

# Gender Differences in Depression: Implications for Treatment

Susan G. Kornstein, M.D.

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.  
(*J Clin Psychiatry* 1997;58[suppl 15]:12–18)

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,<sup>1-3</sup> a finding that has held true in cross-national studies.<sup>2</sup> 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.<sup>3</sup> Analysis of onset risk indicates that this sex difference begins in early adolescence and continues through the mid-50s.<sup>3</sup>

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.<sup>4-6</sup> 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.<sup>7-9</sup> These studies suggest that depressive symptoms in men

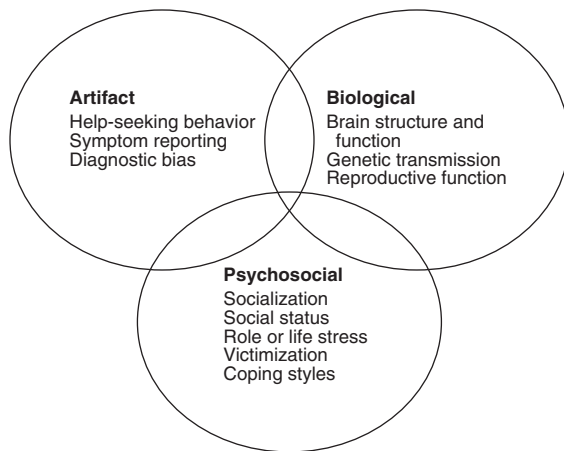
---

*From the Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, Richmond.*

*Presented at the symposium "The Dynamics of Sex: Gender Differences in Psychiatric Disorders," held in conjunction with the 149th annual meeting of the American Psychiatric Association, May 5, 1996, New York, N.Y., and supported by an unrestricted educational grant from Roerig Division of the U.S. Pharmaceuticals Group, Pfizer Inc.*

*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. 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.<sup>10</sup> 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.<sup>7,8</sup> However, some researchers have reported that depression in women tends to be more severe<sup>9,11</sup> and associated with increased functional impairment.<sup>9</sup>

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,<sup>12,13</sup> probably because they tend to use more lethal methods and are less likely to seek help for depression.<sup>13,14</sup> Men are apt to choose more violent means of suicide, such as guns or hanging, while women more often take overdoses or drown.<sup>12,13</sup>

### Course of Illness

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

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

**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.<sup>22,23</sup> 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.<sup>24,25</sup> This observation is consistent with current views of relational models for women.<sup>26</sup>

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.<sup>27</sup>

Women may also experience hormonal triggers of depressive episodes related to reproductive events,<sup>28</sup> 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.<sup>29</sup> It has been reported that psychiatric hospital admissions and suicide attempts occur with a disproportionate frequency during the premenstrual period,<sup>30</sup> 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.<sup>29,31</sup>

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.<sup>32</sup> 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.<sup>33</sup> 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.<sup>34</sup> A prior history of postpartum depression greatly increases the risk of subsequent puerperal episodes.<sup>35</sup>

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

other reproductive events, such as during the premenstrual period and postpartum, are most likely to experience difficulties during menopause.<sup>39</sup>

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.<sup>40,41</sup> In addition, hormonal treatments for infertility are becoming increasingly popular and may have significant mood effects.<sup>42</sup> Hormone replacement therapy, particularly the progesterone component, has also been associated with depressive symptoms in postmenopausal women.<sup>43</sup>

### 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,<sup>44,45</sup> which can complicate the evaluation and treatment of both disorders and has been shown to predict a worse outcome.<sup>20</sup> 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.<sup>46</sup> In a recent study of outpatients with major depression by Fava et al.,<sup>16</sup> 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.<sup>9,16,45</sup> Some have suggested that alcoholism may be a depressive equivalent in men<sup>47</sup> (and thereby account for the gender difference in depression); however, it appears that depression and alcoholism are independent disorders with high comorbidity in men.<sup>48</sup> Differences in medical comorbidity, such as greater prevalence of thyroid disease<sup>49,50</sup> and migraine headaches<sup>51</sup> in depressed women, may also be important considerations in both assessment and treatment.

Regarding Axis II comorbidity, Shea and colleagues<sup>52</sup> 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.<sup>53</sup> 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.<sup>54-57</sup> 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<sup>58,59</sup> and amitriptyline<sup>60</sup> in women, as well as a lower hydroxylation clearance of clomipramine<sup>61</sup> and an increased volume of distribution of trazodone.<sup>62</sup> A recent study by Warrington<sup>63</sup> 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,<sup>55,56</sup> as demonstrated by higher imipramine levels in women taking oral contraceptives,<sup>64,65</sup> and by endogenous hormones, as indicated by studies showing menstrual cycle variation in drug levels during the premenstrual period<sup>66,67</sup> and alterations in dosage requirements during pregnancy.<sup>68</sup>

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<sup>69-72</sup> and appear to respond better to serotonin selective reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors.<sup>73,74</sup> It has also been reported that women may respond more slowly to medication.<sup>7,72</sup> A study by the Old Age Interest Group<sup>69</sup> 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.<sup>74</sup> 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.<sup>70</sup>

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

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

### 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<sup>11</sup> 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.<sup>86</sup> 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.<sup>7</sup> 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).<sup>87</sup> 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.<sup>88-90</sup> 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,<sup>91</sup> 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



**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<sub>3</sub> 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 benefi-

cial, 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).

## REFERENCES

1. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. *Arch Gen Psychiatry* 1977;34:98-111
2. Weissman MM, Bland R, Joyce PR, et al. Sex differences in rates of depression: cross-national perspectives. *J Affect Disord* 1993;29:77-84
3. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity, and recurrence. *J Affect Disord* 1993;29:85-96
4. Wolk SI, Weissman MM. Women and depression. In: *Annual Review of Psychiatry*, vol 14. Washington, DC: American Psychiatric Association; 1995:59-95
5. Blehar MC, Oren DA. Women's vulnerability to mood disorders: integrating psychobiology and epidemiology. *Depression* 1995;3:3-12
6. Nolen-Hoeksema S. Sex differences in unipolar depression: evidence and theory. *Psychol Bull* 1987;101:259-282
7. Frank E, Carpenter LL, Kupfer DJ. Sex differences in recurrent depression: are there any that are significant? *Am J Psychiatry* 1988;145:41-45
8. Young MA, Scheftner WA, Fawcett J, et al. Gender differences in the clinical features of unipolar depressive disorder. *J Nerv Ment Dis* 1990;178:200-203
9. Kornstein SG, Schatzberg AF, Yonkers KA, et al. Gender differences in presentation of chronic major depression. *Psychopharmacol Bull* 1996;31:711-718
10. Angst J, Dobler-Mikola A. Do the diagnostic criteria determine the sex ratio in depression? *J Affect Disord* 1984;7:189-198
11. Thase ME, Reynolds CF, Frank E, et al. Do depressed men and women respond similarly to cognitive behavior therapy? *Am J Psychiatry* 1994;151:500-505
12. Roy A. Suicide. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*, VI. Baltimore, Md: Williams & Wilkins; 1995:1739-1751
13. Isometsa ET, Henriksson MM, Aro HM, et al. Suicide in major depression. *Am J Psychiatry* 1994;151:530-536
14. Kessler RC, Brown RL, Broman CL. Sex differences in psychiatric help-seeking: evidence from four large-scale surveys. *J Health Soc Behav* 1981;22:49-64
15. Burke KC, Burke JD, Regier DA, et al. Age at onset of selected mental disorders in five community populations. *Arch Gen Psychiatry* 1990;47:511-518
16. Fava M, Abraham M, Alpert J, et al. Gender differences in Axis I comorbidity among depressed outpatients. *J Affect Disord* 1996;38:129-133
17. Sargeant JK, Bruce ML, Florio LP, et al. Factors associated with 1-year outcome of major depression in the community. *Arch Gen Psychiatry* 1990;47:519-526
18. Aneshensel CS. The natural history of depressive symptoms. *Res Commun Ment Health* 1985;5:45-74
19. Ernst C, Angst J. The Zurich study, XII: sex differences in depression: evidence from longitudinal epidemiological data. *Eur Arch Psychiatry Clin*

- Neurosci 1992;241:222–230
20. Keitner GI, Ryan CE, Miller IW, et al. 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *Am J Psychiatry* 1991;148:345–350
  21. Winokur G, Coryell W, Keller M, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry* 1993;50:457–465
  22. Bebbington PE, Brugha T, MacCarthy B, et al. The Camberwell Collaborative Depression Study, I: depressed probands: adversity and the form of depression. *Br J Psychiatry* 1988;152:754–765
  23. Karp JF, Frank E. Combination therapy and the depressed woman. *Depression* 1995;3:91–98
  24. Dohrenwend BS. Anticipation and control of stressful life events: an explanatory analysis. Presented at the 47th annual meeting of the Eastern Psychological Association; April 1976; New York, NY
  25. Kessler RC, McLeod JD. Sex differences in vulnerability to undesirable life events. *Am Soc Rev* 1984;49:620–631
  26. Gilligan C. In a Different Voice: Psychological Theory and Women's Development. Cambridge, Mass: Harvard University Association; 1982
  27. Leibenluft E, Hardin TA, Rosenthal NE. Gender differences in seasonal affective disorder. *Depression* 1995;3:13–19
  28. Parry BL. Reproductive factors affecting the course of affective illness in women. *Psychiatr Clin North Am* 1989;12:207–220
  29. Endicott J. The menstrual cycle and mood disorders. *J Affect Disord* 1993;29:193–200
  30. Abramowitz ES, Baker AH, Fleischer SF. Onset of depressive psychiatric crises and the menstrual cycle. *Am J Psychiatry* 1982;139:475–478
  31. Kornstein SG, Yonkers KA, Schatzberg AF, et al. Premenstrual exacerbation of depression. Presented at the 148th annual meeting of the American Psychiatric Association; May 20–25, 1995; Miami, Fla
  32. Gotlib LA, Whiffen VE, Mount JH, et al. Prevalence and demographic characteristics associated with depression in pregnancy and the postpartum. *J Consult Clin Psychol* 1989;57:269–281
  33. Stowe ZN, Casarella J, Landry J, et al. Sertraline in the treatment of women with postpartum major depression. *Depression* 1995;3:49–55
  34. Frank E, Kupfer DJ, Jacob M, et al. Pregnancy-related affective episodes among women with recurrent depression. *Am J Psychiatry* 1987;144:288–293
  35. Garvey MJ, Tuason VB, Lumry AE, et al. Occurrence of depression in the postpartum state. *J Affect Disord* 1983;5:97–101
  36. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Second Edition. Washington, DC: American Psychiatric Association; 1968:36
  37. Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. *Am J Psychiatry* 1991;148:844–852
  38. Griffin S. Menopause and mood. *Depression* 1995;3:56–59
  39. Stewart DE, Boydell KM. Psychologic distress during menopause: associations across the reproductive cycle. *Int J Psychiatry Med* 1993;23:157–162
  40. Slap GB. Oral contraceptives and depression: impact, prevalence, and cause. *J Adolesc Health* 1981;2:53–64
  41. Wagner KD, Berenson AB. Norplant-associated major depression and panic disorder. *J Clin Psychiatry* 1994;55:478–480
  42. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1995:2338–2340
  43. Magos AL, Brewster E, Singh R, et al. The effects of norethisterone in postmenopausal women on oestrogen replacement therapy: a model for the premenstrual syndrome. *Br J Obstet Gynaecol* 1986;93:1290–1296
  44. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry* 1994;151:979–986
  45. Regier DA, Burke JD, Burke KC. Comorbidity of affective and anxiety disorders in the NIMH Epidemiologic Catchment Area Program. In: Maser JD, Cloninger CR, eds. Comorbidity of Mood and Anxiety Disorders. Washington, DC: American Psychiatric Press; 1990:113–122
  46. Judd LL. When anxiety disorders are comorbid with major depression: social and clinical burden. Presented at the 147th annual meeting of the American Psychiatric Association; May 21–26, 1994; Philadelphia, Pa
  47. Williams JBW, Spitzer RL. The issue of sex bias in DSM-III. *Am Psychol* 1983;38:793–798
  48. Merikangas KR, Leckman JF, Prusoff BA, et al. Familial transmission of depression and alcoholism. *Arch Gen Psychiatry* 1985;42:367–372
  49. Reus VI. Behavioral aspects of thyroid disease in women. *Psychiatr Clin North Am* 1989;12:153–165
  50. Whybrow PC. Sex differences in thyroid axis dysfunction: relevance to affective disorder and its treatment. *Depression* 1995;3:33–42
  51. Moldin SO, Scheftner WA, Rice JP, et al. Association between major depressive disorder and physical illness. *Psychol Med* 1993;23:755–761
  52. Shea MT, Glass DR, Pilkonis PA, et al. Frequency and implications of personality disorders in a sample of depressed outpatients. *J Pers Disord* 1987;1:27–42
  53. Golomb M, Fava M, Abraham M, et al. Gender differences in personality disorders. *Am J Psychiatry* 1995;152:579–582
  54. Dawkins K, Potter WZ. Gender differences in pharmacokinetics and pharmacodynamics of psychotropics: focus on women. *Psychopharmacol Bull* 1991;27:417–426
  55. Yonkers KA, Hamilton J. Psychotropic medications. In: Annual Review of Psychiatry, vol 14. Washington, DC: American Psychiatric Press; 1995:59–95
  56. Yonkers KA, Kando JC, Cole JO, et al. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry* 1992;149:587–595
  57. Jensvold MF, Halbreich U, Hamilton JA, eds. Psychopharmacology and Women: Sex, Gender, and Hormones. Washington, DC: American Psychiatric Press; 1996
  58. Moody JP, Tait AC, Todrick A. Plasma levels of imipramine and desmethylimipramine during therapy. *Br J Psychiatry* 1967;113:183–193
  59. Hamilton JA, Grant M, Jensvold MF. Sex and treatment of depressions: when does it matter? In: Jensvold MF, Halbreich U, Hamilton JA, eds. Psychopharmacology and Women: Sex, Gender, and Hormones. Washington, DC: American Psychiatric Press; 1996:241–257
  60. Preskorn SH, Mac DS. Plasma levels of amitriptyline: effects of age and sex. *J Clin Psychiatry* 1985;46:276–277
  61. Gex-Fabry M, Balant-Gorgia AE, Balant LP, et al. Clomipramine metabolism: model-based analysis of variability factors from drug monitoring data. *Clin Pharmacokinet* 1990;19:241–255
  62. Greenblatt DJ, Friedman H, Burstein ES, et al. Trazodone kinetics: effect of age, gender, and obesity. *Clin Pharmacol Ther* 1987;42:193–200
  63. Warrington SJ. Clinical implications of the pharmacology of sertraline. *Int Clin Psychopharmacol* 1991;6:11–21
  64. Abernethy DR, Greenblatt DJ, Shader RI. Imipramine disposition in users of oral contraceptives. *Clin Pharmacol Ther* 1984;35:792–797
  65. Gram LF, Christiansen J. First-pass metabolism of imipramine in man. *Clin Pharmacol Ther* 1975;17:555–563
  66. Kimmel S, Gonsalves L, Youngs D, et al. Fluctuating levels of antidepressants. *J Psychosom Obstet Gynaecol* 1992;13:277–280
  67. Jensvold MF, Reed K, Jarrett DB, et al. Menstrual cycle-related depressive symptoms treated with variable antidepressant dosage. *Journal of Women's Health* 1992;1:109–115
  68. Wisner KL, Perel JM, Wheeler SB. Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993;150:1541–1542
  69. Old Age Depression Interest Group. How long should the elderly take antidepressants? a double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin. *Br J Psychiatry* 1993;162:175–182
  70. Raskin A. Age-sex differences in response to antidepressant drugs. *J Nerv Ment Dis* 1974;159:120–130
  71. Glassman AH, Perel JM, Shostak M, et al. Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry* 1977;34:197–204
  72. Copen A, Whybrow P, Noguera R, et al. The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. *Arch Gen Psychiatry* 1972;26:234–241
  73. Davidson J, Pelton S. Forms of atypical depression and their response to antidepressant drugs. *Psychiatry Res* 1986;17:87–95
  74. Steiner M, Wheadon DE, Kreider MS, et al. Antidepressant response to paroxetine by gender. Presented at the 146th annual meeting of the American Psychiatric Association; May 22–27, 1993; San Francisco, Calif
  75. Prange AJ, Wilson IC, Rabon AM, et al. Enhancement of imipramine antidepressant activity by thyroid hormone. *Am J Psychiatry* 1969;126:457–469
  76. Gorman JM, Hatterer JA. The role of thyroid hormone in refractory depression. In: Nolen WA, Zohar J, Roose SP, et al, eds. Refractory Depression: Current Strategies and Future Directions. West Sussex, England: John Wiley & Sons; 1994:121–128
  77. Whybrow PC. Sex differences in thyroid axis dysfunction: relevance to affective disorder and its treatment. *Depression* 1995;3:33–42
  78. Klaiber EL, Broverman DM, Vogel W, et al. Estrogen therapy for severe

- persistent depressions in women. *Arch Gen Psychiatry* 1979;36:550-554
79. Holsboer F, Benkert O, Demisch L. Changes in MAO activity during estrogen treatment of females with endogenous depression. *Mod Probl Pharmacopsychiatry* 1983;19:321-326
  80. Shapira B, Oppenheim G, Zohar J, et al. Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. *Biol Psychiatry* 1985;20:576-579
  81. Oppenheim G. Estrogen in the treatment of depression: neuropharmacological mechanisms. *Biol Psychiatry* 1983;18:721-725
  82. Prange AJ. Estrogen may well affect response to antidepressant. *JAMA* 1972;219:143-144
  83. Kindler S, Sasson Y, Cohen R, et al. The role of oestrogen augmentation in females with refractory depression. In: Nolen WA, Zohar J, Roose SP, et al, eds. *Refractory Depression: Current Strategies and Future Directions*. West Sussex, England: John Wiley & Sons; 1994:155-158
  84. Sherwin BB. Estrogen and refractory depression. *Advances in Neuropsychiatry and Psychopharmacology* 1991;2:209-218
  85. Schneider L. Issues specific to depression in older women: does estrogen affect antidepressant response? Presented at the 148th annual meeting of the American Psychiatric Association; May 20-25, 1995; Miami, Fla
  86. Jarrett RB, Eaves GG, Grannemann BD, et al. Clinical, cognitive, and demographic predictors of response to cognitive therapy for depression: a preliminary report. *Psychiatry Res* 1991;37:245-260
  87. Lawson JS. Gender issues in electroconvulsive therapy. *Psych Ann* 1996; 26:717-720
  88. Sackeim HA, Decina P, Prohovnik I, et al. Seizure threshold in electroconvulsive therapy: effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry* 1987;44:355-360
  89. Coffey CE, Lucke J, Weiner RD, et al. Seizure threshold in electroconvulsive therapy, I: initial seizure threshold. *Biol Psychiatry* 1995;37:713-720
  90. McCall W, Shelp FE, Weiner RD, et al. Convulsant threshold differences in right unilateral and bilateral ECT. *Biol Psychiatry* 1993;34:606-611
  91. Sackeim HA, Portnoy S, Neeley P, et al. Cognitive consequences of low-dosage electroconvulsive therapy. *Ann NY Acad Sci* 1986;462:326-340