

Gender, Depression, and Antidepressant Treatment

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Focus Points

- Women are twice as likely as men to suffer from depression and are more apt to seek help for their symptoms.
- Women more commonly have atypical depressive symptoms, comorbid anxiety or eating disorders, a chronic and recurrent course of illness, and depressive episodes in relation to stressful life events, seasonal changes, and reproductive events. Men have a greater risk of suicide and comorbid alcohol or substance abuse.
- Compared to men, women respond poorly to tricyclic antidepressants and preferentially to selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors. In both men and women, remission rates may be greater with a dual reuptake inhibitor than with SSRIs. Antidepressant treatment response may be influenced by menopausal status and the use of hormone replacement therapy.
- Both gender and menopausal status should be considered in the evaluation and treatment of depressed patients.

Abstract

Major depressive disorder (MDD) is one of the most common psychiatric illnesses and is marked by a constellation of symptoms encompassing not only feelings of sadness, guilt, and hopelessness, but also changes in neurovegetative functions, such as sleep, arousal, and appetite. Gender differences have been observed with respect to the prevalence, presentation, and course of MDD. Recent evidence suggests that response to antidepressant treatment may also be influenced by patient gender and gender-related factors, including menopausal status and use of hormone replacement therapy. It appears that reproductive hormones play a modulating role in central affective systems, probably via interaction with neurotransmitters such as serotonin and norepinephrine. These neurotransmitters are understood to be intimately involved in the regulation of both mood and the neurovegetative behaviors affected in MDD. This article reviews the literature on gender differences observed in the epidemiologic and natural history characteristics of MDD. Evidence concerning the potential influence of gender and menopausal status on the likelihood of achieving treatment success with different classes of antidepressant agents is also discussed.

Introduction

During the last decade, considerable attention has been given to the study of gender differences in the prevalence, presentation, and treatment response of many of the most common and debilitating medical and psychiatric illnesses, including cardiovascular disease and

major depressive disorder (MDD). The now routine inclusion of female patients in clinical trials of putative and established therapeutic agents has allowed investigators to identify important gender-related differences in treatment response. In the case of depression, gender differences in its epidemiology,

natural history, and treatment response seem likely to arise from multiple interacting factors, including biological and psychosocial influences. This article presents an overview of the current understanding of gender differences in depression and antidepressant treatment response. The potential impact of these gender differences on the clinical evaluation and management of patients with depressive disorders will be considered.

Gender Differences Prevalence

Depression is approximately twice as common in women as in men.^{1,2} In the National Comorbidity Survey (NCS),¹ a large epidemiologic study conducted in the United States, the lifetime prevalence of MDD was 21.3% in women compared with 12.7% in men. Lifetime prevalence rates of dysthymic disorder, a chronic, mild depression, showed a similar gender ratio in the NCS, with rates of 8% reported in women and 5% in men. In contrast, bipolar disorder shows equal prevalence rates in men and women, although depressive episodes of bipolar illness are more common in women.³ Women are not only at greater risk for depression, they are also more likely than men to report their symptoms to others and to seek help.⁴ For these reasons, women are more likely than men to present with depression to healthcare providers.

Interestingly, the gender difference in the prevalence of depression varies over the course of the life cycle. According to NCS data, the gender difference emerges at approximately 10 years of age and persists until midlife, corre-

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sponding roughly to the reproductive years in women.¹ Cross-national studies have found that the greater prevalence of depression in women is observed across different countries and ethnic groups.⁵ This finding suggests that such gender differences cannot be explained by sociocultural factors alone and that biologic variables, such as hormonal factors, are likely to contribute to the difference in prevalence.⁶

Presentation

The symptom presentation of depression may also differ between women and men. Whereas men usually present with classical neurovegetative features of depression, such as decreased appetite and insomnia, depressed women are more likely to present with atypical depressive symptoms, such as increased appetite and weight gain.⁷ Other symptoms that may be more common in women may include sleep disturbance, psychomotor retardation, anxiety, and somatization.^{7,10} Women also tend to report a greater number of depressive symptoms compared with men.¹¹ Men and women generally show a similar severity level of depressive illness, although women tend to report greater distress on self-report measures.^{7,10} Women are also more likely to attempt suicide, although the rate of completed suicides is higher in men.¹² Methods of suicide also differ, with men tending to choose more violent means, such as guns or hanging, while women choose less violent means, such as overdoses or drowning.¹²

Gender differences in psychiatric and medical comorbidities have also been noted. Depressed women have higher rates of comorbid psychiatric disorders, particularly anxiety or eating disorders, whereas alcohol and substance abuse disorders are more commonly seen in depressed men.¹³⁻¹⁵ Generally, the presence of comorbid disorders tends to complicate both the diagnosis and the treatment of depression and is associated with a worse prognosis.¹⁶ Certain general medical disorders, such as thyroid disease, migraine headaches, fibromyalgia, and chronic fatigue syndrome, are also seen more commonly in depressed women and should be considered in treatment planning.¹⁷

Course of Illness

There may also be gender differences in the course of depression. Epidemiological studies indicate that

there is no gender difference in the age of onset of depression^{1,18}; however, some researchers have noted that women tend to have longer episodes of depression than men.¹⁹ Moreover, some evidence suggests that women are more likely to develop a chronic and recurrent course of illness.^{19,22} Among patients with a diagnosis of chronic depression, women are more seriously affected than men, with an earlier age of onset, increased severity of illness, and greater functional impairment.¹⁰

Another course distinction between men and women concerns precipitating factors of depressive episodes. Women appear to be more prone to developing depression following a stressful life event.²³ The type of stressor also appears to be important, with women being more sensitive to marital and family stressors and men to job-related or financial stressors.^{24,25} Seasonal changes are also more likely to trigger episodes of depression in women, as evidenced by the greater than 3:1 ratio of women to men with seasonal affective disorder.²⁶ In addition, many women experience the onset of depression in relation to the reproductive cycle, such as premenstrually, during the postpartum period, and during the perimenopausal years²⁷; some recent evidence suggests that a woman's risk of depression during the postpartum period may be much greater than previously recognized.²⁸

Response to Antidepressant Treatment

Pharmacokinetics

Although women are significantly more likely than men to be prescribed antidepressants,²⁹ existing data on sex differences in pharmacokinetics and pharmacodynamics are limited.³⁰ Differences in drug absorption, bioavailability, drug distribution, metabolism, and elimination have been reported in a number of studies.³¹ Possible physiologic differences in women that may result in pharmacokinetic differences include slower gastric emptying, lower gastric acid secretion, higher percentage of body fat, decreased body weight and volume, decreased hepatic metabolism, and lower renal clearance than in men.³¹ These physiologic differences may lead to higher plasma concentrations and longer half-lives of antidepressants in women. The pharmacokinetics of antidepressants in women may also be altered

by exogenous hormones (eg, oral contraceptives, hormone replacement therapy [HRT]) as well as by endogenous hormonal changes associated with the menstrual cycle, menopause, and pregnancy.

Treatment Response

Gender differences in treatment response are increasingly evident.³⁰ Compared with men, women tend to show poorer response rates and slower clinical improvement with tricyclic antidepressants (TCAs) and appear to respond better to selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs).³²⁻³⁶ A meta-analysis of 35 studies examining male and female response rates to the TCA imipramine found significant differences between the sexes, with 62% of men responding to imipramine compared with 51% of women ($P < .001$).³⁴ In another study, women with atypical depression responded significantly better to MAOIs than to TCAs, whereas TCAs showed superiority to MAOIs in men.³³

Recent data indicate that women respond to SSRIs more favorably than to TCAs.³² In a randomized, double-blind study of 635 outpatients with chronic subtypes of MDD, women responded significantly better to treatment for 12 weeks with sertraline (57%) than with imipramine (46%; $P = .02$).³² In contrast, males showed a significantly higher response rate to imipramine (62%) than to sertraline (45%; $P = .04$).³² The study also showed a significant gender difference in time to response, with women responding more slowly than men to treatment with imipramine. Similar gender differences with sertraline have also been reported in patients with dysthymic disorder.³⁷

A more recent report³⁸ compared the efficacy of venlafaxine with that of SSRIs by gender. This was a pooled analysis of eight double-blind, randomized, active-controlled (four studies also had a placebo control), 6-8-week studies. A total of 2,045 patients with MDD were treated with venlafaxine (immediate or extended release), an SSRI (fluoxetine, paroxetine, or fluvoxamine), or placebo. In women, the response rate (50% decrease in baseline 17-item Hamilton Rating Scale for Depression [HAM-D₁₇] score) with venlafaxine (65%) was significantly greater than with SSRIs (57%) at week 8 ($P = .01$).³⁸ In addition, remission (HAM-D₁₇ ≤ 7) rates

for both men and women were significantly greater with venlafaxine than with the SSRIs. A gender difference in time to response was also observed in this study. In women, response occurred earlier with venlafaxine (2 weeks) than with SSRIs (4 weeks), whereas in men, the time to response was similar with both agents.³⁸

Another large pooled analysis (n=1,746) of nine studies by gender comparing TCAs, MAOIs, fluoxetine, and placebo in depressed outpatients reported results that conflict with some of the other studies reviewed.³⁹ No gender differences were found in response to TCAs or fluoxetine; however, women responded significantly better than men to MAOIs. Older women responded significantly better to TCAs than did younger women, whereas no significant differences were found between older and younger men or women in the MAOI or fluoxetine groups. The authors concluded that neither sex nor menopausal status may be relevant in antidepressant treatment; however, it is important to note that the SSRI group included only one open-label study of fluoxetine, and the sample sizes in the older patient groups were relatively small.

Impact of Menopausal Status and Hormone Replacement Therapy

Several recent studies suggest that antidepressant treatment response may also be influenced by menopausal status, further suggesting that estrogen may play a role in antidepressant response.⁴⁰⁻⁴² One investigation compared the efficacy of the SSRI fluoxetine with that of maprotiline, a tetracyclic antidepressant with selective reuptake inhibition of norepinephrine, in younger (44 years of age) and older (>44 years of age) women.³⁶ Younger women were significantly more responsive to fluoxetine than to maprotiline. Importantly, there was no difference in response rates between the two antidepressants in older women nor in men in either age group.³⁶ Similarly, in a group of chronically depressed patients treated for 12 weeks with sertraline or imipramine, premenopausal women were significantly more likely to respond to sertraline (57%) than to imipramine (43%; $P=.01$), whereas postmenopausal women responded similarly to the two medications (57% versus

56%).³² As in the study with fluoxetine and maprotiline, the differing response rates between the medications were seen only in premenopausal women.³²

Some findings also suggest that the efficacy of SSRIs may be influenced by the use of HRT in postmenopausal women.^{40,41} A pooled analysis of eight studies compared the efficacy of venlafaxine with that of SSRIs (fluoxetine, paroxetine, or fluvoxamine) in younger (<50 years of age) and older (≥50 years of age) women with MDD, and older women who had received HRT.⁴⁰ In the older patients, those who did not report taking some form of HRT showed significantly higher remission rates with venlafaxine than with SSRIs (50% versus 27%; $P<.001$), whereas no significant difference between the two treatments was noted among those taking HRT.⁴⁰ The notion that estrogen may enhance response to SSRIs in older women has been suggested by two previous studies that analyzed response rates to fluoxetine and sertraline with and without concomitant estrogen replacement therapy (ERT),⁴¹⁻⁴² although another study demonstrated no effect of ERT on fluoxetine efficacy.⁴³

Several recent studies have examined the use of estrogen as monotherapy for perimenopausal depressed women.⁴⁴⁻⁴⁶ These studies suggest that estrogen alone may be effective in treating women with perimenopausal depression, including those who meet criteria for MDD or minor depression, although further research is needed to confirm this finding as well as the possible use of estrogen as an antidepressant augmentation strategy. Given the recent Women's Health Initiative⁴⁷ study results reporting increased risks of breast cancer, myocardial infarction, and stroke in women treated with HRT, antidepressants should still be considered the treatment of first choice in depressed peri- and postmenopausal women.

Conclusion

Gender-related differences in the epidemiology, natural history, and treatment response of depression indicate that gender should be considered both when assessing depression and when choosing among treatment options. The evidence reviewed suggests that gender may have an impact on all aspects of presentation and treatment of depression, extending from the initial presenting symptoms to

the process of more formal assessment to the likelihood of treatment success with a given antidepressant. During assessment for depression, care providers should maintain awareness of gender-specific patterns of symptoms and comorbidity. Women may present with atypical symptoms, such as increased appetite and weight gain. While men tend to display alcohol and substance abuse disorders that accompany depression, women are more likely to display anxiety and eating disorders. For female patients, it is also important to determine if symptoms are linked to or triggered by productive hormonal fluctuations, such as those that might accompany menstruation, pregnancy, childbirth, or the perimenopause.

The literature reviewed also indicates that antidepressant treatment response may be influenced by gender; therefore, gender should be considered in treatment choice. For premenopausal women, SSRIs are associated with a higher rate of response than TCAs or MAOIs. Conversely, for men and postmenopausal women, TCAs may offer some therapeutic advantages over SSRIs, although safety and tolerability issues must also be weighed in the decision. Preliminary data further suggest that venlafaxine may be superior to SSRIs for postmenopausal women who are not taking HRT. After choosing an antidepressant, decisions regarding dosing and treatment duration must also be considered in light of patient gender. For women, care providers might consider lower antidepressant doses, based on gender differences in pharmacokinetics, and a longer duration of treatment, given women's tendency toward more chronic or recurrent episodes. In the event of partial or no response, different augmentation strategies might be considered for women than for men, and these might differ according to hormonal status. For example, premenopausal women might benefit from increased dosing premenstrually, while perimenopausal or postmenopausal women might benefit from the addition of ERT.

Clearly, differential consideration must be given to women and men who present with depression, given known gender differences with respect to the risk for, symptoms, course, and treatment response of depression. Continued research is required to objectively identify gender-sensitive clinical practices that maximize antidepressant treatment success. **PP**

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