Chronic Depression in Women

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Chronic depression represents an important public health concern for women. It is underrecognized and undertreated and is associated with significant functional impairment and high rates of comorbidity. Moreover, recent research suggests that chronic depression may affect women more seriously than men; for example, women may experience illness onset at an earlier age and experience more severe psychosocial impairment compared with men. Recent studies have demonstrated the efficacy of both antidepressant medications and psychotherapy in treating chronic depression, with differential responsiveness to some treatments between women and men. Young women should be screened carefully and treated vigorously to prevent the serious consequences of this condition.

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Over the past 20 years, there has been an increasing recognition that depression tends to be a chronic and recurrent disorder, often requiring long-term treatment. This shift in understanding has led to considerable research on chronic forms of depression, which have been shown to be associated with substantial personal, psychosocial, and economic costs. In addition, there is a growing knowledge base on gender differences in chronic depression. This article provides an overview of the status of research on chronic depression, with a focus on issues of relevance to women's health.

EPIDEMIOLOGY AND SUBTYPES

As many as one third of individuals with depressive disorders experience a chronic course lasting 2 years or longer, characterized by prolonged episodes of illness and incomplete remission between episodes.[1] Chronic forms of depression include chronic major depressive disorder (i.e., major depressive episode of at least 2 years' duration), dysthymic disorder, double depression (i.e., major depressive disorder superimposed on dysthymia), and recurrent major depressive disorder with incomplete interepisode recovery.[2] The estimated lifetime prevalence of chronic depression in the general population is above 5%.[3]

In the National Institute of Mental Health Collaborative Depression Study, a prospective and naturalistic study of major depressive disorder, 30% of the cohort studied had not recovered from their index episode within the first year; 20% had not recovered after 2 years[4]; 12%, after 5 years[5]; and 7%, even after 10 years.[6] Of those who remitted, 60% had a relapse or recurrence within 5 years.[7] Rates of recovery for the recurrent episodes were similar to the rate for the index episode, with about 25% of individuals failing to recover after 1 year and 8% failing to recover after 5 years.[8] The risk of developing a chronic depression remained similar with each new episode observed.

On the basis of DSM-IV field trials data, over 75% of individuals with dysthymia experience episodes of major depression during the course of their illness.[9] Among Collaborative Depression Study subjects with double depression, only 39% achieved a full remission of both major depression and dysthymia during the first 2 years of follow-up.[10] The majority of this group showed a return to the dysthymic state once the major depressive episode had ended. Compared with subjects who had major depressive disorder alone, those with double depression showed an increased likelihood of developing a subsequent major depressive episode over the following 2 years.[10] The presence of residual depressive symptoms after a major depressive episode has also been reported to be a risk factor for relapse and recurrence in patients without antecedent dysthymia.[11]

Rates of both major depressive disorder and dysthymia have consistently been found to be about twice as high in women as in men.[3,12,13] Data from the National Comorbidity Survey showed rates of 21.3% in women and 13.7% in men for major depressive disorder and 8.0% in women and 4.8% in men for dysthymia.[3] Weissman et al.[13] reported dysthymia rates of 5.4% in women and 2.6% in men. Studies of sex differences in the risk of chronicity and recurrence of major depressive disorder

have yielded inconsistent results. Several researchers have reported no sex differences in chronicity or recurrence[14–17]; however, a number of longitudinal studies suggest that women may be more likely to suffer a chronic or recurrent course of illness.[18–22] Of note, the Thase et al.[17] study excluded patients with chronic depression, and the most pertinent negative study, by Simpson et al.,[16] was delimited to first lifetime episodes in a prospectively observed nonclinical sample (collected as part of a family study project); thus, relatives with early-onset disorders, including dysthymia, would have been excluded from this analysis.

UNDERRECOGNITION AND UNDERTREATMENT

The problem of underrecognition and undertreatment of chronic depression has been emphasized in the literature.[23–25] While this concern exists for all types of depression, with only 10% to 40% of individuals receiving adequate treatment,[23] patients who are chronically depressed tend to have the lowest treatment rates. The chronicity of their illness, without a normal baseline for comparison, allows for it to more easily go unrecognized by the patients themselves, by family members, and by health care professionals. In a recent study of patients with chronic major or double depression who had an average lifetime illness duration of 16 years, 43% of the subjects had never received antidepressant treatment, and only 20% had received a prior adequate trial of an antidepressant; 41% had never been treated with any form of psychotherapy.[24]

The tendency for women to seek psychiatric help more than men[26] appears to hold true among chronically depressed patients. In the Keller et al.[24] study of patients with chronic major or double depression discussed above, significantly more women than men had received previous treatment for depression with psychotropic medications and/or psychotherapy.[27]

IMPACT OF CHRONIC DEPRESSION

Chronic depression is associated with severe and pervasive functional impairment. The level of impairment tends to be more severe than that caused by many chronic medical disorders, including hypertension, diabetes, and arthritis.[28,29] Evidence suggests that the degree of functional impairment with chronic depression is also greater than that seen with acute major depressive disorder.[29] A lower level of psychosocial functioning is associated with a poorer prognosis for recovery.[29–31] Patients with chronic depression also show a greater frequency of suicide attempts and hospitalizations than those with episodic depression, as well as an earlier age at illness onset.[32]

The areas of impairment in psychosocial functioning with chronic depression include marital, family, and social roles, as well as occupational functioning and overall quality of life.[31] The morbidity costs due to chronic depression, including worker absenteeism and lost productivity, account for a substantial portion of the $44 billion annual cost of depression in the United States.[33] Significant physical impairment is also common in chronically depressed individuals, with high rates of health care utilization.[34]

Important gender differences have emerged with regard to the psychosocial impairment seen in chronic depression. In a recent study of patients with chronic major or double depression, women were less likely to be married and had a younger age at onset and a greater family history of affective disorder compared with men.[27] In addition, women reported greater severity of illness, poorer social adjustment, and poorer quality of life. Differences in types of impairment were also found, with women reporting more difficulties in the area of marital adjustment and men reporting greater work impairment.

A study by Berndt et al.[35] examined the impact by gender of early-onset (before 22 years of age) versus late-onset major depressive disorder on educational attainment and expected lifetime earnings in patients with chronic major or double depression. Early-onset major depressive disorder was found to adversely affect the educational attainment of women but not of men. Using 1995 U.S. Census Bureau data, the authors determined that a 21-year-old woman with early-onset major depressive disorder could expect future earnings that are 12% to 18% lower than those of a 21-year-old woman with late-onset or no depressive illness.

An important consequence of chronic depression in women that deserves emphasis is the potential transgenerational impact with regard to the most fundamental social role of women, i.e., mothering. Although there have been no studies examining the impact of chronic depression per se, the effects of depression on a variety of dimensions of mothering and on the development of psychopathology in offspring have been demonstrated.[36–39] Since depression prototypically begins in the teenage years and may persist for decades, this disorder may be present for virtually a woman's entire reproductive life, with serious consequences for the mental health of future generations.

COMORBIDITY

Chronic depressions are associated with substantial comorbidity, particularly anxiety disorders, alcoholism, and personality disorders. Overall, the presence of comorbid disorders with depression has been shown to worsen prognosis.[19] Markowitz et al.,[40] studying lifetime comorbid disorders among dysthymic patients, found 68% to have major depressive disorder; 68%, an anxiety disorder; 24%, substance abuse; and 85%, a comorbid person-

Table 1. Psychiatric Comorbidity (lifetime) in Men and Women With Chronic Major or Double Depression[a]

Disorder	Percentage of Males (N = 235)	Percentage of Females (N = 400)
Axis I		
Panic disorder	5.1	8.3
GAD	4.3	5.8
Social phobia	14.0	10.8
Simple phobia	3.8	7.3
Alcohol abuse/dependence	39.1	23.3**
Cannabis abuse/dependence	20.0	11.3**
Stimulant abuse/dependence	9.4	5.5*
Cocaine abuse/dependence	6.4	3.5
Hallucinogen abuse/dependence	5.1	1.5*
Anorexia	0.4	1.3
Bulimia	0.4	3.5
Axis II personality disorders		
Avoidant	22.6	26.6
Dependent	8.9	12.0
Obsessive-compulsive	24.3	14.3**
Passive-aggressive	8.9	4.8*
Self-defeating	11.5	18.5*
Paranoid	8.5	7.5
Schizoid	0.9	0.5
Histrionic	2.1	3.5
Narcissistic	6.4	2.8
Borderline	6.4	10.3
NOS	2.6	1.8
Any personality disorder	49.8	51.4

[a]Data from Kornstein et al.[41] Abbreviations: GAD = generalized anxiety disorder, NOS = not otherwise specified.
*$p < .05$.
**$p < .01$.

ality disorder. In the study by Keller et al.[24] of patients with chronic major or double depression, 24% had at least 1 lifetime comorbid anxiety disorder, with social phobia, simple phobia, panic disorder, and generalized anxiety disorder being the most common. Over a third of the subjects reported a lifetime history of alcohol or substance use disorder, and over 50% had at least 1 Axis II disorder, with avoidant, obsessive-compulsive, and self-defeating personality disorders being most frequently diagnosed. These high rates of lifetime comorbidity were found despite the fact that patients with a principal diagnosis of anxiety disorder, patients with active substance abuse or eating disorder, and patients with antisocial, schizotypal, or severe borderline personality disorder were excluded from the study.

Analyses of sex differences in comorbid psychiatric disorders in the Keller et al.[24] study showed significantly higher lifetime prevalence rates in women of panic disorder (11.1% vs. 4.4%), generalized anxiety disorder (5.3% vs. 0.7%), and bulimia (4.7% vs. 0.7%) in the double depression group.[41] Comorbid disorders by gender in the total sample with chronic major or double depression are listed in Table 1. Men were significantly more likely to have a history of alcohol or substance abuse or dependence. No differences in the overall frequency of comorbid Axis II disorders were noted, although the exclusion criteria may have influenced this result. Obsessive-compulsive and passive-aggressive personality disorders were diagnosed significantly more often in men, and self-defeating personality disorder was diagnosed more frequently in women. Gender differences in comorbid general medical conditions may also exist.[42] For example, a higher prevalence of thyroid disease, migraine headaches, fibromyalgia, and chronic fatigue syndrome occurs in depressed women and may contribute to chronicity of course.

TREATMENT RESPONSE

Compared with episodic depression, chronic depression tends to be associated with a poorer response to antidepressant treatment. Response rates typically range from 40% to 55%, which is somewhat lower than that seen with episodic depression.[43–45] Placebo response rates also tend to be lower in this population.[46] Chronically depressed patients are less likely to show a complete remission of symptoms; as noted earlier, patients with double depression often return to their dysthymic baseline, with these symptoms increasing the risk of subsequent relapse and recurrence.[10] In addition, patients with chronic depression tend to show a longer time to response, often requiring 8 to 12 weeks or longer.[24,47]

The antidepressant treatment of chronic depression has been a productive area of study in the recent past, with multiple randomized controlled trials demonstrating the acute phase efficacy of several medications, including imipramine,[48–54] amitriptyline,[55] desipramine,[56] fluoxetine,[57–59] sertraline,[24,51,60] nefazodone,[61] phenelzine,[51,53] moclobemide,[50,54,62] ritanserin,[63–65] amisulpride,[48,58] and tianeptine.[55] Improvement in depressive symptoms has been shown to be associated with improvements in psychosocial functioning, especially in patients who achieve a full remission of symptoms.[31,52]

Since chronicity is a risk factor for recurrence of depression, patients with chronic depression require a long-term approach to management. Only 2 published studies of chronic depression have reported maintenance phase results, which demonstrated the efficacy of desipramine[66] and sertraline[67] for the long-term treatment of chronic depression.

Although psychotherapy was once considered the treatment of choice for chronic depression, there has been little formal study of psychotherapy for these disorders.[68,69] Most of the studies in the literature have used small sample sizes and studied psychotherapy alone without medication. Data from 2 recent investigations suggest the efficacy of sertraline in combination with interpersonal therapy[70] or group cognitive-behavioral therapy[71] for dysthymic patients, although neither study observed a significant additive effect of combination treatment over sertraline alone. A recently published study comparing the Cognitive-Behavioral Analysis System of Psycho-

therapy (CBASP),[72] nefazodone, and a combination of the 2 in the treatment of patients with chronic major depression, double depression, or recurrent major depression with incomplete interepisode recovery showed a dramatic improvement in outcome with combined psychotherapy and pharmacotherapy compared with either treatment alone[61]; this study also included a maintenance phase, the results of which have yet to be reported.

Only 3 studies[73–75] have evaluated sex differences in antidepressant treatment response among chronic patients. Kornstein et al.[73] found a significant gender-by-treatment interaction for both treatment response and dropout rates in a 12-week study of sertraline versus imipramine in 235 men and 400 women with chronic major or double depression. Women responded significantly more favorably to sertraline than to imipramine (57% vs. 46%, p = .02), while men responded significantly better to imipramine than to sertraline (62% vs. 45%, p = .04). It should be emphasized that overall response rates to sertraline and imipramine during the 12-week study were similar,[24] illustrating the importance of analyzing response data by gender. Sex differences in dropout rates were also found, with women being significantly more likely to discontinue from the study during treatment with imipramine than with sertraline. In addition, differences between premenopausal and postmenopausal women were noted in this study, suggesting that estrogen may play a role in antidepressant response; premenopausal women responded better to sertraline than to imipramine (57% vs. 43%, p = .01), whereas no differences in response rates among postmenopausal women were reported (57% vs. 56%).[73] In summary, the differences in response rates between drug classes were seen only in premenopausal women. Other reports have also found a poor response to tricyclics among depressed women,[76] especially younger women,[77] and a preferential response to selective serotonin reuptake inhibitors (SSRIs)[78] or monoamine oxidase inhibitors.[79]

The positive response of chronically depressed women to SSRIs was also noted by Yonkers et al.[74] in a reanalysis of a 12-week study of sertraline, imipramine, and placebo in 410 patients with "pure" dysthymia (i.e., of at least 5 years' duration, with no major depressive episodes in the 6 months preceding the study). As in the above study, the overall results showed no differences in efficacy between sertraline and imipramine, with both antidepressants being significantly more efficacious than placebo.[52] However, differences by gender were evident in this study as well, with significantly more women than men responding to sertraline (64% vs. 42%; p = .02).[74]

Gender differences in treatment response to combined pharmacotherapy and psychotherapy for chronic depression have been examined by Kornstein et al.[75] on the basis of data from the Keller et al.[61] study comparing nefazodone, CBASP, and a combination of the 2. The combination treatment produced significantly greater improvement in both men and women with no sex differences noted across the 3 treatment cells. In a previous study examining sex differences in response rates to combined treatment for depression among patients with recurrent major depressive disorder, Frank et al.[80] found that men were more likely than women to achieve a rapid and sustained clinical response and to be classified as "normal responders" (49% vs. 32%; p = .029) to the combination of imipramine and interpersonal psychotherapy. A meta-analysis of University of Pittsburgh data by Thase et al.[81] revealed that combination treatment with cognitive-behavioral or interpersonal therapy and a tricyclic antidepressant offered no advantage over psychotherapy alone in younger women, while the combination treatment was superior to psychotherapy alone in men and older women. The use of a tricyclic antidepressant in these reports may explain the sex differences found, given the poor response of women versus men to tricyclics noted in other studies.[73,76,77]

EFFECT OF THE MENSTRUAL CYCLE ON CHRONIC DEPRESSION

Women with depressive disorders commonly experience an exacerbation of depressive symptoms during the luteal phase of the menstrual cycle.[82,83] In fact, many women who present seeking treatment for premenstrual syndrome (PMS) are found to have an ongoing mood disorder that worsens premenstrually.[84]

Premenstrual exacerbation of depression has been examined in 2 studies of chronic depression. Kornstein et al.[85] studied 229 women with chronic major or double depression who were premenopausal, had regular menstrual cycles, and were not taking oral contraceptives. Sixty percent of these women reported mood worsening related to their menstrual cycle, and 52% specifically reported a premenstrual exacerbation. The most common mood change reported was greater irritability (in 80% of the women), followed by more depressed mood, mood lability, and increased anxiety. Using prospective daily charting of symptoms in 97 women to document the exacerbations, the investigators found that 27% of the women actually showed a pattern consistent with premenstrual exacerbation, compared with 61% who had reported such changes. These data are consistent with findings in the PMS literature that many women who report having PMS do not have the diagnosis confirmed when they chart their symptoms prospectively.[86] However, even by conservative estimates, the results suggest that over 25% of chronically depressed women may experience a premenstrual exacerbation of their illness. Clinician awareness of this fluctuation in symptoms across the menstrual cycle is essential to accurately assess severity of depression, suicide risk, and response to treatment.

In a similar study of women with "pure" dysthymia, Yonkers et al.[74] found that 53% reported a premenstrual worsening of depressive symptoms. When women with chronic major or double depression and those with dysthymia were compared, there was an increased frequency of mood worsening during menses noted by women who were currently in a major depressive episode.[85] Thus, the duration of the premenstrual exacerbation may be longer when chronically depressed women are in a major depressive episode, extending into the period during menses as well.

In both studies, women with premenstrual exacerbation of depression were highly responsive to antidepressant medication (sertraline or imipramine), with marked improvement seen in premenstrual symptomatology.[74,85] These data suggest that premenstrual worsening of chronic depression tends to improve with antidepressant treatment of the underlying depression.

CONCEPTUAL AND METHODOLOGICAL CHALLENGES

The major challenge in studying chronic depression has been the confusion regarding distinctions among subtypes, particularly those of chronic major depression, double depression, and recurrent depression with incomplete interepisode recovery. Changes in criteria between DSM-III-R[87] and DSM-IV[2] have exacerbated this confusion. For example, a chronic major depressive episode in DSM-III-R was defined as a major depressive episode of at least 2 years' duration with no asymptomatic periods lasting 2 months or longer during the course of the 2 years. In DSM-IV, the criteria were changed so that to be classified as having a chronic major depressive episode, the patient must meet full syndromal criteria for major depression continuously for a minimum of 2 years. The consequences of this change are illustrated by the case of a patient who meets full syndromal criteria for major depression 3 times during the last 2 years with periods of subsyndromal symptoms between episodes and no symptom-free periods. By DSM-III-R criteria, this patient would be classified as having a single chronic major depressive episode with periods of partial remission. By DSM-IV criteria, this patient would have recurrent major depressive disorder with incomplete interepisode recovery, with a total of 3 episodes during the past 2 years. The same course of illness would be classified as 2 different subtypes of chronic depression with different numbers of episodes. This change makes comparisons among subtypes and among studies difficult.

Another methodological challenge in diagnosing the exact subtype of chronic depression is the difficulty in assessing the presence of an antecedent dysthymia in patients with a chronic course of major depressive disorder. The diagnostic distinction between double depression and recurrent major depressive disorder with incomplete interepisode recovery is determined solely by whether or not the patient met full criteria for a major depressive episode or was dysthymic during the first 2 years of illness. In chronically depressed patients, the initial 2 years of illness may date back to the patient's childhood or teenage years and may be difficult to recall with accuracy.

Studies of dysthymia are often difficult to interpret because of the inclusion of not only patients with "pure" dysthymia but also those with double depression. In addition, there has been disagreement about the most appropriate diagnostic criteria for dysthymia. The DSM-IV field trials data suggested that the checklist criteria for dysthymia should omit the neurovegetative symptoms (i.e., sleep and appetite) and include more of the cognitive and behavioral symptoms, such as pessimism, low self-esteem, low initiative, irritability, and social withdrawal.[9] The dysthymia criteria proposed by the Field Trials Committee were included in the appendix of DSM-IV and continue to be a subject of discussion.[88]

Recently, some researchers have encouraged a "lumping" rather than a "splitting" approach with regard to the various subtypes of chronic depression. A recent comparison of patients with DSM-III-R chronic major depression and double depression found no major differences between these 2 disorders with regard to demographic and clinical characteristics, family history, and response to antidepressant medication.[89] Differences may exist, however, when long-term course features, such as risk for relapse and recurrence, are studied.

IMPLICATIONS FOR TREATMENT, PREVENTION, SERVICE DELIVERY, AND MENTAL HEALTH POLICY

In contrast to studies of episodic depression, recent research on chronically depressed patients has shown a younger age at illness onset, greater family history of affective disorder, greater symptom reporting, poorer social adjustment, and poorer quality of life in women compared with men, suggesting that chronicity of depression may affect women more seriously than men.[27,35] Not only are women at greater risk for depression,[12,15] but when they become chronically depressed, they tend to fare worse than their male counterparts.

Given these findings, young women should be screened carefully for the presence of depressive disorders, especially if there is a positive family history of depression, and treated promptly. Early detection and effective treatment of depression are needed to prevent chronicity of the illness and its subsequent psychosocial consequences for women with regard to marital status, educational attainment, and lifetime earnings. Improving the underdiagnosis and undertreatment of chronic depression in women requires education of the public as well as

health care providers in primary care and obstetrics and gynecology, since they are most likely to have contact with young women.

The studies reviewed suggest that successful outcomes, in terms of both symptomatic and psychosocial improvement, can be achieved even among chronically depressed patients with proper recognition and adequate treatment. In addition to ensuring appropriate dosage and duration of the treatment provided, adequate treatment should include attention to gender differences in response rates as well as to the influence of the menstrual cycle, menopausal status, and hormonal therapies on depressive symptoms and treatment response.[75]

Since chronic patients with incomplete recovery are at higher risk for relapse and recurrence, strategies to maximize treatment response must be instituted to assist patients in achieving a full recovery from each depressive episode. The development of psychotherapy models specific for chronic depression offers an alternative to medication.[72] Moreover, combination treatment with pharmacotherapy and psychotherapy has been shown to dramatically improve treatment outcomes and should be made available to all patients with chronic depression.[61]

Because the risk of chronicity and recurrence increases with each subsequent depressive episode, it is imperative that effective treatment strategies are studied and implemented for the long-term management of depression. The efficacy of antidepressant medications in preventing relapse and recurrence has consistently been demonstrated.[90] The development of newer medications with improved tolerability increases the likelihood of patient compliance during long-term treatment. Adjunctive psychotherapy has also been shown to improve long-term prognosis in depressed patients.[91,92]

FUTURE DIRECTIONS

Extensive knowledge gaps remain in the area of chronic depression in women. Chronic depression itself, as a broader category than dysthymia, is a relatively new field of study, and the literature regarding gender issues is still sparse. Future research should include epidemiologic studies of gender differences in the prevalence, presentation, and course of the various subtypes of chronic depression, as well as risk factors for chronicity in women. Better understanding is needed regarding how the chronic subtypes differ from episodic depression, e.g., in terms of psychosocial impairment, symptomatology, and response to treatment. In addition, further study is needed of gender differences in response to various types of pharmacotherapy, psychotherapy, and combination treatment, as well as treatment strategies for nonresponders and partial responders. More studies are needed focusing on the long-term management of chronic depression, including the optimum duration of acute, continuation, and maintenance treatment and the prophylactic effects of pharmacotherapy and psychotherapy in preventing relapse and recurrence. Finally, there is a need for further study of the effects of the menstrual cycle and menopausal status on the course and treatment of chronic depression. In sum, more research is needed in every aspect of this important public health concern for women.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), nefazodone (Serzone), phenelzine (Nardil), sertraline (Zoloft).

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

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