

# Women's Cognitive and Affective Health and Neuropsychiatry

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## Abstract

Recent interest in women's health has focused on the cognitive consequences of aging and hormonal changes. Based on hypotheses about estrogenic effects in the central nervous system (CNS), large-scale clinical trials were designed to address the efficacy of hormone replacement on protection against dementia and cognitive decline. Surprisingly, an absence of risk reduction for dementia and cognitive loss was found and much reanalysis of these findings has focused on timing of hormone replacement. Here we take a broad perspective to address a fuller range of psychological health. Gender differences in other psychiatric conditions including depression and anxiety have been attributed to hormones, and the neurotransmitter systems that are implicated in affective disorders may have an impact on cognitive impairment as well. Hormonal influences on neurotrophic mechanisms, as well as neurotransmitter effects, may be responsible for a breadth of neuropsychiatric conditions, particularly in aging.

This review will focus on cognition, mood and anxiety issues among women, with an emphasis on changes associated with aging. We will review data on the epidemiology of these entities and examine the biological mechanisms that may be involved, with an emphasis on those mechanisms that may contribute to the multiple aspects of neuropsychiatry and women's health.

**Key Words:** Women's health, cognition, affect, estrogen.

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## Introduction

THE PAST DECADE has brought a focus on many aspects of women's health. In neuropsychiatry, there has been specific interest in cognitive and affective health of women as they age. Much of the work in this field has focused on the consequences of estrogen reduction through menopause and the effects of hormone replacement.

Both affect and cognition may be mediated through neurotransmitter manipulations, specifically acetylcholine and serotonin, and estrogen has been shown to have a wide range of effects on both of these systems. Much of the data supporting a clinical benefit of estrogen has come from observational studies of women during menopause, when estrogen levels are reduced. Other observational studies have examined the effect of estrogen replacement therapy (ERT) on cognitive and affective

outcomes. Recently, well-controlled clinical trials have been completed with results that do not confirm some of the observational studies. However, it is not clear how well ERT can improve cognitive complaint and affective disturbances. In addition, recent studies have examined non-estrogenic approaches to intervention for depression as well as a combination of estrogen and other agents to determine the spectrum of benefit from hormone replacement.

Below, we examine the epidemiology and neurobiology of cognitive and affective disturbances in women as they transition through menopause. We will also take an evidence-based approach to the review of therapeutic options to treat these neuropsychiatric conditions. We begin with a review of the changes of menopause and mechanisms of neurobiological effects.

## Menopause

Currently in the U.S., the mean age of menopause is 51 years, and the perimenopausal period begins at a mean age of 47.5 years (1). Perimenopause is defined as the period when menstrual cycles become irregular, follicle-stimulating hormone (FSH) rises as the ovary becomes unresponsive to pituitary stimulation, and there is a

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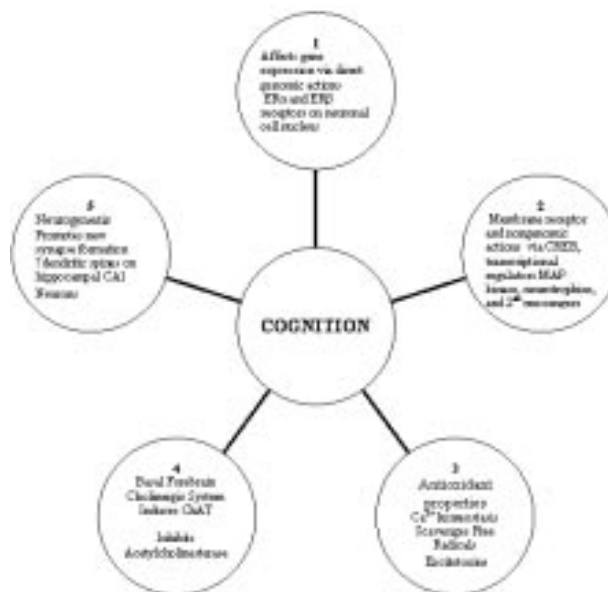
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breakdown in the usual cycle of the hypothalamic-pituitary-ovarian system. Perimenopause is diagnosed even pre-symptomatically if FSH is above 25 IU/L and estrogen less than 40 pg/mL when drawn during the early follicular phase. During this time, there are fluctuations in the levels of gonadal steroids, with initial increase, then marked decrease in estradiol levels. Progesterone, another ovarian androgen, also decreases. Menopause is completed one year after the last menstrual cycle, at which time the post-menopausal phase begins.

The drop in estrogen begins during late perimenopause and is sustained during post-menopausal years without hormone replacement therapy (HRT), conferring a state of relative estrogen deficiency. The change in estrogen level seems to play a role in the physiological, cognitive, and affective vulnerabilities of this transitional period; however, once the transition is complete rates of depression improve and become stable again. While cognitive complaint is common in perimenopause and menopause, there has been less success in documenting this deficit with formal testing. However poor, cognitive deficit increases with age and it has been suggested that persistent estrogen deficiency may contribute to these cognitive deficits.

### Estrogen May Have Neurobiological Effects

Estrogens are steroid hormones with a multiplicity of actions that can have an impact on cognition. This is outlined in Fig. 1. Estrogens act on receptors located in the cell nucleus and affect gene expression. There are two estrogen receptors,  $ER\alpha$ , which appears to be important in cognition and has been associated with estrogen's effect on cognitive processing, and  $ER\beta$ , which has been associated with effects on the serotonergic system and emotional processing. Furthermore, there are also membrane receptors on dendrites, presynaptic terminals and glial cells (2). There are several brain areas associated with cognition in which estrogen appears to have effects, including the basal forebrain cholinergic system, from which neurons project to the cerebral cortex and hippocampus. In this area, estrogen induces choline acetyltransferase (ChAT), which is the rate-limiting enzyme in the synthesis of acetylcholine (2). Other effects of estrogen include trophic effects such as enhancement of insulin-like growth factor-1 receptors, neurite outgrowth and cytoprotection from oxidative damage (2). Estrogen has an important influence in the hippocampal synaptogenesis and is associated with increased dendritic spine density on pyramidal neurons. Estrogen may also have ef-

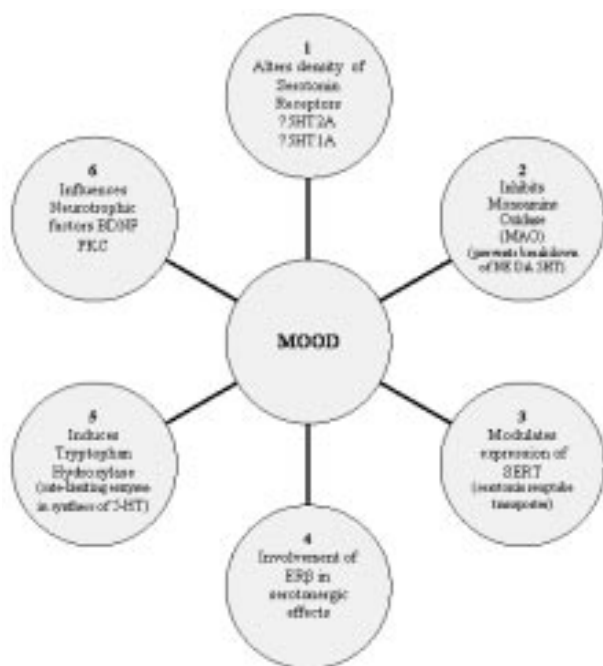


**Fig. 1.** The neurobiology of the effective role of estrogen on cognition.

ChAT = choline acetyltransferase, MAP = mitogen-activated protein, CREB = camp response element-binding [protein].

fects on neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which affects neuronal differentiation, survival and synaptic plasticity. In addition to its direct trophic effect on the cholinergic neurons, estrogen may facilitate serotonin-mediated acetylcholine release in the frontal cortex through the 5-HT<sub>1A</sub> receptor (3). Long-term estrogen replacement enhances serotonin-stimulated acetylcholine release in the adult rat frontal cortex (3). Animal studies suggest that a state of chronic estrogen deprivation is characterized by reduced BDNF in some cortical and hippocampal areas and that these changes are reversible only if estrogen is provided within a certain period of time. This data may be important to recall as clinical studies are evaluated below (4).

The neurobiology of the affective role of estrogen has also been studied and this multiply determined interaction is summarized in Fig. 2. The  $ER\beta$  receptor has been associated with effects on the serotonergic system and emotional processing. In support of this,  $ER\beta$  knockout mice show increased anxiety symptoms, modeled by the fear-like "amygdale-response," possibly through the serotonergic system. Tamoxifen, an  $ER\beta$  blocker, prevents estrogen-induced increase in the serotonergic 5-HT<sub>2A</sub> receptor mRNA in the dorsal raphe nucleus and binding in the frontal cortex, anterior cingulate, primary olfactory cortex, striatum and nucleus accumbens (5). These areas have also been associated with mood and the fear response. Acute 17 $\beta$  estradiol treatment downregulates both the 5-



**Fig. 2.** The neurobiology of the effective role of estrogen on mood.

BDNF = brain-derived neurotrophic factor, PKC = protein kinase C, NE = norepinephrine, DA = dopamine.

HT<sub>1A</sub> receptor mRNA and the 5-HT<sub>1A</sub> receptor in these limbic areas of female rat brain, but the effect is diminished with chronic treatment (2 weeks). Stimulation of the 5-HT<sub>1A</sub> autoreceptor is known to reduce the firing rate of the serotonergic neuron. Studies have suggested that estrogen causes sensitization of postsynaptic 5-HT<sub>1A</sub> receptors in the hippocampus, and desensitization of the presynaptic 5-HT<sub>1A</sub> receptors in the dorsal raphe (5), which predicts a different time course for modulation of cognition and affect.

In laboratory studies, estradiol has been found to inhibit serotonin reuptake transporter (SERT) mRNA, and receptor and transporter protein activity (6). One of the ways estrogen increases serotonin levels is by increasing production of tryptophan hydroxylase, the enzyme responsible for the rate-limiting step in serotonin production. By inhibiting expression of the gene for SERT, estradiol acts as an antagonist of this transporter, in some ways similar to the selective-serotonin reuptake inhibitor (SSRI) (7). 5-HT<sub>1A</sub> receptors are downregulated by both estradiol and antidepressants (8).

### Serotonin and Cognition

Cognitive processes are modulated by neurotransmitter systems via ascending monoamine projections to the prefrontal cortex and investigations are beginning to reveal the role of serotonin in var-

ious aspects of cognition. Neurotransmitter systems including serotonin play a role in regulation of executive functions mediated through the dorsolateral prefrontal cortex, which are responsible for working memory and attentional set shifting. Estrogen can induce changes in serotonin transmission, binding and metabolism in brain regions that are involved in these frontal areas, thereby affecting memory and affect (3). Serotonin is thought to play a role in hippocampal-based learning (2). Estrogen and progesterone, another important hormone, may have a variety of effects on neurotransmitter systems, including those with norepinephrine and dopamine as well as gamma-aminobutyric acid (GABA), all of which may have cognitive and behavioral influences. For a review of these mechanisms see McEwan, 2001 (2).

### Cognition, Women and Aging

Cognitive complaint may occur in women regardless of menstrual status, but clearly increases with age with up to 40% of women between the ages of 48 and 55 complaining of forgetfulness. Many, but not all, of these complaints are associated with menopausal symptoms. However, it has been difficult to document cognitive deficits with neuropsychological testing in both peri and early postmenopausal women. One recent investigation, a birth cohort study of 1,261 women, did find weak evidence of an adverse effect of natural menopause on cognitive function, but this effect was largely explained by pre-menopausal cognitive functioning. Cognitive deficits in this prospective observational cohort were not associated with vasomotor or psychological symptoms and were not associated with a benefit with estrogen replacement. Large cross-sectional studies, however, have failed to find an association between reproductive period, as a surrogate measure of endogenous estrogen exposure, and cognitive performance (9). (For a fuller review and meta-analysis of epidemiologic studies and small clinical trials, see LeBlanc [10]).

Existing studies have not adequately separated the effects of aging on cognition from the potential effects of menopause. Also, other symptoms associated with menopause (e.g., sleep disturbance) may indirectly contribute to cognitive symptoms.

### Cognitive Complaint in Younger Postmenopausal Women

There have been several randomized controlled trials examining the effects of unopposed estrogen (typically estradiol or conjugated equine estrogen [CEE]) on cognitive functioning in

younger (<65 yrs of age) post-menopausal women (11–19) (see LeBlanc et al. [10] for review). Many of these studies had small sample sizes and the duration of use was uniformly short, ranging from 21 days to 6 months. Methodological differences in study design (i.e., cross-over vs. separate experimental and placebo groups); preparation and dose of HRT; cognitive outcome measures; type of menopause (i.e., surgical vs. natural); whether or not women with menopausal symptoms were included; and prior estrogen use made it impossible to combine these trials quantitatively in a meta-analysis.

Nevertheless, some trends were apparent. First, no deleterious effects on cognitive functioning were observed. Second, hormone therapy did not consistently enhance cognitive test performance in women who were not experiencing menopausal symptoms. Among women with menopausal symptoms, however, ERT improved cognitive test performance, especially on tests of verbal memory and attention, as well as abstract reasoning and motor speed (10). Third, the effects are most robust in cohorts who have undergone surgical menopause and are less evident in those undergoing natural menopause. Although not examined directly, it is possible that the cognitive improvement observed in symptomatic women receiving HRT may be attributed to a lessening of other menopausal symptoms (e.g., hot flashes, sleep disturbance, mood changes). Nevertheless, it appears that cognitive improvement—at least in the domains of verbal memory and attention—may be an additional benefit of ERT for these younger women.

Most of the above work was conducted before it became apparent that estrogen should be co-administered with progestational agents to protect the intact uterus from hyperplasia. There have been only two studies to date examining the effects of estrogen progestin combination regimens on cognition in younger women, and they were based on the same cohort of 49 women (20, 21). These 2 studies were designed to compare 3 groups: unopposed estrogen (estradiol valerate), opposed estrogen (estradiol valerate plus dienogest), and placebo. Results revealed that women randomized to unopposed estrogen performed better than the other two groups on a test of verbal learning, while those receiving opposed estrogen performed better on a test of numerical memory.

### Clinical Considerations

Since combination therapy is the standard of care for women with an intact uterus, the data

leaves us in clinical equipoise, with so few studies examining cognitive effects of opposed estrogen therapy. When this prevalent and clinically relevant group has cognitive complaint, it is difficult to know how to counsel them. If they also have menopausal symptoms, the recommendation for HRT is clearly indicated, but the long-term effect on cognition in this young group is not clear. However, since the data from women over the age of 65 is not supportive of cognitive benefit and is associated with other health risks, it seems reasonable to minimize long-term exposure.

### Cognitive Complaint in the Older Postmenopausal Women

Observational studies indicate that estrogen use was associated with a reduced risk of dementia in general and Alzheimer's disease specifically (10, 22). Two meta-analyses of these studies were relatively consistent with approximately a 30% reduction in risk reported by each study. The promise of these observational studies led to an ancillary study by the Women's Health Initiative (WHI) hormone therapy trials, the Women's Health Initiative Memory Study (WHIMS) (23). This sub-study enrolled women aged 65 or older who were free of probable dementia at baseline, from the placebo-controlled, randomized WHI trial. Treatment regimen for the combination hormone therapy was 0.625 mg/day CEE and 2.5 mg of medroxyprogesterone acetate for women with a uterus, and CEE alone for those who had had a hysterectomy. Primary outcome measures of this study were incident dementia and mild cognitive impairment (MCI), defined as performance at or below the 10th percentile in at least 1 area of cognitive function. Secondary analyses examined global cognitive function as assessed by the Modified Mini-Mental State Examination 3MSE. Disappointing results from WHIMS revealed a two-fold increased risk of dementia for women in the estrogen plus progestin group (24). This increased risk translated into an additional 23 cases of dementia per 10,000 women per year. Although the treatment groups did not differ in their risk of developing MCI, a condition thought to be a prodrome to dementia, the secondary outcome of performance on global cognitive function revealed that scores in the treated group had statistically smaller improvements than those in the placebo group.

Results from the Unopposed Estrogen Trial, which had a smaller sample size, did not reveal significant effect of treatment on incidence of dementia or on global cognitive function. When data are combined to include those with and without

medroxyprogesterone, a dramatic decline was observed among women who scored poorly on the cognitive test at their screening visit. This suggests that hormone therapy may have accelerated an existent disease process. This finding parallels that seen in women with dementia, in whom several clinical trials have demonstrated no benefit or cognitive worsening with estrogen (25–27).

### Clinical Considerations

Despite suggestions from observational studies that hormone therapy may play a role in maintaining cognitive health and preventing Alzheimer's disease in older women, findings from the WHIMS have demonstrated clearly that—at least in women age 65 and older—there were no cognitive benefits of CEE, with or without medroxyprogesterone (MPA). Women randomized to active therapy scored lower on a measure of global cognitive functioning and were more likely to develop dementia or mild cognitive impairment. The increased risk of cognitive decline in women randomized to hormone therapy may be due to the vascular effects of estrogens (e.g., increases in thrombin, fibrinolysis, triglycerides, and C-reactive protein) and associated vascular disease in the brain; the high incidence of stroke in patients in both the CEE and CEE+MPA trials supports this claim (28). It is unclear whether the results from the WHIMS will generalize to other hormone preparations; however caution seems warranted in prescribing any hormone replacement therapy to healthy older women for the purpose of preventing cognitive decline.

### Affective Disorders in Women

The lifetime prevalence of depression is 17% overall, and the prevalence in women is twice that in men (29). High-risk periods for the development of depression in women occur when there are significant hormonal shifts. The risk is highest in the period from puberty to menopause, (i.e., the reproductive years). In the prepubertal and postmenopausal stage, depression risk is actually lower. In fact, during these phases rate of depression among females is approximately the same as that of males.

The three periods of rapid hormonal fluctuation and increased susceptibility to affective changes (primarily depression) are premenopause, post-partum, and perimenopause. The psychoemotional symptoms thought to be associated with menopause overlap with depressive symptoms and include disturbed sleep, concentration, anxiety, irritability, frustration, mood lability, depression, and

fatigue (30). Two epidemiologic prospective studies examined the onset of major depression during the menopausal transition and found increased susceptibility during that time (31, 32). Freeman described an increased risk for first-onset clinically significant mood disturbance in perimenopausal vs. premenopausal women (32). In his report, which followed 29 perimenopausal women for 5 years until 6 months after last period (33), Schmidt found that the 24-month period around menopause carried a 14-fold increase in the risk of depression.

There are several factors that appear to increase the risk of depression during the peri-menopause. They include a history of depression (33–36) and a history of premenstrual syndrome (32, 37). Other features associated with menstrual history that appear to increase the risk of depression are reduced parity (36), longer duration of perimenopause (defined as the duration of irregular cycles), presence of hot flashes, and history of post-partum or premenstrual depression. Other social factors that have been associated with depression during this period are non-specific and include stressful life situation, poor health, history of smoking, sleep disturbance and absence of a partner.

The menopausal transition, marked by perimenopause, has been identified as an independent risk factor for depression (36). The frequent coexistence of hot flashes and depression (35, 38) has been thought to reflect an underlying CNS response to estrogen deficiency. The brain's thermoregulatory system involves serotonin's 5-HT<sub>2A</sub> receptors, which decrease in density with the decline in estrogen, thereby implicating serotonin in both affective and vasomotor symptoms. The connection, also supported by the results of a large study, suggest that indicated that perimenopausal period from early menopause to 1 year after the last menses is associated with an increased risk of depressive illness; however, the postmenopausal time is not (36). In terms of major affective disorder, two epidemiologic prospective studies examining the onset of mood disorders during the menopausal transition provide evidence of increased susceptibility during this period (31, 32). Freeman described an increased risk for first-onset, clinically significant mood disturbance in perimenopausal vs. premenopausal women (32). Schmidt found that the 24-month period around menopause carried a 14-fold increase in the risk of depression.

The vulnerability conferred by hormonal shifts may not necessarily mean that low estrogen is the only etiologic factor. The finding of depression onset in early perimenopause (when estradiol levels are actually elevated) and the fact that estrogen and androgen levels in patients with perimenopausal de-

pression do not differ consistently from those of controls (39, 40) suggests that estrogen itself is not the only factor in depressive perimenopausal states. It may be the balance among fluctuating hormones that contributes to affective disturbance.

### **Estrogen as a Treatment for Affective Disorders.**

Several lines of evidence suggest that estrogen may have a mood-elevating effect. Depression during hormonal transition can be seen even in patients without a history of depression (1, 41), and several studies have addressed the issue of whether or not estrogen replacement can improve depression. There is evidence for estrogen's antidepressant effect in depressed perimenopausal patients (42, 43). In the two major randomized, placebo-controlled trials of transdermal estradiol therapy for perimenopausal depression, 60–75% of subjects vs. 20–30% of subjects taking placebo obtained partial or total remission of depressive symptoms (42, 43). In addition, in a pilot study of estrogen augmentation for antidepressant treatment in perimenopausal females (n=17), mood was improved with addition of 0.625 mg estradiol and there was a significant decline in Hamilton Depression Scale (HAM-D) over a 6-week period (p=0.012) (44).

The effect of HRT may differ among peri- and postmenopausal women. To determine if HRT could reduce severity of depressive symptoms among depressed postmenopausal women, Goldstein examined data from 1,160 women aged 60 and older with a diagnosis of major depression or dysthymia who were enrolled in the IMPACT study (45). At baseline, 44.5% of the sample was on HRT; this subgroup tended to be younger, white, married, educated with better health, and more likely to report antidepressant use in the previous 3 months. The group on HRT did not differ statistically from non-HRT users in depression severity as measured by the Symptoms Checklist—90 items (SCL-90). In this study there was no evidence that HRT modified the severity of depression (45).

There is substantial clinical and laboratory evidence suggesting that estrogen may be an important mediator of affect. A placebo-controlled, double-blind study by Heinrich and Wolf examined whether women who are estrogen deficient but not depressed might benefit from the boost in neurotransmitters that laboratory evidence suggests estrogen may produce (46). In their study, 51 women with a mean age of 64 years, who were stable in a postmenopausal state (they had had hysterectomies a mean of 13 years prior and were not on HRT) were randomized into three groups to receive es-

trogen, estrogen/progesterone, or placebo for a 24-week trial. The dose of estrogen in this study was quite high: the combined HRT consisted of estradiol 2 mg/progesterone 100 mg daily and ERT dose was estradiol 2 mg daily (44). Outcome measures were assessed at baseline, 4 weeks and 24 weeks, and included mood, well-being, menopausal symptoms, depression and subjective sleep. Thirty-five of 51 completed the trial and the findings were that neither hormonal intervention was more effective than placebo on the outcome measures. However, the fact that the subjects were not depressed at baseline yielded ceiling effects on the outcomes, making it difficult to observe any benefit.

Almeida considered the possibility that HRT, which combines the potentially antidepressant estrogen with progesterone (which can be a depressant), masks the beneficial effect of unopposed estrogen treatment (47). In a randomized, double-blind, placebo-controlled trial of 20 weeks, the effect of supplemental unopposed estrogen on the mental health outcomes of healthy women older (70+) at risk was examined. A total of 115 women were randomized to estradiol 2 mg or placebo for 20 weeks. The outcome measure of Beck Depression Inventory, quality of life (QOL) by the 36-item short form health study (SF-36) scale was not different than placebo.

### **Treatment of Depression in the Menopausal Transition**

While there is some evidence that estradiol may have a beneficial effect on depression, the effect is not robust or consistent. Treatment of depression in women can be tailored to address symptom profile, as well as stage of life in relation to their level of gonadal steroids, and stage in the menopausal transition. Traditional antidepressants are effective in the peri-menopausal period, although only few studies have specifically addressed this transition stage. One small trial by Ladd (n=16) assessed the effect of venlafaxine on both vasomotor and depressive symptoms in perimenopausal women (48). Several other studies demonstrated the efficacy of antidepressants for depression in the menopausal transition, including studies of citalopram and lexapro as monotherapy, and studies of remerk and celexa given in combination with HRT (49). Cohen reviewed the evidence for delineating subpopulations of women more or less responsive to different classes of antidepressant agents, and the findings are as yet inconclusive, with SSRIs and SNRIs (serotonin norepinephrine reuptake inhibitors) both appearing to be good options (49).

Parry compared groups of depressed peri- and postmenopausal women aged 45–72 receiving

SSRI alone, HRT alone or the combination. The outcomes measures were mood, cognition, and neuroendocrine changes, and the findings did not demonstrate HRT enhancement of mood effects beyond that seen with treatment of SSRI alone (50).

Estrogen may have a role as an augmenting agent in treatment-resistant depression or when first-episode depression occurs in the menopausal transition. SSRI may be the first line of treatment, but short-term use of estrogen may provide added benefit, especially for those women with hot flashes and other physical symptoms of menopause.

There is considerable interest in the use of alternative and complementary medicine therapies, particularly among women during the menopausal transition. There is a need for critical evaluation of botanical supplements used in perimenopause to determine both safety and efficacy for menopausal as well as for affective symptoms. Uebelhack investigated the efficacy of a combination of black cohosh and St. John's wort in a 16-week randomized, double-blind placebo-controlled trial and found it superior to placebo in reducing the menopause rating score as well as the HAM-D score (51). This promising approach requires further research.

### **Menopause and Anxiety**

Some studies have looked at the prevalence of anxiety symptoms during menopause. This task is complicated because anxiety symptoms are often comorbid with depression. However, anxiety disorders are very common, and the National Comorbidity Survey, as quoted by Freeman, revealed a 17% prevalence of anxiety disorders with greater prevalence in women (22.6% vs. 11.8%) (52).

As in depression, women have twice the risk of anxiety disorders as do men. However, while it appears that the female susceptibility to depression is limited to the reproductive years, with the gender differences disappearing in midlife, it is not clear if anxiety symptoms also are mitigated at this point. Anxiety is one of the often-quoted symptoms of menopause, and in this context it is measured as a component of QOL scales and menopausal questionnaires in the research.

Almeida performed a cross-sectional study of 265 older post-menopausal women, mean age 74.6 years. He examined the possible relationship of mood, anxiety and cognitive factors to serum estrogen levels (53). Depression, anxiety and QOL measures were correlated with serum estradiol and estrone levels. Low levels of these hormones were associated with greater depressive and anxiety symptoms, with a majority of significant findings evident with the estrone levels. Of note, the only other non-

hormonal clinical characteristic differentiating the symptom group was the BMI, suggesting to the authors that among other unmeasured factors, physical fitness might be associated with mood (53).

The possibility that anxiety symptoms are less prevalent in post-menopausal years is suggested by a study by Bebbington in the U.K. (54). This investigator looked at the prevalence of depression, and mixed anxiety and depression International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis in the National Survey of Psychiatric Morbidity in the British population, which included 9,792 households. His results showed a decrease in anxiety symptoms in women over age 55. Diagnosis was made by the Clinical Interview Schedule, Revised (CIS-R) clinical instrument. In women over 55, 1.1% had depression and 5.2% had mixed anxiety/depression while women under 55 years of age had nearly three times the prevalence of depression, and twice the prevalence of mixed anxiety (2.7% and 10.8%). Interestingly, the prevalence of both diagnostic categories increased for men as they reached 55 years of age, with depression prevalence of 1.7% vs. 5.3% in younger cohorts, and mixed anxiety/depression of 2.0 vs. 6.4% in younger cohorts. These differences remained after control for important social variables, including marital status, childcare, and employment status (54).

In a six-year population based-study using data from the Penn Ovarian Aging Study that followed 238 women (50% white, 50% African American), starting ages 35–47 who were premenopausal and were not taking any psychiatric drug or HRT (55). Anxiety was measured with the Zung Anxiety Index, a 20-item self-report scale. The findings were that anxiety is strongly associated with hot flashes even after adjusting for menopause stage, smoking, depressive symptoms, BMI, race, age, time and estradiol levels. In fact, anxiety preceded hot flashes in this cohort. Of note, in this study, African American women were 60% more likely than Caucasians to suffer from hot flashes. Depression was noted in about 1/3 of the overall sample and it increased in the early transition to menopause. In the multivariate model, the association of depressive symptoms to hot flashes was not observed (55).

### **Bipolar Disorder and Schizophrenia during Menopause**

Other psychiatric syndromes have been associated with menopause. In women with pre-existing bipolar disorder, an increased risk of mood episodes during periods of hormonal fluctuation has been

shown (32). A small study of 22 women found that estrogen may aid with mood stabilization (32).

It has been suggested that menopause may also be a risk factor for schizophrenia, since it has been observed that nearly 37% of female schizophrenics develop their illness after age 45 and a second peak in incidence (age 45–54 years) overlaps with the menopausal transition and this late onset schizophrenia. And there is often with a predominance of positive symptoms such as hallucinations and delusions. This pattern is distinct from that of males, in whom the development of schizophrenia is usually observed in the mid-twenties. Evidence of protective effects of estrogen is suggest by naturalistic studies in reproductive age female schizophrenia patients, finding that psychopathology scores drop when serum estradiol levels rise (56–58). Based on such findings, therapeutic interventions utilizing hormone replacement have been considered, although primarily as an adjunctive treatment.

### Conclusion

Interest in women's health has included attention to cognitive and psychiatric issues. Hormonal transition is associated with an exacerbation of cognitive and affective complaints. It has been difficult to tease out the degree to which hormonal fluctuation is causative in these problems and the degree to which hormone replacement can mitigate such symptoms. Clearly the evaluation of cognitive and psychiatric symptoms should include a history and status of hormonal stage and expectations for symptom relief, and treatment should take into consideration whether hormonal status is in transition such as in the perimenopause or if it is in a steady-state such as post menopause. The use of hormone replacement to treat cognitive or affective symptoms is not clearly supported by the empirical data. However, when these symptoms are accompanied by menopausal symptoms, including hot flashes, estrogen is clearly indicated and may permit the observation of maximal benefit from other therapies.

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