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Gender-Specific Differences in Depression and Treatment Response

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ABSTRACT ~ Epidemiological studies have shown that the prevalence of depression is about twice as high in women than in men. Both neurobiological and psychosocial factors may contribute to this difference. Gender differences in depression have also been noted with regard to symptom presentation, comorbid disorders, course of illness, and response to treatment. This article provides an overview of gender differences in the phenomenology and treatment of depression, particularly the effect of gender on antidepressant treatment response. Clinicians should consider gender as a factor in both the assessment and treatment of depression. Psychopharmacology Bulletin. 2002;36(suppl 3):99-112

INTRODUCTION

Women are twice as likely as men to suffer from major depressive disorder (MDD), particularly during the childbearing years. In addition, some of the symptoms of MDD and factors involved in the etiology, course of illness, and response to treatment are influenced by gender. However, until recently, women of childbearing age were often excluded from clinical trials and, as such, our understanding of gender differences in presentation and response to treatment has been incomplete. The inclusion of these women in recent studies and a greater interest in examining the relationship between gender and outcome in clinical trials have contributed to a growing body of literature in this area. This article reviews evidence regarding differences in the epidemiology, etiology, and treatment of depression in men and women, with a focus on gender differences in response to antidepressant treatment.

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EPIDEMIOLOGY

According to data from the National Comorbidity Survey,¹ a population-based epidemiological study, the lifetime prevalence of MDD is 21.3% in women and 12.7% in men. Data from a cross-national epidemiological study demonstrated that women have a higher prevalence of depression across different countries and ethnic groups.² A higher rate of MDD was observed in all 10 countries studied (United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand). The difference in depression prevalence between men and women begins in adolescence (by age 15, girls are already twice as likely as boys to have MDD) and continues through the span of childbearing years in women (Figure 1).

ETIOLOGY OF GENDER DIFFERENCES

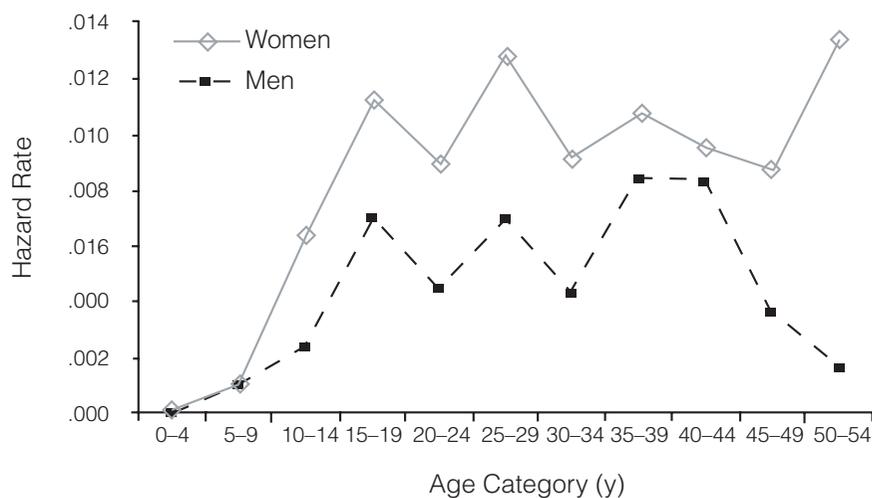
Many theories have been proposed to explain the gender difference in the prevalence of depression. Psychosocial explanations include the effects of social roles, social status, and differences in methods of coping with stressful life events. Because the difference in risk of

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FIGURE 1

MAJOR DEPRESSION HAZARD RATES BY AGE AND GENDER*



*Data from the National Comorbidity Survey; N=8,098.

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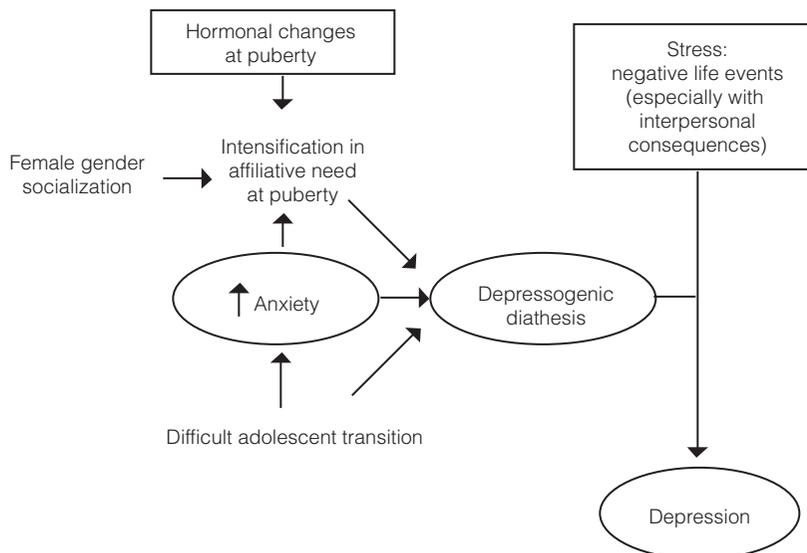
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depression emerges during a short time-span (ie, 5 years), coincident with the onset of puberty, it seems almost certain that psychosocial factors must interact with neuroendocrine development. Figure 2 presents a theoretical model of factors contributing to this phenomenon.³ It is proposed that both social and hormonal influences stimulate affiliative needs for girls during puberty. As an at-risk girl reaches puberty, this heightened affiliative need, in combination with a difficult adolescent transition (eg, insecure parental attachments, an anxious-inhibited temperament, or lack of confidence in ability to cope with stressful life events) may result in a depressogenic diathesis. This gender-specific predisposition may account for the increased risk of depression when an adolescent female is stressed by negative life events (particularly events with interpersonal consequences).

Gender differences in the role of stressful life events, marriage, parity, and educational level in the etiology of depressive illness have been considered in several studies. According to the results of a series of longitudinal studies conducted by Brown and colleagues,⁴ stressful life events appear to be a powerful risk factor for the development of depression in women. Historically, remote traumas such as childhood abuse or

FIGURE 2

FACTORS CONTRIBUTING TO GENDER DIFFERENCE IN DEPRESSION



Source: Cyranowski JM, Frank E, Young E, et al. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. *Arch Gen Psychiatry*. 2000;57:21-27. Copyright 2000. American Medical Association.

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neglect,^{4,6} proximal events in adult life (eg, widowhood or divorce), and feelings of humiliation and entrapment (in addition to the experience of loss/danger) following a severely threatening event⁷ have been associated with an increased risk of depression. Women with preexisting psychosocial vulnerability factors such as negative close relationships, low self-esteem, and lack of social support also have been shown to be at increased risk for developing MDD following a stressful life event.^{8,9} Gender differences in social roles and the development of depression following a recent stressful life event were explored in a community sample of 100 couples.¹⁰ Results showed that women had a greater risk than men of a depressive episode following the stressful life event. Consistent with the importance of social role, this greater risk was entirely restricted to episodes following events involving children, housing, or reproductive problems.

Costello and colleagues¹¹ studied the association between depression and educational history, marital status, childrearing, and/or employment. Results showed that women who were mothers and were still married to their first husband were somewhat healthier and happier than others. However, women with high-school educations, even when married with children, were at a fourfold risk of depression compared with college-educated women. Among those with only a high-school education or those who had not graduated high school, employment outside of the home significantly reduced the risk of depression. Employment did not further reduce the risk of depression for college-educated women who were married with children. Data from epidemiological and longitudinal studies examining relationships including factors of depression, marital status, and/or poverty¹²⁻¹⁴ have shown that single mothers appear to have an approximately twofold greater risk of depression than do married mothers, which may be influenced by the increased likelihood for single mothers to experience financial hardship. One study showed that single mothers were also at greater risk for development of chronic depressive syndromes.¹² Sargeant and colleagues¹⁵ explored gender differences in the role of marital status and/or education in the risk of persistent depression. Their results demonstrated an increased risk of persistent depression after 1 year in women compared with men among subjects who were divorced, widowed, or separated, or who had fewer than 10 years of education.

Most neurobiological theories attribute the higher prevalence of depressive disorders in women to fluctuations in levels of reproductive hormones. From menarche to menopause, women experience monthly fluctuations of gonadal hormones. Such cyclic hormonal fluctuations are not only coincident with the beginning of gender-based differences in the incidence of depression,¹ but are also proposed to account for the

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strong association between premenstrual dysphoric disorder and various major mood disorders.¹⁶ Estrogen, progesterone, and other gonadal steroids all have central nervous system neuromodulatory effects.¹⁶ Changes in these reproductive hormones may directly affect the function of various neurotransmitters (eg, serotonin, norepinephrine) and cerebral function.¹⁷ In particular, estrogen's neuromodulatory effects on serotonergic function have been implicated in the mechanisms associated with depression and its treatment.^{16,18} Various aspects of the estrogen-serotonin interaction may contribute to a possible increased vulnerability to mood disorders in at-risk women. Specifically, changes in estrogen levels have been shown to influence concentrations of serotonin and serotonin-receptor subtypes and to modulate response to serotonin agonists. Although the exact relationship between reproductive hormones and depression in women remains unclear, it is postulated that the neuromodulatory effects of estrogen and the other gonadal steroids may confer an increased risk of mood disorders in women with differential sensitivity to normal hormonal fluctuations (ie, during premenstrual periods, the puerperium, and perimenopause).¹⁸

Some theorists also emphasize that the greater tendency for women to report symptoms and to seek treatment may artifactually inflate the magnitude of gender differences, particularly if clinicians are more likely to ascribe mood disorder diagnoses to women. In fact, women are about three times more likely to seek treatment for depression.¹⁹ However, the increased prevalence of depression in women versus that in men is observed in both clinical and community-based epidemiological studies. Thus, differences in the tendency to seek treatment do not account for the differences in prevalence.²⁰

GENDER DISPARITY: SYMPTOMS, COURSE OF ILLNESS, AND COMORBIDITY

Although the increased prevalence of depression in women is well documented, there has been less study regarding gender differences in clinical presentation. There is some evidence that supports differences in three areas: characteristic symptoms, course of illness, and comorbidities.

Symptoms

The so-called atypical or reverse vegetative symptoms of depression (eg, hypersomnia, hyperphagia, carbohydrate craving, weight gain) are seen more often in women than in men.²¹⁻²³ However, as research has moved from inpatient to ambulatory settings and the average age of onset has decreased into the 20s, these symptoms are no longer considered atypical. Women also tend to endorse a greater number of depressive symptoms compared with men and, for a particular level of

severity, a higher degree of subjective distress.^{24,25} Specifically, women report a greater frequency of symptoms such as sleep disturbance, psychomotor retardation, feelings of worthlessness or guilt, anxiety, and somatization.^{23,25,26} The association between somatic symptoms of depression and the observed gender difference in the prevalence of depression was analyzed among subjects with MDD from the National Comorbidity Survey.²⁷ Patients were divided into those who met the overall criteria for major depression and exhibited somatic depression (ie, fatigue, appetite, and sleep disturbance) versus those with pure depression (ie, met the overall criteria for MDD but did not exhibit somatic criteria). Women exhibited a higher prevalence of somatic depression than men but not a higher prevalence of pure depression. This finding could be consistent with the theory that the gender difference in prevalence of depressive disorders may result from a difference in expression of physical symptoms during emotional distress. Also of note, somatic depression was associated with a high prevalence of anxiety disorder and, among female subjects, with body aches and onset of depression during early adolescence. Suicidality, another indicator of global severity, occurs approximately three times as often in women, although men are much more likely to complete the act.^{28,29}

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Course of Illness

Epidemiological and clinical studies have observed mixed results in terms of gender differences in the age of onset of depression,^{1,30} with only a few studies reporting an earlier age of onset in women.^{25,31} Not surprisingly, some longitudinal studies have shown that women are more likely to have a chronic and recurrent course of illness (ie, correlates of an early onset of depression),^{15,32-34} while other studies have shown no gender differences in course of illness.^{1,2,23,35-37} One specific form of recurrent depression, seasonal affective disorder, appears to be markedly more common among women.^{38,39} There is also evidence to suggest that chronic depression may affect women more seriously than it does men. Specifically, Kornstein and colleagues²⁵ found that women exhibit greater symptom severity and more functional impairment, especially in the areas of marital and family adjustment.

Comorbidity

Comorbidities that are more frequent in women include anxiety disorders (especially panic and phobic symptoms) and eating disorders, whereas comorbid alcoholism and other substance abuse disorders occur more frequently in men.^{28,31,35,40}

GENDER DIFFERENCES IN ANTIDEPRESSANT TREATMENT

Pharmacokinetics

Pharmacokinetic differences (ie, differences in absorption, bioavailability, distribution, metabolism, and elimination) have been observed in both men and women.⁴¹⁻⁴³ Although these differences may result in higher plasma levels of antidepressants in women, they can be attributed predominantly to the average differences in body weight between men and women. However, when selecting an antidepressant and determining appropriate dosing, these pharmacokinetic differences appear to be too subtle to be clinically relevant. Hence, the majority of medications will not routinely require adjustment of dose.

Additional factors that can influence the pharmacokinetics and dose requirements of antidepressants in women include the menstrual cycle, pregnancy, and exogenous hormone use. The late luteal or premenstrual phase of the menstrual cycle has been associated with multiple changes in pharmacokinetic parameters, including slower gastric emptying and small-intestinal transit times and reduced gastric acid secretion.⁴¹ The predominant effect of these changes is to decrease drug levels of antidepressants premenstrually, as has been demonstrated with desipramine, trazodone, and nortriptyline.^{44,45} Another report found no changes in fluoxetine levels,⁴⁶ although this finding may be attributable to the long half-life of fluoxetine.

Physiological changes during pregnancy can influence pharmacokinetic factors (eg, increased hepatic metabolism, decreased protein binding, increased gastrointestinal motility), resulting in increased dosage requirements of some antidepressants. In a study including eight pregnant women, the doses of tricyclic antidepressants (TCAs) required to maintain symptomatic improvement and therapeutic plasma concentrations increased during the second half of pregnancy.⁴⁷ During the final trimester, the mean dose requirement was 1.6 times greater in the pregnant women compared with the doses required when they were not pregnant. Chronic administration of exogenous hormones, such as long-term oral contraceptive use, alters hepatic blood flow in women and may result in decreased hepatic metabolism and higher plasma levels of antidepressants that are significantly metabolized by the liver.⁴⁸

Response to Antidepressant Treatment

Although antidepressants have been used for the treatment of depressive disorders for more than 40 years, the issue of whether there are differences in response between men and women did not receive serious attention until the mid-1990s.

A meta-analysis of 35 imipramine studies (342 men and 711 women) evaluated gender-specific response rates across two decades of use.⁴⁹

Results showed a modest but statistically significant difference favoring tricyclic response in men compared with women. It is important to keep in mind that the data in the analysis represented only 19% of the available imipramine trials. Moreover, the gender differences were not predicted a priori, and post-hoc analyses can be confounded by other unrecognized biases. However, this difference supports an earlier study⁵⁰ of gender differences between men and younger women in response to TCAs; older women had similar response rates to men, but younger women responded preferentially to treatment with monoamine oxidase inhibitors compared with the TCAs.

An analysis of gender differences in antidepressant response during a single, randomized, double-blind study was recently reported.⁵¹ The trial examined 12 weeks of treatment with either sertraline or imipramine in 235 men and 400 women with chronic major depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*,⁵² or double depression. Analysis of the intent-to-treat study population at the 12-week study endpoint showed that men and women with chronic depression responded differently to sertraline than to imipramine. Men were more likely to respond to imipramine, while women were more likely to respond to sertraline. This may reflect differential efficacy of these agents in treating different subtypes of depression (atypical versus melancholic features) presented by women and men, respectively. Differential effects of gonadal hormones on the efficacy of various antidepressants also may be a plausible explanation for the observed gender differences in response rates to these agents. Although the younger women were also less tolerant of imipramine side effects than were the men, the difference in response rates was not simply an artifact of differential attrition.⁵¹

A secondary analysis was performed to evaluate the response in women to imipramine or sertraline as a function of menopausal status.⁵¹ As depicted in Figure 3, premenopausal women responded significantly better to sertraline than to imipramine (57% versus 41%; $P=.01$). This difference was not evident in postmenopausal women, in whom response rates were similar for both sertraline and imipramine (57% versus 56%; $P=.88$). Although further research is warranted to determine the role of hormones in the efficacy of selective serotonin reuptake inhibitors (SSRIs) compared with TCAs, these results suggest that female reproductive hormones may play a role in the response to antidepressant treatment in women of different age groups.

An interesting interaction between gender, age, and treatment type was observed in a study conducted by Martenyi and colleagues.⁵³ The response to treatment with an SSRI (ie, fluoxetine) was compared with the tetracyclic antidepressant maprotiline, a relatively selective

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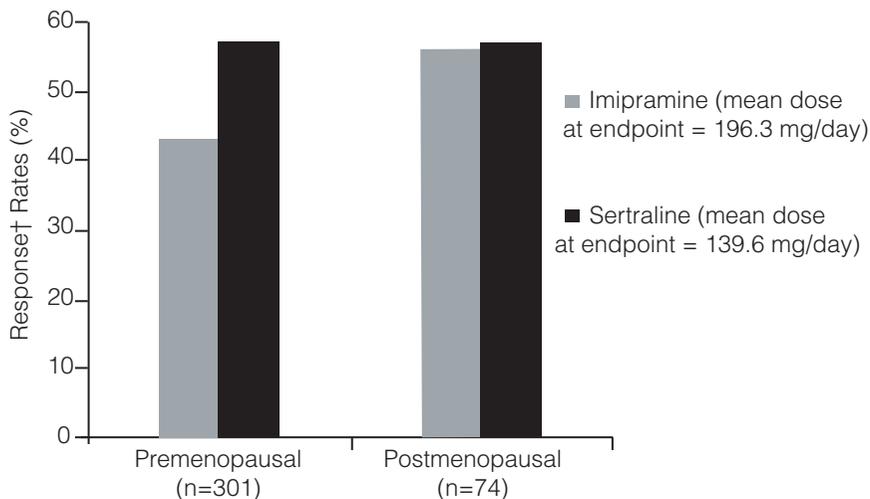
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norepinephrine reuptake inhibitor, in a 6-week, double-blind study of 105 patients with major depression. Results showed a significant difference between treatment groups in favor of fluoxetine in women but not in men. Moreover, the efficacy advantage for fluoxetine was entirely explained by the outcomes of women younger than 44 years of age. The difference between treatment groups in women age 44 and older was not statistically significant. Results for the maprotiline group were similar in men and women and did not differ on the basis of age. It is plausible that the role of age in response to treatment with fluoxetine in this study was a marker for estrogen status, as the age divisions correspond closely with menopausal status.

More recently, a pooled analysis of eight multicenter, double-blind studies of SSRIs versus venlafaxine or venlafaxine extended release (XR) comparing response and remission rates in 2,045 depressed patients⁵⁴ was reexamined to determine whether age and gender influenced response to these treatments.⁵⁵ During double-blind treatment in the pooled studies, patients were randomized to receive one of the following: venlafaxine/venlafaxine XR 75–375 mg/day, fluoxetine 20–80 mg/day, paroxetine 20–60 mg/day, fluvoxamine 100–200 mg/day, or placebo.

FIGURE 3

RESPONSE BY MENOPAUSAL STATUS IN CHRONIC DEPRESSION:
SERTRALINE VERSUS IMIPRAMINE*



* $P = .01$.

†Response=50% decrease in score on the Hamilton Rating Scale for Depression (HAM-D), HAM-D score of ≤ 15 , a score of ≤ 3 on the Clinical Global Impressions-Severity scale, or a score of 1 or 2 on the Clinical Global Impressions-Improvement scale.

Am J Psychiatry. 157:1445-1452, 2000. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Copyright 2000, The American Psychiatric Association; <http://ajp.psychiatryonline.org>. Reprinted with permission.

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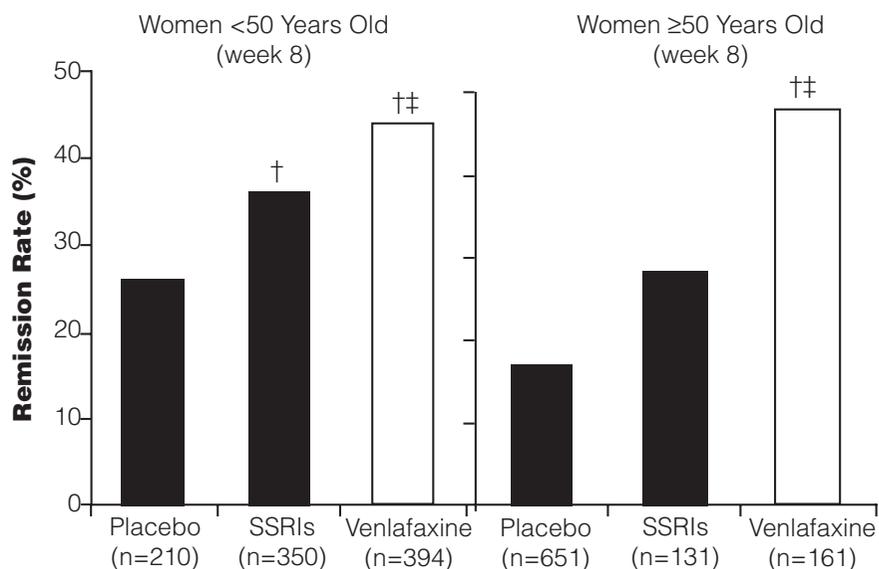
In the overall patient population, remission rates (defined as a score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression) at week 8 were significantly greater in patients treated with venlafaxine compared with those treated with SSRIs. A comparable response to treatment was observed in men and in women treated with venlafaxine. Similarly, gender did not influence response to SSRI treatment. The efficacy advantage for venlafaxine, which may be attributable to dual-reuptake inhibition, was thus apparent for men and women.⁵⁵

Following the results of the analysis by Kornstein and colleagues,⁵¹ the pooled data were further analyzed (M. Thase, R. Entsuah, S. Kornstein, unpublished data, 2002) to compare remission rates among the treatment arms in women, by age group (ie, those <50 years of age and those ≥ 50 year of age, Figure 4). In the absence of reproductive data history, these age divisions were used as a proxy indicator of menopausal status.

FIGURE 4

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COMPARATIVE REMISSION ANALYSIS BY AGE: VENLAFAXINE VERSUS SSRIS

*Remission=score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression.

† $P \leq .05$ drug versus placebo.

‡ $P \leq .05$ venlafaxine versus the SSRIs fluoxetine, fluvoxamine, and paroxetine.

SSRIs=selective serotonin reuptake inhibitors.

Source: Entsuah R, Cantillon M, Thase ME. Venlafaxine and SSRIs in the treatment of depression: comparison among age and gender variables. Poster presented at: the Thirtieth Annual Meeting of the North American Society for Psychosocial Obstetrics and Gynecology; February 20-23, 2002; Cancun, Mexico.

Kornstein SG, Sloan DME, Thase ME. *Psychopharmacology Bulletin*. Vol 36. Suppl 3. 2002.

Results of the analysis showed that remission rates at week 8 were significantly higher with venlafaxine compared with SSRIs and placebo in both older and younger women, with a fairly comparable stair-step increase in efficacy from placebo to SSRIs to venlafaxine in both age groups. An interesting observation in this analysis is that younger women responded somewhat better to SSRIs compared with older women (36% in younger women versus 28% in older women), whereas rates with venlafaxine were similar in both age groups (44% in younger women versus 48% in older women). Although the differences in both age groups were statistically significant, the relative magnitude of the effect for venlafaxine compared with SSRIs was 2.5 times greater among the older women than among the younger women. These findings suggest that the noradrenergic effects of venlafaxine might convey added benefit for older women. Further research with larger patient populations are required to confirm this interesting but preliminary finding.

ROLE OF EXOGENOUS ESTROGEN IN ANTIDEPRESSANT RESPONSE IN POSTMENOPAUSAL WOMEN

A further analysis of the data by Thase and colleagues (M. Thase, R. Entsuah, S. Kornstein, unpublished data, 2002) stratified women >50 years of age according to their use of concomitant hormone replacement therapy (HRT). The use of HRT did not appear to augment the venlafaxine response but was associated with a trend upward for both placebo response and SSRI response. SSRI-treated women who were receiving HRT had a higher remission rate than those who were not taking concomitant HRT (35% versus 27%, respectively), whereas venlafaxine-treated women had relatively comparable remission rates regardless of concomitant HRT use (50% versus 44%). Although the number of patients in these groups was small, the trends are interesting and indicate that HRT may augment the efficacy of SSRIs in older (ie, postmenopausal) women. In contrast, the efficacy of venlafaxine appears comparable in younger women and older women, with and without concomitant HRT.

The results of these analyses (M. Thase, R. Entsuah, S. Kornstein, unpublished data, 2002) suggest that estrogen not only may play a role in the pathophysiology of depression, but it might also influence the probability of response to serotonergic antidepressants. Reports on the efficacy of estrogen as an adjunct to antidepressant therapy have been mixed, however. In a 6-week, placebo-controlled, double-blind study of fluoxetine in elderly depressed women, patients on estrogen replacement therapy (ERT) plus fluoxetine had substantially greater improvement than patients using ERT plus placebo, but fluoxetine was

not significantly more effective than placebo in patients not on ERT.⁵⁶ In contrast, a recent study examining estrogen as an adjunct therapy to fluoxetine showed no benefit with estrogen in achieving remission or in preventing relapse in menopausal women.⁵⁷ Two recent studies suggest that estrogen as monotherapy may be efficacious in treating perimenopausal depressive disorders.^{58,59} Although estrogen regulates various aspects of noradrenergic, serotonergic, γ -aminobutyric acidergic, and dopaminergic transmission that could affect mood and depressive states, the explicit processes involved in or responsible for its potential antidepressant effects are not well understood. Further research on the neural mechanisms by which estrogen may act as an antidepressant and the efficacy of estrogen as antidepressant adjunctive therapy is warranted.

CONCLUSION

Women experience a higher incidence of major depression throughout adulthood compared with men. Although not fully elucidated, the etiology of this difference is likely a result of both psychosocial and neurobiological factors. The differences discussed in this review suggest that clinicians need to consider gender as a factor in both the assessment of depressive illness and in decisions regarding the best course of treatment. When assessing depression, physicians should take into account differences in symptomatology, course of illness, and comorbidities between women and men. Treatment considerations when selecting an antidepressant should include the patient's gender, age, and, in women, menopausal status, including the use of concomitant HRT. Further research is needed to refine and extend the existing knowledge base regarding these gender differences in the phenomenology and treatment of depression, including the role of endogenous and exogenous gonadal hormones in response to antidepressant treatment. ❀

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