Proceedings

Depression, perimenopause and the quality of life.

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Introduction

This chapter focuses on depression during the perimenopause and the potential impact of perimenopause-related depression on health-related quality of life. First, background information will be provided on depressive disorders, including their prevalence, sexual dimorphisms, diagnostic methodologies, course, and treatment outcomes. Second, recent findings will be presented related to the impact of depression on quality of life measures. Third, evidence will be described that documents a relationship between events related to the perimenopause (but not the postmenopause) and the onset of depressive illness, including the results of several randomized, placebo-controlled trials examining the antidepressant efficacy of estradiol in depressed perimenopausal and postmenopausal women. Fourth, data will be examined regarding the relevance of several risk factors for depression during the perimenopause. Finally, recommendations will be provided to guide future studies of the effects of the perimenopause on measures of quality of life and the potential impact of depressive illness in these studies.

Background

Prevalence of depression

Major and minor depressions are the two most prevalent forms of acute depressive illness. Major depression has an estimated lifetime prevalence of 17% and affects approximately twice as many women as men.1,3 The exact prevalence of minor depression is unclear due to differences in the diagnostic criteria used across studies; however, its prevalence is thought to at least approximate that of major depression.4,5 Minor depressions are not distinguished from major depressions of moderate severity by family history,6,7 course (i.e., both major and minor depressions occur in subjects over their lifetime),6,8 or several biological characteristics.6,10 In one study, elderly patients in a primary care setting with minor depression were observed to have a five-fold increased risk of developing major depression during a one year follow-up compared with non-depressed patients.11 Thus, minor depressions not only contribute to a substantial disability on their own but also increase a person's risk for developing more severe forms of depressive illness.

The importance of minor depressions also has been emphasized by studies of mood disorders that occur during periods of reproductive endocrine change in women. Indeed, the perinatal and perimenopause stages of reproductive life are associated with increased risks for both major and minor depressions. In a study of 116 women who presented to our clinic with perimenopausal depression, as many women met criteria for minor depression as they did for major depression. (Steinberg, unpublished data) Similarly, a recent meta-analysis of studies examining the prevalence of postpartum depression found that major and minor depressions occurred during the puerperium with approximately equal prevalence rates.12 Thus, the impact of minor depressions is considerable, and they should not be dismissed on the basis of their lesser clinical significance.

Criteria for the diagnosis of major and minor depressions

Depression is under-diagnosed by health care-providers and, therefore, also under-treated.13-17 Standardized criteria for diagnosing both major and minor depressions have been developed18 to distinguish depressive symptoms, which may be multi-determined, from depressive syndromes, which have particular familial patterns, biological features, and treatment response characteristics. The American Psychiatric Association’s Diagnostic and Statistical Manual - Fourth Edition (DSM-IV)19 specifies selected core symptoms of depression (five for major depression and three for minor depression), which must persist for at least a two week period, be associated with clinically significant distress or impairment in social or occupational functioning, and not be caused by medications, a medical condition (e.g., hypothyroidism), or bereavement (Table 1). Structured diagnostic interviews are employed in research settings to establish the presence of a diagnosis of depression (e.g., Structured Clinical Interview for DSM-IV), and modifications of these diagnostic instruments may be used to screen patients for the presence of depression in medical settings.20,21 For example, recent studies employing one of these screening scales, the PRIME-MD,22 have identified rates of mood disorder in women of approximately 31% in primary care clinics and 13% in gynecologic clinics.23 As
stated earlier, mood disorders are frequently under-diagnosed by the care provider; in one of these studies, the current episode of mood disorder had not been recognized by the primary physician in 80% of the women.23

One characteristic that contributes to the failure of physicians to recognize depression, particularly in general medical settings, is the presence of somatic symptoms in depressed men and women. In addition to the typical symptoms of depressive illness listed in Table 1, a considerable proportion of depressed outpatients experience symptoms of fatigue, generalized musculoskeletal pain, weakness and disturbed sleep. Somatic and behavioral symptoms are not uncommon accompaniments of depression, even those depressions that occur at stages of life other than the perimenopause. However, the presence of somatic symptoms, like hot flushes, in the context of depression does not necessarily indicate a causal relationship between these two phenomena. Clinicians once believed that somatic symptoms caused depression; however, recent evidence suggests that these symptoms may be a manifestation of, rather than a cause of, depression.24 Multiple somatic complaints have been observed in up to 50% of depressed men and women,25 with a greater number of depressed women reporting somatic complaints than depressed men.26 Somatic symptoms occurring in the context of a depressive illness are clinically important and could lead to a delay in diagnosis,25 decreased treatment-seeking behavior,27 and differential treatment response characteristics.28 Thus, depression (even minor depression) accompanied by somatic symptoms, as may occur in depressed perimenopausal women who also report hot flushes, should not be presumed to reflect an "appropriate" reaction to disturbing somatic symptoms.

Sexual dimorphisms in depression
In addition to sex differences in both the prevalence of depression and the frequency of accompanying somatic symptoms, several other sex differences in depression have been identified. For centuries, medical observers have suggested that a special relationship exists between female reproductive function and/or dysfunction and disturbances in central nervous system activity. More recently, a putative interaction between gonadal steroids, in particular estradiol and progesterone, and central nervous system function has been suggested to contribute to a number of observed epidemiologic, phenomenologic, and treatment response characteristics in women compared with men. As stated earlier, studies have consistently identified a two-fold increased lifetime prevalence of depression in women compared with men.29-33 This increased prevalence has been observed in a variety of countries.31 A two- to three-fold increased prevalence of dysthymia and threefold increase in seasonal affective disorder24 in women has also been noted,78 while bipolar illnesses is equi-prevalent in men and women79,35,36 (and reviewed in31). Pre-pubertal depression prevalence rates are not higher in girls,36,39 possibly reflecting ascertainment bias/reporting bias (depressed boys may be more likely to come to the attention of health care providers) or the possibility that pre-pubertal major depression is premonitory to bipolar illness.40 As mentioned earlier, women are more likely to report anxiety, atypical symptoms, or somatic symptoms,25,26,34,41,43,45 are more likely to report antecedent stressful events,47,48 display increased comorbidity of anxiety and eating disorders,49-52 thyroid disease,52,54 and migraine headaches,55 and have lower lifetime prevalence rates of substance abuse and dependence.55,56,57 Reported differences in treatment response characteristics in women compared with men (for review see57) include poor response to tricyclics,58-61 particularly in younger women,59 superior response to SSRIs or MAOIs,52,64 and a greater likelihood of response to triiodothyronine (T3) augmentation.62 The extent to which these dimorphisms reflect sex-related differences in pharmacokinetics57,66-72 remains to be determined. Finally, while the prevalence of bipolar disorder is comparable in men and women, women are more likely to develop rapid cycling73 and may be more susceptible to antidepressant-induced rapid cycling.73

The course and treatment of depression
The occurrence of an episode of depression will increase an individual's risk of developing recurrent episodes of depression.72 Estimates of the duration of a major depressive episode range from an average of four to eight
months.74,75 with one study reporting that 50% of episodes of major depression remit within three months regardless of treatment.75 However, in approximately 20% of patients with major depression, the episodes become chronic (i.e., the duration of illness exceeds two years).

Treatments for both major and minor depression include psychotherapy (time-limited focused cognitive or interpersonal therapy), antidepressant medications, and other somatic therapies (e.g., electroconvulsive therapy for severe major depression).76 Reported response rates to therapy in major depression vary across studies; however, one study estimated that 50% of ambulatory subjects with major depression will respond to treatment with either time-limited psychotherapy or antidepressant medication.77 The results of recent effectiveness trials examining treatment outcomes after standard antidepressant therapies observed comparable rates of response. Remission rates in depression (defined as the elimination of symptoms) after treatment with the selective serotonin reuptake inhibitor citalopram varied with the outcome measure employed but were approximately 30%,79 whereas, a clinically significant response (defined by a reduction of ≥ 50% relative to pre-treatment depression severity scores) was observed in approximately half of the participants.79 An additional 25% (approximately) of patients will experience a remission after either a change to a different antidepressant medication or the augmentation of the therapeutic regimen with a second antidepressant.79,80 Unfortunately, despite these promising therapeutic interventions, in 50% of subjects with depression, remission does not occur with standard antidepressant therapies. Therefore, there is a clear need for supplemental effective treatments.81

In addition to the demand for novel therapies for those depressed patients who do not respond to standard antidepressants, there is also a need for improved access to acceptable and appropriate treatment. Recent epidemiologic studies in the United States observed that only 20% of patients with major depression receive adequate care — defined by at least four visits to any type of physician and ≥ 2 months of medication, or psychotherapy involving at least eight visits lasting ≥ 30 minutes with a health care professional.82 Indeed, patients with major depression were nearly as likely to receive care from a non-health care provider (e.g., religious/spiritual advisor) who generally would be less able to administer standard effective therapies than a psychiatrist.83,84

**Impact of depression**

Major depression has been identified as a leading source of disease-related disability in developed countries, and it is predicted to be a leading cause of disability worldwide by the year 2020 (second only to heart disease).84-85 In the United States the estimated annual cost of depression alone is approximately 50 billion dollars.85 As noted earlier, minor depressions, by definition, have fewer and less severe symptoms than major depressions.86,87 Nonetheless, they are associated with disability comparable to that of major depression.88-90 Compared with non-depressed men and women, those with depression have multiple forms of disability involving social function, work productivity, physical ability, and emotional functioning.4,91-97 Depression also is associated with higher rates of dropout from high school and college,98 higher rates of teenage pregnancy,99 marital dissatisfaction,100 and divorce.101

In addition to the functional disability that is directly attributed to major and minor depressions, adverse medical sequelae of major depression have been identified, including increased risks for cardiovascular disease, Alzheimer’s dementia, premature ovarian failure, osteoporosis, and the metabolic syndrome.102-107 Depression might also represent a modifiable risk factor for the onset of some of these conditions. If depression exists as a co-morbid condition, it may increase both the morbidity and mortality of several medical illnesses including heart disease.108-111 Indeed, several studies have identified a substantially increased health care utilization cost associated with a variety of medical conditions when they are comorbid with depression.112,113

**The influence of depression on quality of life measures**

Quality of life measures are patient-reported outcomes that evaluate the quality of social relationships, emotional well being, physical health, and functioning in a variety of capacities.
(e.g., work and family life). In some studies, measures of economic status, marital satisfaction, and access to appropriate health care are also included. Additionally, scales employed to assess quality of life typically evaluate the severity of several symptoms including affective, behavioral, cognitive and somatic symptoms (see Table 2). Quality of life outcomes have become an increasingly important component of the evaluation of both disease and health care access. These measures have been employed in public health settings to identify disparities in health care access, as well as in general medical clinics, where they serve to supplement biomarkers of disease activity as adjuncts to the evaluation of the course of chronic or incurable medical conditions. However, the role of quality of life measures is less well defined in many behavioral conditions such as depression in which reliable biomarkers of disease activity do not exist.

Investigators have administered specific quality of life scales to depressed men and women. As expected, these studies confirm a substantial disability associated with depression compared with both non-depressed subjects and those with chronic medical conditions. Numerous demographic characteristics have been identified as contributing to the reduced quality of life associated with depression, including the following: the age of onset of depression, ethnicity, marital and employment statuses, family income, educational level and insurance status. However, the principal source for the reduced quality of life in depression is the severity of the depressive symptoms. Thus, there is considerable overlap between measures of depression symptom severity and measures of quality of life, which could contribute to methodological problems in some settings. For example, in epidemiologic studies examining quality of life, depression may represent a considerable confound to the interpretation of the results of quality of life measures. In women who have a lifetime prevalence of major depression of approximately 20%, the potential impact of depression on quality of life measurements throughout the life cycle is considerable. Particularly during the menopause transition, depression could be an important potential confound in studies of quality of life.

**What is the evidence of an association between the menopause transition and depression?**

The majority of women do not develop depression during the perimenopause. In fact, epidemiologic studies examining gender and age-related differences in the six month to one year prevalence of major depression reported no increased prevalence of major depression in women at midlife (age range approximately 45-55 years). Similarly, others have concluded that the onset of the menopause is not associated with an increased risk for developing depression, however, in four studies symptoms were observed more frequently in perimenopausal than postmenopausal women. Indeed, in several other longitudinal, community-based studies, the perimenopause (or the presence of menstrual cycle irregularity and hot flushes) was reported to be associated with an increased risk for depression, consistent with studies of women attending gynecology clinics. The Study of Women's Health Across the Nation (SWAN) employed a measure of "psychological distress" as a proxy for the syndrome of depression by requiring that core depressive symptoms (sadness, anxiety, and irritability) persist for at least two weeks. SWAN's initial cross-sectional survey observed that perimenopausal women reported significantly more "psychological distress" than either pre- or postmenopausal women (defined by self-reported menstrual cycle status). The results of several studies published during the last three years have found similar results. First, in a longitudinal study, Freeman et al. found an increased risk for clinically significant depression (defined by elevated CES-D scale scores and the Primary Care Evaluation of Mental Disorders [PRIME MD]) during the perimenopause compared with the pre- or postmenopause. Moreover, this association remained after adjusting for several variables, including past history of depression, severe premenstrual syndrome, poor sleep, and hot flushes. Levels of depression were increased relative to those found in postmenopausal women; however, only 3% of the sample (approximately ten women) were followed through to the perimenopause. In a second prospective...
study, we followed 29 asymptomatic, premenopausal women until six to 12 months after their last menstrual period. A 14-fold increase in the rate of onset of depression was observed during the 24 months surrounding the final menstrual period (FMP), relative to the 31 years used as a comparison time period. These data document a clustering of depressive episodes in women during the late perimenopause relative to the premenopause. Third, Cohen et al. evaluated the risk of depression in 460 women who were followed prospectively for up to seven years and who had no past history of depression. The risk of new onset depression (defined by Structured Clinical Interview SCID-IV) in the perimenopause was nearly twice that observed in the premenopause (adjusted OR = 1.8). Finally, in a similar study to that conducted by Cohen et al., Freeman et al. demonstrated a significantly increased (2.5 times greater) rate of new onset depression in women with no history of depression during the late perimenopause compared with women who remained premenopausal. These data notwithstanding, the majority of women in these studies remained asymptomatic throughout the perimenopause. However, these data suggest that events surrounding the final menstrual period may predispose some women to develop clinically significant depressive illness.

The stage of the perimenopause (i.e., late perimenopause) during which depressions appear supports a pathophysiological role of endocrine events, since the late perimenopause is characterized by estradiol (E2) "withdrawal" relative to either the postmenopause or the early perimenopause. Thus, the temporal appearance of the depressions observed suggests an endocrine trigger related to the perimenopause (E2 withdrawal and/or recent-onset of prolonged hypogonadism) in the onset of perimenopausal depression.

An association between the endocrine events related to the perimenopause and the onset of depression is also implicated (albeit indirectly) by reports of the mood enhancing effects of estradiol in depressed perimenopausal women. Recently, three double-blind, placebo-controlled trials, which employed similar methodologies and identical preparations of estradiol (i.e., 17 beta estradiol), have examined the efficacy of estradiol in perimenopausal and postmenopausal women with major and minor depressions.

First, the therapeutic efficacy of estradiol (17 beta estradiol) was examined in a double-blind, placebo-controlled trial in 34 perimenopausal women (late perimenopause by STRAW criteria who also met standardized diagnostic criteria for major and minor depression). After three weeks of estradiol, depression rating scale scores were significantly decreased compared to baseline scores and significantly lower than scores in the women receiving placebo. A full or partial therapeutic response was seen in 80% of subjects on estradiol and in 22% of those on placebo, which is consistent with the observed effect size of 0.7 in a meta-analysis of studies examining estrogen's effects on mood. The therapeutic response to estrogen was observed in women regardless of the presence of major or minor depression, a history of non-perimenopausal-related depression, and presence of hot flushes. Finally, neither baseline nor post-treatment estradiol levels predicted the observed therapeutic response. In keeping with recent community-based cross-sectional surveys, these data suggest that estrogen's effect on depression is not solely a product of its ability to reduce the distress of hot flushes. These findings also are consistent with data from Montgomery et al. and Saleh et al., which document the beneficial effects of estradiol on mood in perimenopausal women reporting depressive symptoms.

A second randomized, double-blind, placebo-controlled study by Soares et al. confirmed the observations of Schmidt et al. Soares et al. reported a significant and beneficial effect of estradiol replacement compared to placebo in women with perimenopause-related major depression (as defined by the PRIME MD) and, additionally, reported that baseline plasma estradiol levels did not predict response to estrogen treatment. In contrast, a recent study using a similar design to that employed in perimenopausal women failed to observe a significant antidepressant effect of estradiol relative to placebo, in depressed women who were 5-10 years post menopause.

The evidence that younger perimenopausal, but not older postmenopausal depressed women, respond to estrogen therapy suggests that the mood disorders occurring in perimenopausal women are more similar to those found in the perimenopause.
pausal women are caused by changes in hormones (e.g., withdrawal or fluctuations) rather than prolonged ovarian steroid deficiency.

What factors influence the risk for depression during the menopausal transition?

As described in the previous section, several epidemiologic studies have surveyed the presence of depressive symptoms in women at midlife and have identified rates of depressive symptoms ranging from 8-40%. However, the samples in most of these studies consisted of women at midlife who were in different phases of reproductive aging, and symptoms often were assessed independently of the presence of clinically meaningful depressive syndromes. These findings, therefore, are not directly translatable to either prevalence figures or risk factors for depressive syndromes associated with the reproductive endocrine changes characterizing the perimenopause. Nonetheless, these studies of women who become depressed during midlife have identified several variables associated with depression, including the following: previous episodes of depression, longer duration of the perimenopause (defined by menstrual cycle irregularity), presence of hot flushes, retrospective reports of premenstrual dysphoria (PMD) or postpartum depression (PPD), stressful life circumstances, complaints of poor health, history of smoking, disturbed sleep, reduced parity, and being unmarried. Many of these factors also are associated with an increased risk of developing depression during other stages of life (i.e., past history of depression, stressful life events, reports of PMD or PPD, smoking and sleep disturbance) and, therefore, are not specific to depression during the perimenopause. As discussed earlier, recent studies have identified the menopausal transition to be an independent risk factor for depression at midlife in women. These findings suggest that in some women ovarian aging and the events surrounding the perimenopause increase the vulnerability to develop depression. Finally, several proposed risk factors such as insomnia, increased stress, and complaints of poor health, may be symptoms of, but are not necessarily a cause of, a current depressive episode.

In the study by Schmidt et al., nine women followed prospectively who developed depression during the perimenopause were not distinguished from those not developing depression by any variable associated with the onset of perimenopausal depression. There also was no increased onset of depression in women with a past history of depression (diagnosed by structured clinical interview). In fact, of the depressions that were observed, a similar percentage occurred in women with no prior history of depression (9/20) as in those with a past history (3/6) (small sample size notwithstanding). Nor did the three women with histories of PPD develop perimenopause-related depression, suggesting that the presence of one episode of a reproductive endocrine-related mood disorder (i.e., PPD) does not predict the uniform occurrence of depression during a subsequent period of hormonal change (i.e., the perimenopause). The apparent lack of association between the onset of major or minor depression during the peripuerium and the perimenopause also was observed in a cross-sectional study (Steinberg, unpublished data). In this study of 116 women with perimenopausal depression, less than 10% had a history of postpartum depression (defined by the SCID interview). Nonetheless, prior studies employing retrospective reports of the onset of premenstrual dysphoria (PMD) have suggested that it is both an accompaniment and, possibly, a predictor of depression during the perimenopause. In the study by Schmidt et al., (the first to prospectively evaluate, using daily symptom ratings, self reports of the onset of PMD in women entering the perimenopause), PMD rarely accompanied perimenopausal depression. In fact, in those women who became depressed during the perimenopause, only one woman met criteria for PMD in the four years before the FMP, and two additional women met criteria for significant premenstrual cyclicility intermittently in 3-5 menstrual cycles over the course of the four years prior to the FMP. Nonetheless, recent cross-sectional data suggest a higher than expected co-occurrence of prospectively confirmed PMD and perimenopausal depression. Women with perimenopausal depression (n = 70) (and who were not amenorrheic) were

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significantly more likely to meet criteria for PMD than asymptomatic perimenopausal controls (n = 35) (21% compared with 3%). However, despite the higher rate of PMD, the majority of women with perimenopausal depression did not meet criteria for PMD, consistent with the longitudinal observations. Thus, PMD is neither a uniform accompaniment nor a necessary antecedent of perimenopausal depression. Nevertheless, the presence of PMD in perimenopausal depression may identify a subgroup of women in whom mood disturbance is directly linked to reproductive events.

Hot flushes also are frequently reported to accompany depression in the perimenopause and are viewed as potentially causal. Consistent with the domino cascade theory, hot flushes are hypothesized to disturb sleep and, by so doing, contribute to daytime mood symptoms. For this relationship to be tenable, one would expect that reported hot flushes would occur prior to the onset of depression (i.e., as a precipitant of depression). Moreover, as stated earlier, the presence of comorbid somatic symptoms in depression cannot be presumed to reflect a causal relationship between somatic illness and the onset of depression. Nonetheless, data from both the SWAN study and Freeman and colleagues demonstrated that hot flushes and the perimenopause are independent risk factors for depression. Thus, both hot flushes and perimenopause-related ovarian events may impart separate risks for developing depression at midlife. In our prospective study, hot flushes were not uniformly present in all women and, when present, did not necessarily precede the depression. Consistent with prior studies, eight of the nine women experiencing depression reported the onset of hot flushes at some point during the perimenopause, however, the timing of the relationship varied from several years before to several years after the onset of depression. Only four (44%) of the women who developed a depression during the perimenopause reported the onset of hot flushes proximate to the development of their depression. Thus, hot flushes appear to be neither a necessary nor sufficient accompaniment of depression during the perimenopause, and perimenopausal depression cannot be dismissed as epiphenomenal to hot flushes.

Finally, stressful life events are a frequent accompaniment of depression and, in some depressed subjects, may contribute to its onset. Stressful events have been reported in association with depressive symptoms at midlife as well as in women with major and minor depression during the perimenopause. However, in the latter study, women with perimenopausal depression did not report a greater number of exit events (i.e., personal losses) than asymptomatic perimenopausal women. Indeed, exit events, if they do occur, are not necessarily associated with negative mood symptoms in women at midlife. Thus, although stressful events are an accompaniment of both midlife and perimenopausal depression, there is no evidence to support the concept that depressions at this time in a woman's life are caused by the "empty nest" syndrome.

In summary, several factors, including perimenopausal reproductive status, are associated with developing a depression at midlife. Indeed, many of these factors frequently accompany perimenopausal depression; however, none are uniformly present in these depressed women. Notably, a past history of depression, whether or not related to reproductive endocrine change (i.e., PPD or PMD), fails to predict the onset of perimenopausal depression. As a caveat, however, our inability to identify predictors of the onset of depression may reflect the small sample sizes of depressed perimenopausal women examined. Future studies will clarify whether specific factors exist that predict or increase the risk of developing depression during the perimenopause, independent of those factors that increase a woman's risk for depression at other times across the life cycle.

Recommendations for future studies of quality of life during the perimenopause

In her review of studies examining quality of life during the menopause transition, Matthews identified 12 cross-sectional, community-based, epidemiologic studies that observed a significant reduction in quality of life measures in women who were in the menopause transition compared with women who were in the premenopause. In these studies, perimenopausal depression was significantly more likely to meet criteria for PMD than asymptomatic perimenopausal controls (n = 35) (21% compared with 3%). However, despite the higher rate of PMD, the majority of women with perimenopausal depression did not meet criteria for PMD, consistent with the longitudinal observations. Thus, PMD is neither a uniform accompaniment nor a necessary antecedent of perimenopausal depression. Nevertheless, the presence of PMD in perimenopausal depression may identify a subgroup of women in whom mood disturbance is directly linked to reproductive events.

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Pausal women reported more role limitations due to physical or emotional health, poorer perceived health, and more somatic symptoms including pain than premenopausal women. However, when these studies controlled for the presence of affective symptoms, the differences in quality of life measurements (including somatic symptoms and physical disabilities) between perimenopausal women and premenopausal women were largely eliminated. Thus, in epidemiologic studies depression during the perimenopause could be a large source of variability in measures of quality of life in women at this stage of life.

Depressive symptoms not only contribute to the significant reductions in quality of life observed in perimenopausal women participating in epidemiologic studies, but also to the outcomes of some clinical trials evaluating the effects of hormone therapies on quality of life in peri and postmenopausal women. The study by Hlatky et al. suggested that the beneficial effects of hormone therapy on quality of life measures were associated primarily with improvement in depressive symptoms. Thus, the presence or absence of depressed women in clinical trials also could represent a significant confound to the observed outcomes after hormone therapy. In particular, the selection of relatively asymptomatic women in two previous studies that examined the impact of hormone therapy on quality of life measurements were confounded by the relative absence of symptomatic and depressed women.

The recent community-based studies estimate that 26-33% of women will develop a lifetime first episode of depression during the menopause transition. The 2005 U.S. Census recorded 25+ million women in the 45-54 year-old age range. Thus, approximately 6.5-8.3 million women are at risk for new onset depression during the menopause transition (Joffe, H, personal communication). Thus, the impact of depression on measurements of quality of life in women during the menopause transition will be of both epidemiologic and clinical significance. Because the presence or absence of depressed perimenopausal women in the sample studied could represent a significant confound to the interpretation of quality of life data, studies of quality of life during the menopause transition must identify the presence and evaluate the severity of depression in the women studies.

Future studies of the association between depression, the menopause transition, and quality of life should consider several caveats. First, in depression, it is not clear whether quality of life measures will provide additional information beyond that obtained from standardized depression rating scales. Second, the use of a multidimensional quality of life scale will not adequately evaluate the impact of other symptoms of the menopause transition (such as hot flushes, sleep disturbance, or musculoskeletal pain) unless the quality of life measures control for the presence of depression. Finally, the presence or absence of depression in the samples of perimenopausal women will substantially affect evaluations of the impact of hormone therapy on quality of life measurements.

This work was written as part of Peter J. Schmidt's official duties as a Government employee. The views expressed in this article do not necessarily represent the views of the NIMH, NIH, HHS, or the United States Government.
Tables:

Table 1. DSM-IV Core Symptoms of Major and Minor Depressive Episodes

1. Depressed mood most of the day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day.
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite.
4. Insomnia or hypersomnia.
5. Psychomotor agitation or retardation.
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Five (or more) of the above symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Symptoms (1) – (8), if present, should be present nearly every day. Adapted from the American Psychiatric Association 1994.

Table 2

Items Included in Quality-of-Life Measures
- General Health
- Physical Functioning
- Role Limitations due to Physical Problems
- Bodily Pain
- Energy and Fatigue
- Social Functioning
- Role Limitations due to Emotional Problems
- Mental Health
- Modified Mini-Mental State Examination
- Depression Score
- Sleep Disturbance
- Satisfaction with Sex

Legend for Table 2
The items listed are from the RAND 36-Item Health Survey modified for the Women’s Health Initiative Study.

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