Effects and Management of the Menopausal Transition in Women With Depression and Bipolar Disorder

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Unipolar and bipolar disorders are major causes of disease burden for women in the United States. For some women, the menopausal transition can represent a time of increased vulnerability to depression, a greater risk of recurrence or instability of bipolar disorder, and an overall poorer quality of life (QOL). The physical and psychological changes of menopause and symptoms of depression may overlap, but QOL is affected doubly for women experiencing menopause-related complaints concomitantly with a unipolar or bipolar disorder. Treatments for the symptoms of menopause and for unipolar or bipolar disorder need to be chosen with careful consideration for the different stages of the menopausal transition, as well as safety, tolerability, and impact on QOL. Menopausal-related symptoms can be treated with hormonal therapies, antidepressants, and herbal supplements, but a critical window of opportunity may exist for these interventions. Bipolar disorder presents differently in women than in men and may require different medication. For instance, in women, lithium may be less effective for patients who have rapid cycling; adjuvant antidepressant medication may be required with valproate or carbamazepine; and lamotrigine may also be effective. Most of the medications that are standard treatment for bipolar disorder affect bone mineral density, and the risk for impaired QOL should be considered when choosing medication for women during this period. Insufficient information is available, however, to assess the best strategy to treat women with bipolar disorder and depression as they age. *(J Clin Psychiatry 2007;68[suppl 9]:16–21)*

Depression has a substantial impact on aging women's quality of life (QOL). Unipolar depression was shown to be a substantial cause of disease burden in women in the United States according to Michaud and colleagues' study,[1] which used the disability-adjusted life-year (DALY) scale to examine medical conditions. Unipolar depression had a greater impact on women than on men, and the disease burden associated with unipolar depression for women was greater than that of familiar medical conditions such as breast cancer or osteoarthritis.

In bipolar disorder, gender differences can also be observed. The lifetime prevalence of bipolar I disorder is about equal in men and women (1%), but bipolar II disorder has a lifetime prevalence of 5% to 10% in women.[2] In women, rapid cycling occurs approximately 3 times more often.[3] Women are also more likely to have mixed episodes, worsened physical health and pain disorders, and higher rates of substance use.[2,4] These differences could be credited to the fact that women spend more time depressed and women with bipolar disorder are treated more often with antidepressants than are men.[5] Estrogen and other hormones also seem to impact how bipolar disorder presents in women, a finding that appears to be particularly true during the menopausal transition.[2]

THE MENOPAUSAL TRANSITION

Many clinicians and researchers refer to menopause as a period of high risk for depression, which may be misleading for several reasons. One reason is that this may be a misuse of the term; *menopause* means the achievement of 12 months of amenorrhea (usually around the age of 51 or 52 years) and marks the permanent cessation of menstruation at the end of reproductive life.[6] *Menopausal transition* is a more accurate term to refer to the dynamic process that extends from the beginning of wide fluctuations in reproductive hormones and irregular cycles until the final menstrual period. The Stages of Reproductive Aging Workshop (STRAW)[7] attempted to clarify the stages of reproductive aging and nomenclature for each stage (Figure 1). The recommended terms were

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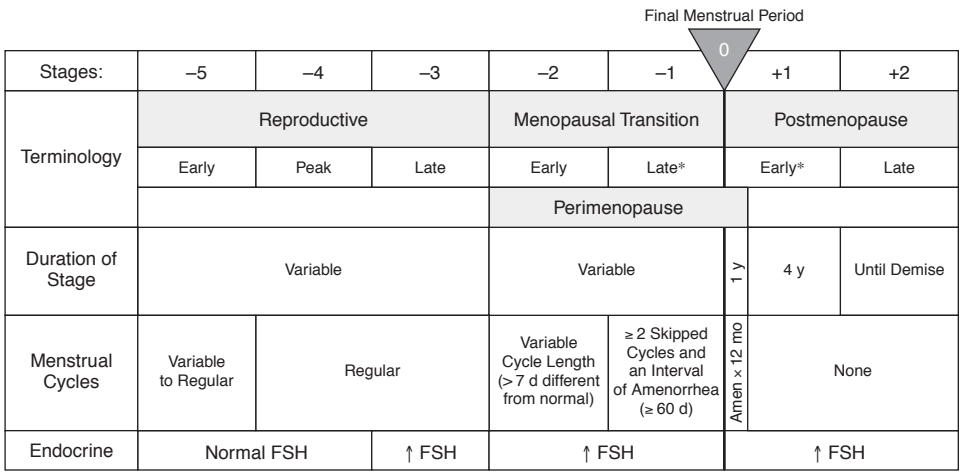
Figure 1. Stages of Reproductive Aging in Women[a]



[a]Reprinted with permission from Soules et al.[7]
Abbreviations: Amen = amenorrhea, FSH = follicle-stimulating hormone, d = day, mo = months, y = year.
Symbols: * = Stages most likely to be characterized by vasomotor symptoms; ↑ = Elevated.

menopausal transition, *menopause*, and *postmenopause*. *Postmenopause* refers to the phase dating from the final menstrual period. The term *perimenopause,* meaning about or around the time of menopause, was recommended for use only in the lay press and with patients.[7,8]

Menopausal transition may last on average 4 or 5 years, and the mean age at onset of changes and irregular cycles is 47 years. During the menopausal transition, women may have a higher risk for depression, anxiety, symptoms of bipolar disorder, and poorer QOL.[8] The process of menopausal transition is dynamic, and all women may not exhibit the same physical and emotional changes.[7] The process is not defined by absolute levels of hormones, such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH), but is characterized by clinical and hormonal changes and changes in menstrual cycle length, flow, and regularity.

Currently, the impact of the menopausal transition is substantial. In the United States, almost 40 million women are now more than 50 years old and are likely to be perimenopausal or early postmenopausal.[9,10] Furthermore, recent estimates suggest that, given current life expectancy in North America, most women will spend at least one third of their lives in the postmenopausal years and will therefore face the concomitant physical and emotional consequences that this stage of life might confer.[11]

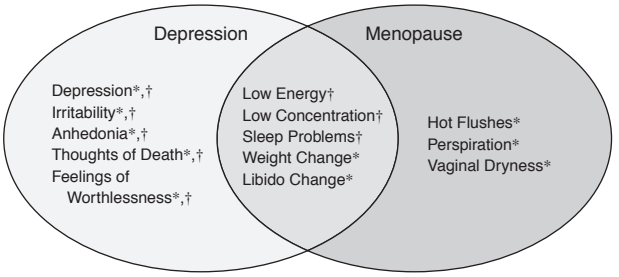
The menopausal transition is context related; that is, it is experienced differently across different cultural, hormonal, and psychiatric backgrounds.[7] For instance, women who are seeking treatment for menopausal symptoms in menopause and gynecologic clinics are more likely to have depression, anxiety, and symptoms of mood disorders as compared with women in the general population and in community-based studies.[12] Nonetheless, calling menopause a time of absolute risk for depression may be misleading. Although the menopausal transition is now recognized to be a period of higher vulnerability for several psychiatric problems and poorer QOL for some women, most women do not experience such problems.[12]

MENOPAUSE AND MOOD

One of the situations in which the menopausal transition is experienced differently across cultures or subpopulations could be at least in part explained through concepts such as the "empty nest syndrome" or the "revolving door syndrome."[12,13] For many years, depressive symptoms identified in menopausal populations were related to psychosocial hypotheses known as the empty nest syndrome. It was thought that women would be more likely to feel depressed and sad when children were leaving home, i.e., when women were coping with the loss of raising their children. Many now disagree with that theory and argue that women feel happier when children are leaving home and sadder when children return.[12,13]

An Australian study[13] examined what researchers there called the revolving door syndrome. Dennerstein and colleagues prospectively followed women whose children had left home and then later decided to return. The QOL for women, particularly for those who were not worried about children leaving home, improved significantly after their children left. These women reported having more opportunities to reframe their social interactions and improve their sexual life with their partners. The return of

Figure 2. Physical and Psychological Changes Associated With Menopause and Depression[a]



[a]Based on Soares and Cohen[12] and Joffe et al.[21]
*Based on Soares and Cohen.[12]
†Based on Joffe et al. [21]

their children was seen as a stressful event. This research is an interesting example of how results differ when a comparison is made between cultures or even between generations within the same culture. In older generations, the empty nest syndrome may have had a larger impact on women's functioning, but more recently, women's professional and social roles have changed, and children leaving home may not be perceived as a solely negative event.

The menopausal transition is also not necessarily experienced as negative. Although this may be a time of life when some women are at greater risk for depression, the majority of women do not develop depression or any major psychiatric illness during menopausal transition.[12] Most women have a positive or neutral attitude toward the menopausal transition and are not expecting negative changes in their physical health or psychological well-being.[12] Similarly, the postmenopausal period, when women are no longer having menstrual cycles, is not associated with an increased risk for developing depression.[12]

When the processes of aging and menopause are examined together, however, the menopausal period can be seen as a "sentinel event" marking a time during which physicians should watch for clinical changes that may affect QOL.[10,14] Changes such as an increase in inflammatory markers have been related to high risk for depression.[15] Aging women also have a higher incidence of visceral adiposity and metabolic syndrome, both of which are conditions that can affect QOL.[16] Studies[14,17] also show a detrimental impact on memory and attention during this period in life. Some of those changes are transient. Although women can be more symptomatic during the menopausal transition, patients often feel much better once they reach the postmenopausal period. Lastly, more recent studies[18–20] suggest an increased risk for mood disorders during the menopausal transition, and Freeman and colleagues' study[19] suggests a decline of such risk during the postmenopausal years.

The physical and psychological changes of menopause and depression often overlap and are difficult to tease apart (Figure 2).[12,21] Low energy, low concentration, sleep problems, weight changes, and changes in libido could be related primarily to menopause or could be symptoms of depression.

Several community-based and prospective studies suggest that the menopausal transition is a time of increased vulnerability for the development of unipolar depression or worsening of bipolar depression.[18,22] In the Study of Women's Health Across the Nation (SWAN), Bromberger and colleagues[22] examined more than 16,000 women aged 40 to 55 years who were African-American, white, Chinese, Hispanic, and Japanese for psychological distress as a proxy for depression. Women in the menopausal transition had a significantly higher risk of depression or psychological distress compared with women who were premenopausal or postmenopausal (28.9% vs. 20.9% and 22.0%). The positive association between the menopausal transition and high risk for depression existed even after controlling for the vasomotor symptoms of hot flushes and night sweats, or sleep complaints.

An increased likelihood ($p = .03$) of depressive symptoms was again found during the transition to menopause and a decreased risk occurred after menopause in a study[19] of 218 African-American and 218 white women aged 35 to 47 years. The Center for Epidemiologic Study of Depression Scale (CES-D scale) was used to measure depression. Similarly, a study of 27 subjects by Schmidt and colleagues[18] demonstrated a 14-fold increased risk for new episodes of depression 1 year before and 1 year after the final menses compared with a life-long (average 30 years) follow-up.

The Harvard Study of Moods and Cycles[20] examined the risk for developing depression in women with no prior history of depression after they initiated the transition to menopause. Compared with women who remained premenopausal, women who entered perimenopause had an increased risk (OR = 1.9, 95% CI = 0.9 to 4.0) for developing severe first-onset of depression. The risk was even higher (OR = 2.5, 95% CI = 1.1 to 5.8) if women became perimenopausal and developed substantial vasomotor symptoms, although the risk seemed to be attenuated by the use of hormone therapies.

In bipolar disorder, the symptomatology of the illness appears to be altered during the menopausal transition; however, data on this subject are lacking, and most information comes from the Structured Clinical Interview for DSM-IV and patients' self-reports. One[23] of these studies examined how all reproductive events affected women with bipolar disorder. Among 22 women with DSM-IV bipolar disorder who were perimenopausal or postmenopausal, 12 reported a worsening of symptoms such as depression, irritability, and mania as they entered the menopausal transition. Women not using hormone therapy were

more likely to report a worsening of mood. Wehr et al.[24] studied 51 patients, 47 of whom were women who had rapid-cycling bipolar disorder, and found no effect of menopause in those already established as rapid cyclers. However, in Kukopulos and colleagues' study,[25] in one third of the women with bipolar disorder that became "continuous circular," it did so around the menopausal transition. Research by Blehar and colleagues[26] showed that of 56 postmenopausal women with bipolar I disorder, up to 11 (20%) reported severe emotional disturbances, mania, depression, or anxiety/agitation in relation to menopause. These studies indicate that during the menopausal transition, women are at greater risk for new onset or recurrence of depression and instability in bipolar disorder.

A review by Matthews and Bromberger[27] of 12 cross-sectional reports and 3 longitudinal studies showed that the menopausal transition affected health-related QOL primarily through higher levels of somatic symptoms. Most studies assessed health-related QOL by measuring the frequency and severity of symptoms via rating scales or questionnaires. Although the rating scales and questionnaires measured several domains including functioning at work, social relationships, and sexual function, the somatic symptom domain seemed to be most affected during the menopausal transition.

MANAGEMENT OF MENOPAUSE SYMPTOMS, DEPRESSION, AND BIPOLAR DISORDER

Given the impact of the menopausal transition on patients with depression and bipolar disorder, the question arises whether treatments could be readjusted to ameliorate patients' symptoms. A critical window of opportunity may exist when interventions for different systems, including cognition, mood, and health systems, are effective in patients who are getting older, suffering from depression or bipolar disorder, and making the transition to menopause. The main controversy is whether certain interventions may become more ineffective or even deleterious during this period in life.

Hormonal Therapies

Menopause-related hormone therapy has been the subject of intense controversy, given the recent study[28] questioning its long-term safety and efficacy. It appears that menopause-related hormone therapy may be ineffective or even harmful if given at times other than during the critical window (i.e., early menopausal years). The Women's Health Initiative Study[28] showed that estrogen plus progestin used in postmenopausal women aged 50 to 79 years not only did not prevent cardiovascular disease as previously thought, but increased the risk for stroke and breast cancer such that the trial had to be stopped early due to risks outweighing benefits. Estrogen plus progestin also increased the risk for probable dementia in postmenopausal women aged 65 years or older and did not prevent mild cognitive impairment in the same group of women.[29] Further analyses revealed that these risks were minimized or even absent if estrogen was given alone (one of the study arms had offered estrogen alone for those who had undergone hysterectomy).[30] Furthermore, estrogen alone was effective for the short-term treatment of depression when given to women going through perimenopause, a period of chaotic hormonal changes and wide hormonal fluctuations,[31–34] but it was ineffective for the treatment of depression or mood in postmenopausal women, i.e., for those who had been deprived of estrogen for many years.[34,35]

Treatment for Hot Flushes

Hot flushes are an important QOL issue for women in the menopausal transition. Several treatments, besides estrogen, exist for hot flushes.[21] The options include herbal supplements, soy, and antidepressants. Among the best alternatives to estrogen for the treatment of menopausal hot flushes are the antidepressants venlafaxine and paroxetine controlled release, which, with a fast response at low doses, showed a positive impact compared with placebo.[36,37]

Antidepressants

Some evidence suggests that estrogens, particularly transdermal estradiol, can have a significant antidepressant effect in perimenopausal women.[31,32] However, antidepressants, when used alone in this population, may not only treat depression efficaciously but may also promote similar improvement of menopause-related symptoms and QOL compared with that observed with the use of menopause-related hormone therapy.[38] Overall, the evidence suggests that perimenopausal women with first-onset depression and vasomotor symptoms are more likely to respond to estrogen alone or in combination with antidepressants than are postmenopausal women with a history of multiple depressive episodes and no vasomotor symptoms.[10,34]

Treatment for Bipolar Disorder

Many medication options exist in the treatment of bipolar disorder, and some of the drugs that work best are affected by gender.[5] For example, the standard treatment for bipolar disorder is often lithium, which is quite effective in individuals who spend most of their time depressed. However, lithium is less effective for individuals who have rapid cycling or who have a mixed presentation of bipolar disorder, which both occur more often in women as opposed to men.

Other medications frequently used in the treatment of bipolar disorder include the anticonvulsants carbamazepine and valproate.[5] These 2 medications, while having a demonstrated response in individuals with rapid cycling,

may require use of adjuvant medications such as antidepressants because these anticonvulsants are a less optimal form of treatment for people who have a major depressive component in their presentation. This is relevant for women with bipolar disorder because they seem to be more prone to present as depressed, whereas men are more likely to present as manic. Women are especially vulnerable to becoming manic when antidepressants are used, so this type of treatment is not always the best option for them.

Lamotrigine has been approved in the United States for maintenance treatment of bipolar I disorder, but few studies examine how the agent affects women, especially postmenopausal women.[5] In Canada, lamotrigine is a first-line treatment for bipolar II depression and for bipolar II maintenance, the types of bipolar disorder seen more frequently in women than in men.[39]

Pharmacokinetic differences exist between women and men in the metabolism of medication. Women have lower hepatic metabolic rates, reduced absorption rates, and slower renal elimination than men.[2] All these factors should be taken into account when choosing medication for this patient population.

Bone Mineral Density

An important health concern for women is osteoporosis. Depression may be a risk factor for decreased bone mineral density (BMD)[40] and thus increased fracture rates in women,[41] although not all studies support this hypothesis.[42] Several possible theories[42] have been put forward to account for this decrease in BMD but the most likely explanations involve deficiencies in cortisol, abnormalities with the hypothalamic-pituitary-adrenal axis, and general health issues such as anorexia or feeding status. No studies examining bipolar disorder and BMD specifically are currently available, but since individuals with bipolar disorder spend much of their time in a depressive phase when they are ill, they are exposed to similar physiologic changes and, therefore, have a similar risk profile.

Several other mechanisms also contribute to decreased BMD and osteoporosis, but the one of most relevance to women with bipolar disorder is increased bone turnover, a normal biological process that seems to be adversely affected by mood stabilizers or anticonvulsants.[43] Individuals with epilepsy treated long-term with anticonvulsant medications were found to be at higher risk than controls for osteoporosis and to have a fracture rate of 61%, independent of seizures.[44] In a study of children,[45] valproate was associated with a 14% decrease in BMD in the lumbar spine and a 10% to 12% decrease in the distal radius. These results correlated to an increased risk of fractures over time. Lithium is less likely than some other medications to affect BMD in terms of bone turnover, but it causes increases in parathyroid hormone and affects renal calcium resorption, which leads to decreased mineral density.[46] Carbamazepine affects the cytochrome P450 system and increases vitamin D breakdown, and this leads to decreased intestinal calcium resorption, affects serum phosphate, and leads to secondary hyperparathyroidism.[47] Although less information is available about lamotrigine, preliminary reports indicate that it does not affect BMD to the same extent as other medications.[43,47] Pack and colleagues[47] examined women taking carbamazepine, lamotrigine, or valproate monotherapy. The lamotrigine group was found to be the only one without patients in the insufficient range for vitamin D levels, and unlike carbamazepine and valproate, lamotrigine did not significantly affect serum calcium concentrations.

CONCLUSION

The management of depression and bipolar disorder during the menopausal transition and postmenopausal years should be individualized, and several factors should be taken into account when choosing the appropriate treatment for these patients. When considering the risk for developing new symptoms or experiencing recurrence of symptoms versus the benefit of improving QOL, clinicians should keep in mind the efficacy and safety of both hormonal and nonhormonal interventions that can be helpful for these patients. Perimenopausal women, in particular, may benefit from a combination of antidepressants and estrogen. To improve QOL, it is important to manage somatic symptoms including hot flushes, vasomotor symptoms, and sexual dysfunction. Finally, clinicians need to consider the risk of osteoporosis and decreased BMD, a process of aging itself, but one that may be accelerated by the use of some medications. More information is needed to assess the best strategy to treat women with bipolar disorder as they get older and have a high risk for decreased BMD.

Drug names: carbamazepine (Equetro, Tegretol, and others), estradiol (Menostar, Vivelle, and others), estrogen (Premarin, Cenestin, and others), estrogen conjugated medroxyprogesterone acetate (Prempro, Premphase), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), paroxetine (Paxil, Pexeva, and others), valproate (Depacon and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; estradiol, estrogen, and estrogen conjugated medroxyprogesterone acetate are not approved for the management of mood symptoms; and paroxetine and venlafaxine are not approved for the treatment of bipolar disorder and hot flushes.

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