Gender Differences in Depression: Implications for Treatment

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The study of gender differences in psychiatric disorders has received increasing attention in recent years. Depression has emerged as an important area of focus, as epidemiologic data have consistently shown that depression is twice as common in women as in men. In addition to this difference in prevalence, there may be gender differences in presentation, course of illness, and treatment response to both medications and psychotherapy. This article reviews current knowledge of gender differences in depression and presents recommendations for gender-specific assessment and treatment of depression.
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The emphasis on women's health issues today has brought needed attention to gender differences in the prevalence, presentation, and treatment response of various medical and psychiatric disorders. In the area of depression, gender has been shown to be a major risk factor, with women outnumbering men by a 2:1 ratio. Given this difference in prevalence, one might expect to find other gender-related differences that may be important in the clinical assessment and treatment of men and women with depression. Because of the exclusion of women from clinical trials in the past and the lack of data analysis by gender, our knowledge in this area is limited, yet it is rapidly increasing. This article presents an overview of our understanding of gender differences in depression and the clinical relevance of these findings for the evaluation and management of patients with depressive disorders.

GENDER DIFFERENCES IN PREVALENCE OF DEPRESSION

Epidemiologic studies have consistently shown that depression is about twice as common in women as in men,[1–3] a finding that has held true in cross-national studies.[2] Data from the recent National Comorbidity Survey show that the lifetime prevalence of major depression in women in the United States is 21.3%, compared with 12.7% in men, a female-to-male relative risk of 1.7.[3] Analysis of onset risk indicates that this sex difference begins in early adolescence and continues through the mid-50s.[3]

Many theories have been put forth to explain the gender difference in prevalence of depression, encompassing both the biological and psychosocial arenas (Figure 1). Artifact theories have emphasized sex differences in help-seeking behavior and symptom reporting, as well as possible diagnostic bias. Biological theories have focused on differences in brain structure and function, including neurotransmitter, neuroendocrine, and circadian systems, as well as genetic transmission and reproductive function. Psychosocial explanations for the higher rates of depression in women include the effects of gender-specific socialization, low social status, role and life stress, victimization, and maladaptive coping styles. Several excellent review articles provide overviews of these theories and the evidence to support or refute them.[4–6] It is most likely that gender differences in depression result from the interaction of many factors, including biological, psychological, and sociocultural influences.

GENDER DIFFERENCES IN CLINICAL FEATURES OF DEPRESSION

In addition to the difference in prevalence, is there any evidence of gender differences in the clinical manifestations of depression, such as symptom presentation, severity of illness, course features, comorbidity, or response to treatment?

Symptoms and Severity

Only a few studies have examined gender differences in depressive symptomatology using clinical samples.[7–9] These studies suggest that depressive symptoms in men

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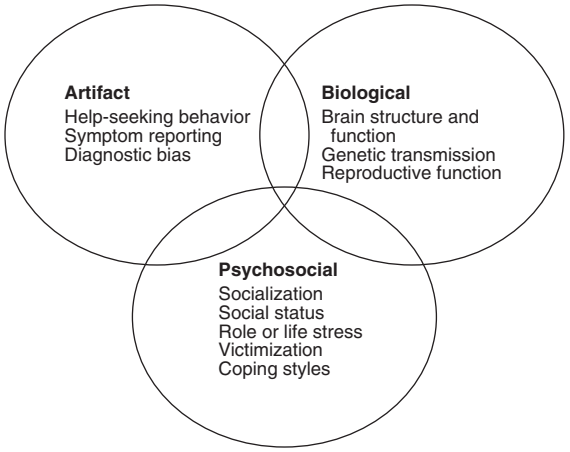
Figure 1. Theories to Explain Gender Differences in Depression



and women tend to be fairly similar, except that women appear to be more likely to present with reverse vegetative or atypical symptoms, such as increased appetite and weight gain, as well as anxiety and somatic symptoms, while men tend to report more weight loss. Depressed women are also more likely to report a greater number of symptoms compared with depressed men.[10] Most studies have found no gender difference in severity of depression, except for higher scores in women on self-report measures and on depression scales that include atypical symptoms.[7,8] However, some researchers have reported that depression in women tends to be more severe[9,11] and associated with increased functional impairment.[9]

The gender difference in suicide rates among depressed individuals is well known. Although women are more likely to attempt suicide, the rate of completed suicide is higher in men,[12,13] probably because they tend to use more lethal methods and are less likely to seek help for depression.[13,14] Men are apt to choose more violent means of suicide, such as guns or hanging, while women more often take overdoses or drown.[12,13]

Course of Illness

Age at onset. Most studies have shown no gender difference in age at onset of depression[2,3,7,11,15]; however, two recent studies have noted an earlier age at onset in women.[9,16]

Chronicity and recurrence. While cross-sectional studies have shown no sex differences in chronicity or recurrence,[2,3,7,9] several longitudinal studies have reported that women have longer episodes that are more likely to develop into a chronic and recurrent course of illness.[17–21]

Triggers of episodes. Gender differences in course of illness also include differential triggers of depressive episodes. Several researchers have found that women may be more sensitive to developing depression following stressful life events. Specifically, women are significantly more likely than men to report a stressful life event in the 6 months prior to the onset of a major depressive episode.[22,23] Moreover, the stressful life events that may provoke depression in women may involve events not only in their own lives but also in the lives of those around them.[24,25] This observation is consistent with current views of relational models for women.[26]

Another sex difference in triggers for depressive episodes is seasonality. Women have been shown to be much more susceptible to developing a seasonal pattern to their depression, with the female-to-male ratio for seasonal affective disorder being greater than 3 to 1.[27]

Women may also experience hormonal triggers of depressive episodes related to reproductive events,[28] such as during the premenstrual period, during pregnancy and the postpartum period, and around the time of menopause, as well as during exogenous hormone therapy.

The menstrual cycle may have a considerable effect on the course of depression in some women. There is an increased vulnerability during the premenstrual phase of the cycle for the onset of a depressive episode as well as the worsening of an ongoing depression.[29] It has been reported that psychiatric hospital admissions and suicide attempts occur with a disproportionate frequency during the premenstrual period,[30] a finding that supports the increased risk of both onset and worsening of depressive disorders during this time. Such worsening of depression may manifest in increased severity of ongoing depressive symptoms, the appearance of new symptoms (such as irritability or anxiety), and less control of aggressive and suicidal impulses.[29,31]

Both pregnancy and the postpartum period may also serve as triggers for depressive episodes. About 20% of women experience depressive symptoms during pregnancy, and about 10% develop a major depression.[32] Postpartum depression affects 10% to 15% of new mothers and usually begins from 2 weeks to 6 months after delivery. For many women, their first depressive episode occurs during the postpartum period.[33] Women with a previous major depressive disorder are at increased risk for postpartum depression; Frank and colleagues have reported that 33% of a group of women with recurrent depression who had children had experienced at least one postpartum episode.[34] A prior history of postpartum depression greatly increases the risk of subsequent puerperal episodes.[35]

In the past, menopause was considered an important trigger for a depressive episode. The DSM-II, published in 1968, included a disorder termed *involutional melancholia*, which was a specific depressive syndrome attributed to menopause.[36] Although such a condition is no longer thought to exist, many women do experience minor mood changes during the perimenopausal period,[37] and some women may experience the onset of a major depressive episode during this time.[38] It appears that those who have previously been vulnerable to mood disturbance related to

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other reproductive events, such as during the premenstrual period and postpartum, are most likely to experience difficulties during menopause.[39]

Another potential hormonal trigger for onset of depression in women is exogenous hormone therapy. Hormonal contraceptives, including both oral contraceptives and newer long-acting agents, such as levonorgestrel implants and depot medroxyprogesterone acetate, may be easily overlooked as etiologic factors in depressive episodes.[40,41] In addition, hormonal treatments for infertility are becoming increasingly popular and may have significant mood effects.[42] Hormone replacement therapy, particularly the progesterone component, has also been associated with depressive symptoms in postmenopausal women.[43]

Comorbidity

Data from both the National Comorbidity Survey and the Epidemiologic Catchment Area (ECA) Study suggest that depressed women have higher rates of comorbidity than depressed men,[44,45] which can complicate the evaluation and treatment of both disorders and has been shown to predict a worse outcome.[20] In particular, anxiety disorders and eating disorders are often comorbid with depression in women. In the ECA Study, 51% of respondents with major depression had a comorbid anxiety disorder, and the female-to-male ratio in this group was 3:1; among the anxiety disorders, phobia and panic disorder were the most prevalent in depressed women.[46] In a recent study of outpatients with major depression by Fava et al.,[16] women had higher rates of comorbid simple phobia and bulimia nervosa than men. In contrast, men with major depression have been reported to have a higher lifetime prevalence rate of alcohol and substance abuse and dependence.[9,16,45] Some have suggested that alcoholism may be a depressive equivalent in men[47] (and thereby account for the gender difference in depression); however, it appears that depression and alcoholism are independent disorders with high comorbidity in men.[48] Differences in medical comorbidity, such as greater prevalence of thyroid disease[49,50] and migraine headaches[51] in depressed women, may also be important considerations in both assessment and treatment.

Regarding Axis II comorbidity, Shea and colleagues[52] reported no gender difference in prevalence of comorbid personality disorder in the NIMH Collaborative Study of the Psychobiology of Depression; however, a recent study by Golomb et al.[53] showed a greater prevalence of narcissistic, antisocial, and obsessive-compulsive personality disorders in depressed men compared with depressed women.

GENDER DIFFERENCES IN TREATMENT

There may also be gender differences in response to various treatments for depression, including medications, psychotherapy, and electroconvulsive therapy.

Medications

Several excellent reviews have recently been published on gender differences in pharmacokinetics and pharmacodynamics of psychotropic medications.[54–57] Sex differences in pharmacokinetics may include differences in drug absorption and bioavailability, drug distribution, and drug metabolism and elimination. The exclusion of women until recently from early clinical trials has greatly limited our knowledge in this area, especially considering that the majority of psychotropic medications are prescribed to women.

The clinical implications of these pharmacokinetic differences are that women may have altered plasma levels and longer half-lives of drugs, as well as more side effects and drug toxicity compared with men. Examples of gender-related differences in pharmacokinetics of antidepressant medications include higher plasma levels of imipramine[58,59] and amitriptyline[60] in women, as well as a lower hydroxylation clearance of clomipramine[61] and an increased volume of distribution of trazodone.[62] A recent study by Warrington[63] showed lower plasma levels and a shorter elimination half-life of sertraline in young men compared with women or elderly men. It has long been known that age is a significant factor in pharmacokinetics, but it is becoming increasingly clear that gender may also be an important consideration.

Levels of antidepressant medications in women may also be altered by exogenous hormones,[55,56] as demonstrated by higher imipramine levels in women taking oral contraceptives,[64,65] and by endogenous hormones, as indicated by studies showing menstrual cycle variation in drug levels during the premenstrual period[66,67] and alterations in dosage requirements during pregnancy.[68]

Remarkably few studies in the literature have looked at gender differences in treatment response to antidepressant medications. Several studies suggest that women respond more poorly to tricyclics compared with men[69–72] and appear to respond better to serotonin selective reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors.[73,74] It has also been reported that women may respond more slowly to medication.[7,72] A study by the Old Age Interest Group[69] in Britain compared dothiepin, a tricyclic, and placebo in elderly men and women with major depression and found that men responded better to dothiepin than did women. In another recent study, Steiner et al.[74] compared paroxetine, imipramine, and placebo in outpatients with major depression and found that women responded better to paroxetine than to imipramine. These studies suggest gender-specific differences in efficacy and tolerability of antidepressant medications. Differential responsiveness in pre- and postmenopausal women has also been suggested, with older women showing a better response to imipramine compared with younger women.[70]

Gender differences in augmentation strategies have also been discussed. Triiodothyronine (T_3) has been shown

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to be more likely to potentiate antidepressant response to tricyclics in women than in men.[72,75–77] Studies of estrogen in women with refractory depression both alone and in combination with antidepressant medication have shown mixed results.[78–85] The use of estrogen as an adjunct to antidepressant treatment in postmenopausal women appears quite promising.[85]

Psychotherapy

The literature on gender differences in response to psychotherapy for depression is similarly sparse. While women have been understudied in drug trials, men are notably lacking from psychotherapy studies of depression. Thase and colleagues[11] compared depressed men and women treated with cognitive behavior therapy and found similar outcomes; however, in the subgroup with more severe depression, women showed a significantly worse response than men. They also found that men were less compliant with psychotherapy than women in terms of keeping appointments. In a smaller study, Jarrett et al.[86] also reported that sex did not predict response to cognitive therapy in a sample of depressed outpatients. Thase and Frank (unpublished data, 1995) have found comparable results in depressed men and women using interpersonal therapy as well.

Combination Pharmacotherapy and Psychotherapy

Only one published study to date has examined gender differences in response to combination pharmacotherapy and psychotherapy for depression. In their study combining imipramine and interpersonal psychotherapy, Frank et al.[7] found that men were significantly more likely to demonstrate a rapid and sustained clinical response than women. The authors suggest that the more rapid response in men may indicate that they responded primarily to the pharmacotherapy, whereas the women needed both the pharmacotherapy and the slower acting psychotherapy to respond.

Electroconvulsive Therapy

A recent article by Lawson addresses gender issues in electroconvulsive therapy (ECT).[87] He notes that women may have lower seizure thresholds during ECT than men, as indicated by several studies in which men required higher electrical stimulus doses than women.[88–90] In addition, there may be gender differences in cognitive side effects from ECT, namely less cognitive impairment from right unilateral ECT in women compared with men,[91] a finding attributed to sex differences in the lateralization of brain functions.

CLINICAL APPLICATIONS

These findings suggest some important gender considerations in the assessment and treatment of patients presenting with depression.

Table 1. Gender-Specific Assessment of Depression

Look for atypical symptoms, more symptoms, greater comorbidity in women; increased suicide risk in men
Look for different patterns of comorbidity
Assess course features: longer episodes, more chronic and recurrent illness in women
Look for triggers of episodes: stressful life events, seasonal pattern, reproductive events in women
Look for premenstrual exacerbation of illness
Assess psychosocial factors, eg, victimization, role stress in women

Gender-Specific Assessment of Depression (Table 1)

First, when assessing symptomatology, keep in mind that women may not always present with the usual neurovegetative symptoms. Consider the presence of atypical symptoms, such as increased appetite and weight gain, as well as anxiety and somatic symptoms. Be aware that women may present with a greater number of symptoms, increased severity of illness, more comorbidity, and greater functional impairment. In men, look for more classic endogenous symptoms and less obvious distress but an increased risk of suicide, which should be assessed and monitored very carefully.

Look for different patterns of comorbidity in men and women, such as anxiety disorders and eating disorders in women and alcohol and substance abuse disorders in men, as well as different comorbid personality disorders.

Remember to ask about the course of the depression, such as age when the patient first became depressed, number of previous episodes, and length of the current episode, which may be indicators of prognosis. Know that women may have longer episodes and an increased likelihood of developing a chronic and recurrent course of illness.

Look for gender-specific triggers of episodes, including stressful life events, seasonal patterns, reproductive events, and other hormonal factors, such as exogenous hormone therapy.

Remember to ask a female patient where she is in her menstrual cycle at the time of evaluation and if she experiences a premenstrual worsening of depression. This is especially important in assessing severity of depression, suicide risk, and response to treatment, since there may be fluctuations in symptoms related to the menstrual cycle.

Carefully assess psychosocial factors, especially a history of victimization and current role stress in women, as well as unresolved loss issues related to past abortions, miscarriages, or infertility. Be sure to take a complete reproductive history in women.

Gender-Specific Treatment of Depression (Table 2)

When deciding on an antidepressant, consider an SSRI as a first-line choice for women, especially if the patient is premenopausal, and lean away from the tricyclics. The SSRIs appear to have the advantage of better response and

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Table 2. Gender-Specific Treatment of Depression

Consider SSRIs as first-line choice for women, lean away from tricyclics
Women may take longer to respond and require longer course of treatment, lower dosage
Look for increased side effects in women, drug interactions with exogenous hormones
Consider comorbid disorders in choosing treatment
Consider influence of menstrual cycle, menopausal status
Consider different augmentation strategies
Consider combination pharmacotherapy and psychotherapy in women

better tolerability, and they are much less likely to cause weight gain, which is already a problem for many depressed women. In men and postmenopausal women, on the other hand, an as good or better response may be obtained with a tricyclic, but side effect profiles and cardiovascular implications must also be considered. Know that because of a possible increased risk for an episode to become chronic or recurrent and a possible slower response to treatment in women, an antidepressant may need to be continued for a longer duration or even long term.

Be aware of the possible need for a lower dosage in women because of altered plasma levels, and of an increased likelihood of side effects, especially with tricyclics. Be on the lookout for possible drug interactions between psychiatric medications and exogenous hormones, such as oral contraceptives. Remember that hormonal therapies may themselves cause mood changes, which can confound the clinical picture.

In choosing a particular treatment strategy, consider the presence of different comorbid disorders in men and women, both medical and psychiatric, and possible drug-drug interactions. When choosing an antidepressant treatment, try to choose one that would treat both disorders, such as an SSRI for a female patient with depression and panic disorder.

Consider the effect of the menstrual cycle on treatment response. Know that some drug levels may vary over the course of the menstrual cycle. Premenstrual exacerbation of depression may improve markedly with treatment of the depression, particularly with the SSRIs. In cases in which this does not occur, consider increasing the dosage of antidepressant medication premenstrually, adding another medication, such as low-dose alprazolam during the premenstrual time, or adding a monophasic birth control pill to inhibit the hormonal fluctuations during that phase of the cycle.

Consider different augmentation strategies in men and women. Women may be more likely to respond to T_3 augmentation, while men may do better with the addition of a tricyclic to an SSRI. Consider adding estrogen for refractory depression in peri- and postmenopausal women.

A combined treatment approach with medications and psychotherapy may be especially helpful in women. In addition to individual therapies, groups may also be beneficial, given women's emphasis on interpersonal issues. Couples therapy may also be important in some cases, since relationship difficulties may play a role in the maintenance of depression in women.

CONCLUSIONS

Although the literature is sparse, notable gender differences in depression appear to exist and are important to consider in the evaluation and treatment of depressed patients. It is hoped that, with the current emphasis on gender issues and women's health, knowledge in this area will increase dramatically over the next few years.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), clomipramine (Anafranil), imipramine (Tofranil and others), levonorgestrel (Norplant and others), medroxyprogesterone acetate (Depo-Provera and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others).

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