressed Women During Comparative and Placebo-Controlled Trials[a]



[a]G.M., data on file, Bristol-Myers Squibb Company. Abbreviation: SSRI = selective serotonin reuptake inhibitor.
[b]Nefazodone vs. fluoxetine, sertraline, and paroxetine for up to 16–46 weeks of treatment after 6–8 weeks of acute phase treatment.
[c]Nefazodone vs. placebo, up to 36 weeks in patients who responded to 16 weeks of nefazodone treatment.
*p < .006 vs. SSRIs.

tinue for an extended period of time, it is important to consider the potential impact of a medication on sexual functioning in the initial decision about choice of an antidepressant. Treatment options exist that do not require the patient to compromise her sexual functioning to treat her depression.

Weight Gain

Another area of tremendous importance to female patients is weight gain. Many women will refuse to take a medication that may cause them to gain weight. Moreover, depressed women often present with weight gain as a symptom of their depression, so it is already a common concern before they even start a medication.

According to Sachs and Guille,[103] 25% of all obesity is related to medication use. Cheskin and colleagues[104] note that the psychotropics (particularly the antidepressants, lithium, and the antipsychotics) are the most notable offenders among all medication classes. Benazzi[105] suggests that the weight gain with antidepressant treatment is a factor of recovery and may not be associated with iatrogenic causes; however, this perspective is uncommon in the literature.

Antidepressant effects on weight. Weight gain is a common side effect in patients taking the older antidepressants, such as the tricyclics and the MAOIs.[106,107] Some of the newer medications may also cause weight gain; for instance, patients taking mirtazapine often show weight gain, as has been demonstrated in a placebo-controlled trial.[108] Although clinical trials found that SSRIs tend to cause weight loss, more recent research suggests that patients taking SSRIs during long-term treatment may experience weight gain, which may occur even after a few months of treatment.[106,107] Since clinical trials rarely track long-term adverse effects, the weight gain associated with long-term SSRI use was not documented initially; however, substantial weight increases (i.e., over 20 lb) have been reported in some patients.

Some antidepressants have been shown to have minimal weight-gain effects or even to cause weight loss. As mentioned, patients taking SSRIs may experience weight loss during the acute phase of treatment; however, weight loss may also be an adverse effect for depressed patients, since many of them experience weight loss as a symptom of their depression. A few antidepressants have been shown to have minimal effects on weight. Specifically, nefazodone, bupropion, and venlafaxine have been associated with little-to-no weight change.[106,107]

The impact of long-term treatment on weight in depressed women was examined using pooled data from comparative and placebo-controlled trials with nefazodone (G.M., data on file, Bristol-Myers Squibb Company; Figure 4). A total of 351 women participated in long-term follow-up treatment for up to 16 to 46 weeks in 6 studies in which nefazodone was compared with SSRIs (fluoxetine, sertraline, or paroxetine) after 6 to 8 weeks of acute-phase treatment. There was a significantly greater incidence of weight gain with the SSRIs compared with nefazodone. A 7% or greater increase in body weight occurred in 18.9% of women in the SSRI group, compared with only 8.7% among women in the nefazodone group, which was a highly significant difference.

A second analysis examined the impact of nefazodone on weight during up to 36 weeks of treatment in 160 women who were randomly assigned to either nefazodone or placebo after responding to nefazodone 16-week, open-label treatment. No significant difference between nefazodone and placebo was found with regard to the incidence of weight gain. In the placebo group, 8.6% of the women experienced a weight gain of at least 7% of their body weight, compared with 7.6% in the nefazodone group. Thus, nefa-

zodone appears to have a weight-neutral effect, even during long-term treatment.

CONCLUSION

The clinical care of women with depression requires special considerations with regard to both evaluation and treatment. Adequate assessment includes attention to reverse vegetative symptoms, comorbid disorders, and the influence of reproductive events. Although research has been limited, there is growing evidence of sex differences in pharmacokinetics, tolerability, and treatment response. An antidepressant choice for women should effectively treat depressive symptoms and minimize treatment-emergent side effects, including sleep disturbances, sexual dysfunction, and weight gain. Women who experience these side effects may be at heightened risk for relapse or recurrence if they fail to comply with their treatment regimen.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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