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Menopausal Symptoms and Their Management

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INTRODUCTION

The menopause transition is experienced by 1.5 million women each year and often involves troublesome symptoms, including vasomotor symptoms, vaginal dryness, decreased libido, insomnia, fatigue, and joint pain.[1–3]

In one population-based assessment of 386 Australian women, 86% consulted a clinician at least once to discuss menopausal symptoms.[4] Several symptoms bear an obvious relationship to the changing hormonal milieu associated with menopause, and most women make direct linkages between menopause and the common symptoms of hot flashes, vaginal dryness, and disrupted sleep (with or without associated night sweats). In addition, during menopause, women may develop depressive symptoms and cognitive difficulties, which are more subtly and inconsistently linked to hormones. Depression and cognitive impairment can be burdensome for women and also compound the burden of medical illness for the aging female population. As postmenopausal women are already at risk for osteoporosis and cardiovascular disease, it is important to address potentially changeable psychiatric issues that may make medical issues more difficult to treat. An understanding of the risk factors, clinical presentation, and management of these common menopausal symptoms allows for improved patient care and health outcomes for older female patients.

THE CORE 4 SYMPTOMS: VASOMOTOR, VAGINAL, INSOMNIA, AND MOOD

Epidemiology

Population-based, epidemiologic studies of menopausal women have recently been conducted and are yielding reliable and consistent information about the incidence, prevalence, and severity of several menopausal symptoms. However, the field is relatively

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new, and it is likely that there are subsets of women who are more or less vulnerable to particular symptoms or sets of symptoms. In 2005, a state-of-the-science conference on menopausal symptoms was convened, with a worldwide panel of expert evaluators who were tasked with determining which among the large set of midlife symptoms are most likely to be due to menopause. Symptoms were evaluated for their proximity to menopause, apart from the aging process, and the likelihood that estrogen is effective in relieving symptoms.[2] Based on this evidence review, 3 symptoms emerged as having good evidence for linkage to menopause: vasomotor symptoms, vaginal dryness/dyspareunia, and difficulty sleeping/insomnia. After this conference and based on 3 seminal studies,[3,5,6] adverse mood/depression was added to the list. Adequate longitudinal studies on cognitive function during the menopause were not yet available but have also become subsequently widely reported.[2,3,5,7,8]

It is clear that there are many other symptoms that are reported by menopausal women. These include joint and muscle aches, changes in body contour, and increased skin wrinkling.[1] Several studies have examined the associations between these symptoms and menopause. Given the methods of ascertainment, the subjective nature of the complaints, the likelihood that there is publication bias (wherein positive studies demonstrating linkage to menopause are more likely to be published than negative studies), and their variation over time, it has been difficult to establish a true relationship between these symptoms and menopause. Other symptoms, such as urinary incontinence (UI) and sexual function, have mixed data for efficacy of estrogen treatment and linkage to menopause, apart from the aging process. For these reasons, this article addresses the core 4 symptoms and includes cognitive issues because they are of great importance and concern to aging women.

Vasomotor symptoms

Vasomotor symptoms afflict most women during the menopausal transition, although their severity, frequency, and duration vary widely between women. Hot flashes are reported by up to 85% of menopausal women.[7] Hot flashes are present in as many as 55% of women even before the onset of the menstrual irregularity that defines entry into the menopausal transition[9] and their incidence and severity increases as women traverse the menopause, peaking in the late transition and tapering off within the next several years.[10–12] The average duration of hot flashes is about 5.2 years, based on an analysis of the Melbourne Women's Health Project, a longitudinal study that included 438 women.[11] However, symptoms of lesser intensity may be present for a longer period. Approximately 25% of women continue to have hot flashes up to 5 or more years after menopause. A meta-analysis of 35,445 women taken from 10 different studies confirmed a 4-year duration of hot flashes, with the most bothersome symptoms beginning about 1 year before the final menstrual period and declining thereafter.[10]

The exact cause of the hot flash has not been elucidated. The most accessible theory purports that there is a resetting and narrowing of the thermoregulatory system in association with fluctuations in or loss of estrogen production. In the past, hot flashes were thought to be related solely to a withdrawal of estrogen; however, there is no acute change in serum estradiol during a hot flash. Others have related hot flashes to variability in both estradiol

and follicle-stimulating hormone (FSH) levels.[6] It is thought that decreased estrogen levels may reduce serotonin levels and thus upregulate the 5-hydroxytryptamine (serotonin) (5-HT_{2A}) receptor in the hypothalamus. As such, additional serotonin is then released, which can cause activation of the 5-HT_{2A} receptor itself. This activation changes the set point temperature and results in hot flashes.[13] Regardless of the exact cause of the hot flash, both hormone therapy and nonhormonal regimens can help to relieve vasomotor symptoms (Table 1).

Vulvovaginal atrophy

Urogenital tissues are exquisitely sensitive to estrogen, and the fluctuations in estrogen that occur during the menopausal transition, followed by sustained low levels after menopause, can render these tissues fragile and cause distressing symptoms. Multiple population- and community-based studies confirm that about 27% to 60% of women report moderate to severe symptoms of vaginal dryness or dyspareunia in association with menopause.[14,15] In addition to vaginal atrophy, narrowing and shortening of the vagina and uterine prolapse can also occur, leading to high rates of dyspareunia. Furthermore, the urinary tract contains estrogen receptors in the urethra and bladder, and as the loss of estrogen becomes evident, patients may experience UI. Unlike vasomotor symptoms, vulvovaginal atrophy does not improve over time without treatment.

Menopausal hormone therapy (MHT) is an effective treatment of vaginal atrophy and dryness. For this purpose, systemic or vaginal estrogen can be used, although locally applied estrogen is recommended and can be administered in very low doses (Table 2). These low doses are believed to be safe for the uterus, even without concomitant use of a progestin. Data are currently insufficient to define the minimum effective dose, but vaginal rings, creams, and tablets have all been tested and demonstrated to reduce vaginal symptoms.[16]

Although MHT is effective in reversing changes associated with vaginal atrophy,[17,18] it is not beneficial for UI. The Women's Health Initiative Hormone Trial found that women who received MHT and who were continent at baseline had an increase in the incidence of all types of UI at 1 year. The risk was highest for women in the conjugated equine estrogens (CEE)-alone arm. Among women experiencing UI at baseline, the frequency of symptoms worsened in both arms, and these women reported that UI limited their daily activities. This evidence clearly shows that the use of MHT increases the risk of UI among continent women and worsened the characteristics of UI among symptomatic women after 1 year of use.[19]

Women who have urogenital atrophy symptom require long-term treatments. Over-the-counter lubricants and moisturizers may have some effectiveness for milder symptoms; however, for those with severe symptoms, hormonal treatment is the mainstay. Vaginal estrogen can be given locally in very small doses (see Table 2). Until recently, there were no alternatives available. However, the FDA approved ospemifene, a systemically administered selective estrogen receptor modulator, for vulvovaginal atrophy in 2013. Dehydroepiandrosterone vaginal preparations are also being tested for effectiveness in treating menopausal urogenital atrophy.[20] These 2 compounds may be particularly helpful for women who have estrogen-sensitive cancers, such as breast cancer, in whom exogenous

estrogen use is contraindicated. It is too early to evaluate the comparative effectiveness of these treatments.

Sleep disturbances and insomnia

Sleep quality generally deteriorates with aging, and menopause seems to add an additional, acute layer of complexity to this gradual process. Women report more trouble sleeping as they enter into the menopausal transition, and sleep has been shown to be worse around the time of menses, both by self-report as well as by actigraphy.[21,22] Actigraphy studies indicate that as much as 25 minutes of sleep per night can be lost when a woman is premenstrual in her late reproductive years.[21]

Women report sleep difficulties approximately twice as much as do men.[23] Further compromise in sleep quality is associated with the hormonal changes associated with the menopausal transition and with aging, apart from hormones. Over time, reports of sleep difficulties increase in women such that by the postmenopause more than 50% of women report sleep disturbance.[2] Women seem to experience more detrimental effects on sleep in association with aging, when compared with men.[24]

Hormonal changes alone are not likely to provide the complete explanation for the relationship between sleep difficulty and menopause. Consistent with this concept is the fact that hormones are not always successful in treating sleep problems in midlife and beyond.[25] Chronic poor sleep hygiene habits and mood disorders contribute further to sleep problems.

The nature of the sleep disturbance can help guide the clinician to appropriate treatment. Women who report nighttime awakening in association with night sweats are candidates for hormone therapy. However, the clinical history is not often so simple. Women with mood disorders, particularly anxiety and depression, may experience difficulty falling asleep and/or early awakening. Women aged 40 years and older also frequently report difficulty staying asleep. Lower socio-economic status (SES), white race, and low marital happiness are social factors that have all been associated with worse sleep.[26] Disorders such as sleep apnea and restless leg syndrome need to be considered. The clinical consequences of a poor night's sleep include daytime fatigue and sleepiness, which can be subjectively measured and form the basis for a referral for a sleep study. Table 3 displays a clinically useful scale that can help the clinician estimate the daytime impact of the sleep complaint.

Polysomnography has become a clinically useful tool for assessing sleep complaints.[26] When polysomnography is not available, clinicians can use sleep questionnaires to ascertain the principal issues surrounding the sleep complaint. Using polysomnography, investigators in the Study of Women's Health Across the Nation (SWAN) study observed 20% of women with clinically significant apnea/hypopnea and 8% with periodic leg movements.[26]

Treatment of sleep complaints depends on the clinical findings. For insomnia, the reader is referred to the practical clinical review by Buysse.[27] Sleep apnea is often treated with continuous positive airway pressure devices. Restless leg syndrome can be treated with dopamine agonists, gabapentin, and opioids.[28] Hormone therapy can be considered for

women with difficulty maintaining sleep because of vasomotor symptoms but seems to be effective mostly in postmenopausal women with surgically induced menopause.

Adverse mood

One-fifth of the US population will have an episode of depression in their lifetime, and women are twice as likely to be affected.[29] Although depression is more likely to occur in young adults, with peak onset in the fourth decade of life, there is evidence that the perimenopause represents another period of vulnerability for women. Several large prospective cohort studies have shown an increased risk of depressed mood during the menopause transition and an approximately 3-fold risk for the development of a major depressive episode during perimenopause compared with premenopause.[3,5,30,31] Although a previous episode of depression has been shown to confer an increased risk, women with no previous episode of depression are still 2 to 4 times more likely to experience a depressive episode during the menopause transition compared with the premenopause. Anxiety symptoms have been found to precede depression in some instances, and anxiety may also be viewed as increasing a woman's vulnerability to a midlife depressive episode.[32]

Other independent risk factors for the development of depressed mood during the menopause transition include poor sleep, stressful or negative life events, lack of employment, higher body mass index, smoking, younger age, and race (African Americans twice as likely to have depressive symptoms). In addition, there is evidence that hormonal changes occurring during menopause play a role, as evidenced by increased risk for depression in association with variability in estradiol levels, increasing FSH levels, surgical menopause, the presence of hot flashes, and a history of premenstrual syndrome. Contrary to prior belief, hot flashes are not necessary to the development of depression. Some have proposed the cascade theory, in which hot flashes lead to sleep disturbance and then to daytime fatigue, poor quality of life, and then depressive symptoms. Research instead shows that depressive symptoms more often precede hot flashes when they co-occur.[33]

There may also be significant environmental stressors present at the time that a woman reaches menopause. During midlife, a woman may be faced with changes in her marriage and family structure, with children no longer living in the home. She may experience changes in her career path, possibly returning to work or retiring. She may be taking on new responsibilities as a caregiver to her parents or in-laws, a well-known risk factor for depression. Although these factors do not likely cause depression on their own, they can certainly contribute and should be considered, particularly if supportive resources may be of help (Box 1).

As the menopause transition involves significant instability in estrogen levels, with intense irregular fluctuations, many researchers have focused on understanding the association between estrogen level and mood changes. As stated above, in longitudinal prospective studies, women who developed depression were more likely to have increased variability in estrogen levels, particularly in the early to midperimenopause.[30] The absolute level of estrogen is not associated with risk, however. Some studies have used gonadotropin-releasing hormone (GnRH) agonists in order to induce menopausal changes in premenopausal women, so that measurement of hormones, evaluation for mood symptoms,

and response to add-back hormone therapy can be more easily determined.[35] In a group of healthy premenstrual women, without a psychiatric history, administration of a GnRH agonist did not uniformly precipitate depressive symptoms. In another related study involving withdrawal of estradiol treatment in women with and without a history of perimenopausal depression, those with history of this type of depression were more likely to experience depressive symptoms as a result of withdrawal of estradiol therapy (Box 2).

A major depressive episode is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) (1994) as 5 or more of the following symptoms, present most of the day nearly every day for a minimum of 2 consecutive weeks. At least 1 symptom is either depressed mood or loss of interest or pleasure.

The DSM-IV criteria for depressive disorders, as for other mental disorders, require that the depressive episode cause significant distress or dysfunction. A depressive episode can be classified as mild, moderate, or severe, with or without psychotic symptoms. Psychotic symptoms can include hallucinations (usually auditory perceptual disturbances) and delusions (false beliefs). A depressive disorder may be recurrent if a patient has had an episode in the past. A person whose depressive symptoms do not meet criteria for a major depressive episode may be classified as having minor depression or/and adjustment disorder with depressed mood if a significant recent stressor is present. Chronic symptoms of depression not meeting criteria for a major depressive episode may represent a dysthymic disorder.

A depressive episode can also occur in the setting of bipolar disorder, a mood disorder that also involves at least 1 previous manic episode. Before treatment of depression, a bipolar-type disorder should be ruled out because of different effective treatment regimens. As anxiety disorders are very common in women with depression, assessment for panic symptoms, generalized worry, as well as obsessive thoughts and compulsive behaviors should be included. In addition, evaluation for substance abuse and dependence, which can significantly affect mood, should be included. Medical workup for illnesses that can present with depressive symptoms, such as hypothyroidism and anemia, is also appropriate.

A complete interview for depressive symptoms in every perimenopausal patient is not necessary or time efficient. Screening tools can be used to determine who will need further evaluation. Referral of patients to a mental health specialist depends on the primary care provider’s level of expertise in assessment and treatment of depression, the availability of mental health resources, and patient/family preference. Even if a provider initiates treatment, there may be reason for referral at a later point (Table 4).

First-line treatment of a major depressive episode may involve psychotherapy, antidepressants, or a combination thereof. Treatment is often tailored to patient preference and severity of depression. Certainly, a more severe episode would require combined psychotherapy and pharmacotherapy. A mild to moderate episode may respond to either psychotherapy or an antidepressant alone, and if a patient is interested in a trial of medication, it may benefit significantly if this is started soon after the diagnosis is made.

Primary care practitioners frequently make the initial diagnosis of depression and are in a position to begin this treatment in a timely manner when possible.

Selective serotonin reuptake inhibitors (SSRIs) are the first-line medications used in the treatment of depression. These SSRIs include fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), sertraline (Zoloft), and paroxetine (Paxil). Each of these medications is equally likely to be effective and share similar side effect profiles. Patients often describe gastrointestinal upset, jitteriness, or headache, but these symptoms usually abate in the first few weeks of therapy. Once initiated, it may take 6 to 8 weeks for a patient to respond; however, often, patients notice a difference within the first month of treatment. Dosage can be titrated to achieve improved effectiveness, with increases approximately every month as tolerated. Of particular concern in this population is the risk for sexual side effects (decreased libido and difficulty with arousal and achieving orgasm). As depression can also affect a woman's sexual function, however, the risks of discontinuation of medication may outweigh the burden of these side effects. A switch to a different SSRI or another antidepressant class or the addition of bupropion (Wellbutrin), which acts on the dopaminergic system, may be helpful. As stated previously, estrogen can be helpful in treating perimenopausal depression and changes in sexual function as well. Conversely, several different SSRI antidepressants have been shown to be effective in treating perimenopausal vasomotor symptoms (Box 3).[38]

Serotonin and norepinephrine reuptake inhibitors, such as venlafaxine (Effexor) or duloxetine (Cymbalta) can be particularly helpful in patients with comorbid anxiety. Bupropion can be helpful when patients have low energy, but it can exacerbate anxiety and insomnia. Psychostimulants such as modafinil (Provigil) or methylphenidate (Ritalin) can sometimes be useful in these cases but have less evidence for efficacy. Tricyclic antidepressants and monoamine oxidase inhibitors are useful in treatment-resistant depression but often have more significant side effects, particularly in older patients. Electroconvulsive therapy is often very well tolerated, safe, and effective in these older patients who fail to respond to or do not tolerate medications. There is also growing evidence for the utility of transcranial magnetic stimulation in this group (Box 4).

Several forms of psychotherapy may be beneficial for patients with depression, including cognitive behavioral therapy, interpersonal therapy, and psychodynamic psychotherapy. A range of providers with psychotherapy training are available (social workers, psychologists, nurse practitioners, psychiatrists), but resources may be limited because of the patient's insurance, location, and financial situation.

In double-blind placebo-controlled trials, perimenopausal women receiving short-term 17β-estradiol transdermally had remission rates as high as 80%.[37,39] In other randomized controlled trials, when estrogen was given to postmenopausal women with depression, there were no significant improvements in symptoms[40] or the treatment was not superior to an SSRI agent.[36] So it seems that the low estrogen levels involved in the menopause transition is an important factor in the development of depression in some women but does fully explain the increased risk for depression in this population. Moreover, these data indicate a

window of opportunity for estradiol's antidepressant effects, with women with perimenopausal but not postmenopausal depression responding to estrogen therapy (Box 5).

Menopause and cognition

Many women complain of changes in their cognitive function during the menopause transition, with the majority reporting worsening of memory. Verbal memory (word list learning and recall), which women generally excel at when compared with men, is often the type of complaint noted. Women may notice difficulty remembering names and other verbally told information. In addition, they may report other cognitive challenges, with more trouble organizing and planning or possibly with concentration. In one study of 205 menopausal women, 72% reported some subjective memory impairment.[41] Symptoms were more likely to be associated with perceived stress or depressive symptoms than perimenopausal stage, but overall, cognitive symptoms were more prevalent early in the menopause transition. Aside from being bothersome, these symptoms raise women's concerns regarding their risk for dementia; however, it remains unclear whether these symptoms correspond to an increased risk for more serious chronic issues.

The first cross-sectional study to measure cognitive change in association with menopause showed that women in early menopause, late menopause, and postmenopause did not vary in memory performance according to stage and did not have abnormalities in memory testing.[42] Overall, women who had initiated any form of hormone replacement therapy before their last period performed better on memory testing than those who started it after menopause. Longitudinal study of menopausal status and measured cognitive performance[8] showed no impairments in overall cognitive function, but women entering menopause failed to improve as much on repeated tests compared with premenopausal women (they would be expected to improve over time with practice on the same test) (Box 6).

An important question is whether women who have cognitive difficulties during the menopause transition are at greater risk for cognitive impairment later in life. Patients and their clinicians can be reassured, however, that for most women cognitive function is not likely to worsen in the postmenopause in any pattern other than that expected with normal aging. Although it is not likely that cognitive function returns to a woman's premenopausal baseline in postmenopause, she may adapt to and compensate for the symptoms with time.

A gradual decline in some cognitive functions is expected to occur with normal aging, beginning in midlife, around the age of 50 years. Decreases in processing speed are often present, and sometimes mild changes in memory for newly learned information and executive function can also occur. However, some types of cognitive changes, collectively called mild cognitive impairment (MCI), are thought to be a manifestation of very early dementia. MCI and dementia are highly unlikely in people younger than 50 years, but risk increases significantly with age, with greater than 10% of the population older than 65 years at risk for developing dementia. (Those diagnosed with MCI have an increased risk of conversion to dementia like that in Alzheimer disease [AD], with approximately 10% developing dementia each year).[43] AD is by far the most common type of dementia, but other types of dementia can occur with varying presentations, including vascular dementia, Lewy body dementia, and frontotemporal dementia. AD often presents with impaired

memory first, but other types of dementia can present with impaired language, behavioral changes, or motor abnormalities (Box 7).

In some individuals with MCI, dementia may never develop and cognition can even improve over time. Depression can also be present with MCI, and it can be difficult to discern whether the depression is causing the memory impairment, if a common pathologic process is causing depression and cognitive MCI, or if MCI puts one at risk of developing depression. Depression can also be an early manifestation of cognitive decline. In the unlikely situation that MCI presents in an individual younger than 50 years, it rarely represents a predementia syndrome, and search for another, possibly more treatable cause is important.

Dementia is more common in women than in men, even after controlling for the effects of the female population's greater longevity. For this reason, many have focused on the role that estrogen plays in the risk for developing dementia. Estrogen interacts with both the cholinergic and serotonergic systems that are the main brain systems involved in normal cognitive functioning. In animal models, estrogen has positive effects on the cholinergic system, interacting with trophic factors for neuronal development and plasticity, with associated improved cognitive functioning.[44] Furthermore, studies have shown that estradiol can improve cognitive deficits produced by anticholinergic agents in normal postmenopausal women (Box 8).[45]

Evidence supports a significant role for estrogen in cognitive functioning. In premenopausal women, higher achievements in verbal memory performance occurred during phases of the menstrual cycle associated with high estrogen levels,[46] and hormone users in the SWAN sample had better cognitive performance in the perimenopause (although the same was not true for postmenopausal hormone use[8]). There was also early evidence in observational studies for a decreased risk of AD in women on hormone replacement therapy.[47] The relationship between estrogen and cognitive function has proved to be complicated, however, with varying effects with different formulations/combinations and when initiated during menopause, before the age of 65 years in postmenopause, and after the age of 65 years in the postmenopause. In several studies, estrogen alone in younger postmenopausal women showed some benefit to verbal memory but had neutral effects on older postmenopausal women.[48] CEE plus medroxyprogesterone acetate resulted in a negative change in the memory of younger and older postmenopausal women. Other formulations may be beneficial, with one study showing promise for the combination of estradiol valerate and dinogest in younger postmenopausal women[49] and another demonstrating a positive effect with cyclic oral estradiol and norethindrome in older postmenopausal women (Box 9).

Women experiencing a surgical menopause after hysterectomy and bilateral oophorectomy have also been a focus of study, because cognitive complaints are common in this subgroup and hormonal changes are certainly more abrupt and clearly defined. There is evidence that these women do develop impairments in verbal memory that can be prevented by administration of estrogen therapy.[46,50]

When a perimenopausal or postmenopausal woman presents with cognitive complaints, the practitioner is most often able to reassure the patient that these complaints are common and not necessarily progressive and may even improve over time. As in those with depressive symptoms, patients with cognitive impairment often present to primary care providers first and the gynecologist is in the position to evaluate for more serious issues and to provide education regarding prevention of chronic conditions such as dementia.

In 2001, the American Academy of Neurology (AAN) published practice guidelines for the early detection of memory problems (Petersen and colleagues, 2001). The AAN workgroup of specialists identified the criteria for an MCI diagnosis (Table 5). Patients with MCI do not meet criteria for dementia (see Table 5), which involves impaired daily functioning.

The evaluation for MCI and dementia includes a thorough history provided by the patient and preferably a partner or family members in close contact with the patient. Medical history and review of systems aid in determining if any other medical illnesses could be contributing (particularly infectious illnesses or disorders of the cardiovascular, neurologic, or endocrine systems). A medication history is also particularly important because often analgesics, anticholinergics, psychotropic medications, and sedative-hypnotics can affect cognition. Family history to elicit information regarding family member with dementia; possibly early onset; before the age of 60 years; and other neurologic disorders is also important. Physical examination, including a basic neurologic examination and some cognitive assessment should also be completed.

The cognitive test most often used as a screen for cognitive impairment is the mini mental state exam (MMSE),[52] which takes approximately 7 minutes to complete. MMSE tests a broad range of cognitive functions including orientation, recall, attention, calculation, language manipulation, and constructional praxis (Box 10).

MMSE scores may be influenced by age and education, as well as language, motor, and visual impairments. Other cognitive tests are available for use in the office, such as the Montreal cognitive assessment test.[53] When a diagnosis of MCI is possible, however, a referral for more complete neuropsychological testing may be best. Initial laboratory work should include assessing thyrotropin and vitamin B_{12} levels to rule out potentially reversible causes of cognitive impairment (hypothyroidism and vitamin B_{12} deficiency). Brain imaging (computed tomography or preferably MRI) should be completed if MCI or dementia diagnosis is determined.

Once a diagnosis of MCI or dementia is made, these patients should often be referred to a neurologist or geriatric psychiatrist for further evaluation and/or treatment. Studies can be done to more clearly determine the risk for developing dementia in those with MCI (such as APOE allele, lumbar puncture with cerebrospinal fluid studies, functional imaging studies, and neuropsychological testing) and to clarify the type of dementia.

Medications are not clearly helpful in addressing these cognitive issues. Acetylcholinesterase inhibitors have been to shown to provide benefit for patients with early dementia but have not been shown to decrease the rate of progression to dementia in patients with MCI. As noted before, estrogen may be useful in some women, but its use is not

recommended for this purpose. Antidepressant medications may result in improved cognition if comorbid depression is also present. Atomoxetine, the selective norepinephrine reuptake inhibitor often used to treat adult attention deficit disorder, has recently been shown to provide significant subjective improvement in memory and attention in perimenopausal and postmenopausal women presenting with midlife-onset subjective cognitive difficulties.[54] Similarly, stimulant medication may have a role in the treatment of subjective cognitive impairment, particularly for women with comorbid fatigue or impaired concentration, who are not showing evidence of objective impairment (Box 11).

There is some evidence that modifying lifestyle factors can decrease the risk for dementia and even cognitive decline associated with normal aging. Patients should be encouraged to exercise regularly; to eat a nutritious diet, with adequate fruits, vegetables, and fish; to engage in regular social activities; and to participate in cognitive exercise (reading, crossword puzzles, etc.) Patients should also be encouraged to maintain good cardiovascular health, with treatment of hyperlipidemia, hypertension, and diabetes mellitus.

SUMMARY

The menopausal transition and postmenopausal years are associated with significant symptoms. Vasomotor symptoms and adverse mood often demonstrate improvement after a woman is postmenopausal, whereas sleep complaints, vaginal dryness/dyspareunia, and cognitive complaints tend to persist or worsen in association with aging. There is evidence that the changing hormone milieu, with significant changes in estrogen levels, can affect the brain systems involved in mood and cognition. Patients often present to their primary care provider with these symptoms first, and endocrinologists are in a position to identify more serious issues, provide education, begin treatment, and make appropriate referrals to when necessary. A better understanding of the nature of the risk for these common symptoms in menopausal women will aid in prevention, detection, and treatment.

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KEY POINTS

- The late menopause transition (when women begin to experience 60 or more days of amenorrhea) is the point in time when hot flashes, adverse mood, vaginal dryness, and sleep complaints accelerate in prevalence.
- The duration of hot flashes (vasomotor symptoms) maybe longer than previously thought, with newer studies indicating durations of as long as 10 or more years.
- There are nonestrogenic alternatives that are now approved by the US Food and Drug Administration (FDA) for the treatment of menopause-related vulvovaginal atrophy.
- Both depression and anxiety increase in prevalence as women traverse the menopause, and the most vulnerable women are those without any prior episodes.
- Cognitive changes related to estrogen withdrawal include deficits in verbal and working memory, with almost three-fourths of women having a subjective sense of memory loss.

Box 1

Science revisited

Estrogen affects the mood-regulating pathways of the brain: Depression is thought, albeit in part, to be caused by dysregulation of the monoaminergic pathways in the central nervous system, and changing estrogen levels can lead to alterations of these serotonergic and noradrenergic systems. In animal models, estrogen administration can induce changes in serotonin neurotransmission in the amygdala, hippocampus, and hypothalamus, brain regions that are involved in affect regulation. In humans, studies of menopausal women undergoing estrogen treatment showed changes in mood as well as serotonin transmission relative to hormonal status.[34]

Box 2

Evidence at a glance

Timing is everything: A 4-year cohort study by Freeman and colleagues,[30] involving a balanced randomly identified sample of African American and white women aged 35 to 47 years showed an increased risk for depressive symptoms in early menopause (with variable cycle length more than 7 days) compared with late menopause (at least 2 skipped cycles and >60 days of amenorrhea) and no elevated risk in the postmenopause. Other researches have suggested that the late menopause transition represents a time of increased risk for depression[5,30,31]; overall, perimenopause seems to pose more risk than premenopause or postmenopause.

Box 3

Evidence at a glance

SSRIs are the first choice: In a treatment study by Soares and colleagues,[36] the SSRI escitalopram proved superior to a combination of estrogen and progesterone in treating depression as well as other menopausal symptoms. Almost 75% of women on escitalopram achieved remission of depression compared with 25% of those on hormone replacement therapy. In this study, however, subjects' depressive symptoms did not necessarily begin during the menopause transition. Other treatment studies showing benefit of estrogen in treating depressive symptoms have focused solely on women with depression beginning during menopause.[37]

Box 4

Tips and tricks

Watch out for drug-drug interactions: In older women, with multiple medical comorbidities, citalopram or escitalopram are often preferred because they have fewer interactions with the metabolism of other medications.

Start low and go slow: Older women may be more prone to side effects of antidepressants; however, doses of antidepressants in the higher range may be necessary to achieve remission, particularly when comorbid anxiety is also present. So continue to adjust the dose as necessary while monitoring the patient every few weeks.

Box 5

Caution!

Use hormone replacement therapy with care: Estrogen can be helpful in treating depression in some perimenopausal women. Although estrogen is often recommended to treat hot flashes, women with depression with comorbid vasomotor symptoms are not more likely to respond to estrogen therapy.[37] Estrogen should be avoided in treating depressive symptoms in postmenopausal women, however, with lack of evidence for efficacy and increased risk of adverse events and side effects.

Box 6

Evidence at a glance

Again, timing may be key: The SWAN study[8] was a 4-year, multisite longitudinal study of cognitive function in women aged 42 to 52 years. Results showed that verbal memory and processing speed were improved with repeated testing in premenopausal, early perimenopausal, and postmenopausal women, but not in late perimenopausal women. Hormone use before the final menses was associated with better processing speed and verbal memory in all groups compared with current hormone use in postmenopause.

Box 7

Tips and tricks

Some cognitive changes are normal in aging

- More difficulty recalling newly learned lists, names, and other verbal information
- Slower rate of learning
- Decreased ability to perform newly learned complex tasks
- Shortened attention span

Some changes may be warning signs

- Loss of vocabulary or language skills
- Impaired reading comprehension
- Loss of older memories/fund of knowledge
- Inability to perform independent activities of daily living (shopping, handling finances, using transportation, using telephone, housekeeping, food preparation)
- Disorientation

Box 8

Science revisited

Serotonin plays a role here too: There is ample evidence from animal studies showing that changes in serotonergic transmission can have effects on memory tasks. Administration of estradiol in ovariectomized rodents also does result in changes in serotonin levels and metabolism.[34] In humans, memory has repeatedly been shown to be impaired by tryptophan (TRP) depletion, a manipulation that results in rapid reduction of brain TRP and serotonin levels, and there is now some evidence that estrogen therapy may protect menopausal subjects from these effects.[34]

Box 9

Evidence at a glance

Is there a critical window? The Women's Health Initiative Memory Study[51] demonstrated that MHT would not protect women from dementia as once thought and even showed an increased risk when used in older postmenopausal women. This study was limited to women between the ages of 65 and 79 years, however, and there is further evidence that hormone replacement therapy initiated earlier in the postmenopausal period may not present the same risk. More research is needed to determine whether a critical window exists when estrogen or combined MHT might protect cognitive function.

Box 10

MMSE Sample Items

Orientation to Time

"What is the date?"

Registration

"Listen carefully. I am going to say three words. You say them back after I stop.

Ready? Here they are…

APPLE (pause), PENNY (pause), TABLE (pause). Now repeat those words back to me." [Repeat up to 5 times, but score only the first trial.]

Naming

"What is this?" [Point to a pencil or pen.]

Reading

"Please read this and do what it says." [Show examinee the words on the stimulus form.]

CLOSE YOUR EYES

Box 11

Caution!

Hormone replacement therapy for memory? A trial of estrogen therapy or combined estrogen/progesterone may prove beneficial for some types of cognitive complaints in some perimenopausal or early postmenopausal women. However, estrogen therapy has not been shown to be useful in treatment and prevention of cognitive decline in older postmenopausal women (>65 years old). Monitor patients on HRT often and be sure to thoroughly explain known risks and benefits to your patient.

Table 1

Hormonal and nonhormonal formulations for the treatment of hot flashes

Trade Name	Estrogen	Progestin	FDA Approved	Dose
Hormonal Therapies				
Premarin	CEE	—	Yes	0.3–1.25 mg po daily
Cenestin	Synthetic CE	—	Yes	0.3–1.25 mg po daily
Menest	Esterified estrogen	—	Yes	0.3–1.25 mg po daily
Estrace	17β-estradiol	—	Yes	1–2 mg po daily
Estinyl	Ethinyl estradiol	—	Yes	0.02–0.05 mg po 1–3 times daily
Evamist	17β-estradiol	—	Yes	1–3 sprays daily
Alora, Climara, Esclim, Menostar, Vivelle, Vivelle-Dot, Estraderm	17β-estradiol	—	Yes	1 patch weekly to twice weekly
EstroGel	17β-estradiol	—	Yes	1.25 g daily transdermal gel (equivalent to 0.75 mg estradiol)
Estrasorb	17β-estradiol	—	Yes	2 foil pouches daily of transdermal topical emulsion
Activella	Estradiol 1 mg	NETA 0.5 mg	Yes	1 tablet po daily
Femhrt	Ethinyl estradiol 5 μg	NETA 1 mg	Yes	1 tab po daily
Ortho-Prefest	17β-estradiol 1 mg	Norgestimate 0.09 mg	Yes	First 3 tablets contain estrogen, next 3 contain both hormones; alternate pills every 3 d
Premphase	CEE 0.625 mg	MPA 5 mg	Yes	First 14 tablets contain estrogen only and remaining 14 tablets contain both hormones. 1 tab po daily
Prempro	CEE 0.625 mg	MPA 2.5 or 5 mg	Yes	1 tab po daily
CombiPatch	17β-estradiol	NETA	Yes	1 patch transdermal twice weekly
Climara Pro	17β-estradiol	LNG	Yes	1 patch weekly
Estrace	17β-estradiol vaginal cream	—	Yes	2–4 g daily for 1 wk, then 1 g 3 times weekly
Femring	Estradiol vaginal ring	—	Yes	1 ring inserted vaginally every 3 mo

Trade Name	Estrogen	Progestin	FDA Approved	Dose
Duavee	CEE 0.45 mg/ bazedoxifine 20 mg	—	Yes	1 tablet daily
Nonhormonal Therapies				
Brisdelle	Paroxetine[a] 7.5 mg	—	Yes	7.5 mg daily
Effexor	Venlafaxine 36.5–300 mg	—	No	37.5–75 mg daily
Pristiq	Desvenlafaxine	—	No	50–100 mg daily
Lexapro	Escitalopram	—	No	10–20 mg daily
Celexa	Citalopram	—	No	10 mg daily
Prozac	Fluoxetine[a]	—	No	10–20 mg daily
Zoloft	Sertraline	—	No	50–100 mg daily
Neurontin	Gabapentin	—	No	300–900 mg up to tid
Lyrica	Pregabalin	—	No	50–10 mg tid

Abbreviations: CE, conjugated estrogen; CEE, conjugated equine estrogen; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.

[a]Inhibitor of CYP2D6; unsafe for use in conjunction with tamoxifen.

Table 2

Treatments for vulvovaginal atrophy

Trade Name	Hormone	FDA Approved	Dose
Premarin vaginal 0.625 gm	Conjugated equine estrogens	Yes	0.5–2 gm qd × 2–3 wk, off 1 wk, repeat prn[a]
Estrace vaginal 0.01% cream	Estradiol	Yes	1 gm biweekly to triweekly
Estring 2 mg	Estradiol	Yes	One ring every 3 mo
Osphena	Ospemifene	Yes	60 mg po qd

[a]Lower dosing/less-frequent application may be appropriate per patient preference.

Table 3

The Epworth sleepiness scale

Situation	Chance of Dozing
Sitting and reading	
Watching television	
Sitting inactive in a public place (eg, a theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Responses are recorded on a 4-point scale of 0 to 3 (0, no; 1, light; 2, moderate; 3, high chance of dozing). A total score of greater than 9 merits further evaluation.

Adapted from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:541; with permission.

Table 4

DSM-IV criteria for major depressive disorder and reasons for further psychiatric evaluation

Major Depression	Indications for Further Psychiatric Evaluation
At least one of these *must* be present: Depressed mood Loss of interest or pleasure in most or all activities	Evidence of suicidal ideation, inability to care for self or dependent others, or aggressivity/homicidal ideation
Four or more of the following must be present:	Failure to respond to or is intolerant of initial treatment trial
Insomnia or hypersomnia Change in appetite or weight Psychomotor retardation or agitation Low energy Poor concentration	Patient or clinician interested in modalities requiring specialty expertise (psychotherapy or electroconvulsive therapy, transcranial magnetic stimulation)
Thoughts of worthlessness or guilt	Psychotic symptoms present
Recurrent thoughts about death or suicide	History of bipolar disorder or psychotic disorder
	Significant psychiatric comorbidity (anxiety disorders, substance use, cognitive disorder)
	Unclear diagnosis of depression

Table 5

Differentiation of MCI and dementia

MCI	Dementia (DSM-IV Criteria)
Memory complaint, preferably confirmed by an informant	Impairment in handling complex tasks
Objective memory impairment on standard neuropsychological batteries assessing memory (for age and education)	Impairment in reasoning ability
Normal general thinking and reasoning skills	Impaired spatial ability and orientation
Ability to perform normal daily activities	Impaired language
—	The cognitive symptoms must significantly interfere with the individual's work performance, usual social activities, or relationships with other people
—	This must represent a significant decline from a previous level of functioning