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Review Article

Hormonal Therapy of Menopause and Mental Health

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Abstract:

During the menopausal transition, which begins 4 to 6 years prior to stopping menstruation, women at this stage experience progressive changes in ovarian activity and physiological impairment of hypothalamic-pituitary-ovarian axis function associated with fluctuations in levels. hormonal; where they can suffer symptoms related to menopause such as vasomotor symptoms, sleep disorders, mood changes, memory problems and genitourinary syndrome of menopause. Neurological symptoms such as sleep disturbance and mood swings are the most important discomfort in the transition to menopause, which impacts quality of life, productivity and physical health. A review of the associations between menopause and/or hormone levels with sleep problems, mood and reduced cognitive performance is performed. During the transition to menopause, women experience dramatic fluctuations in the levels of sex hormones such as estradiol, progesterone, and androgens, responsible for changes in behavior, cognition, mood, and sleep.

Keywords: hormonal therapy for menopause; cognition; mood; sleep; mental health; depression; hormonal cycle; insomnia; sleep disorders; vasomotor symptoms; aging

Introduction

During a woman's life, there are fluctuations in the levels of sexual hormones estradiol (E2), progesterone (P4) and androgens, from menarche to menopause; which impact the body, including the central nervous system (CNS) that may be responsible for modifications in behavior, cognition and mood. Sexual steroids play a role in the brain, both in cortical and subcortical structures, through genomic and non-genomic pathways1; it is believed that several molecular and cellular processes are involved in determining changes in the structure and function of neuronal systems through the modulation of gene expression and activation of signaling pathways. Sexual steroids modify several functions, such as behavior, cognition, memory, sleep, mood, pain and coordination, among others. They exert their function through receptors in the nuclei and along membranes in the synapse, spine, and mitochondria; glia provide regulation in myelin formation and potentially in demyelinating diseases.

Steroid hormones active in the CNS are called neurosteroids. They can be peripherally produced steroids capable of crossing the blood-brain barrier or synthesized in the CNS and peripherally by neurons and glial cells, through de novo synthesis from cholesterol or local metabolism of intermediate steroids produced in the periphery. Even if the levels of steroid hormones in peripheral blood are different from those in the CNS, the measurement of their plasma levels remains important to understand their role in CNS activity, since they can cross the blood-brain barrier. Different hormones provide brain regulation in a sexually specific manner: the neuroprotective effects of estrogens are more evident in women than in men, and androgens are more active in men in the recovery from demyelinating events, whereas progestins are more effective in men in reducing apoptosis and abnormal proliferation after trauma or stroke2. In the CNS there is a wide distribution of estrogen receptors (ER) localized in brain areas involved in memory and brain function. The ER isoform, ERβ, is mainly expressed in the cerebral cortex and hippocampus, whereas ERα signaling is largely represented in magnocellular cholinergic neurons of the basal forebrain. In the basal forebrain and hippocampus, E2 has been shown to induce a trophic effect critical for memory and brain function; estrogens mediate neurotransmitter interactions in the prefrontal cortex, which is relevant for brain function3. Estrogens are also associated with an increase in neurogenesis of the dentate gyrus part of the hippocampal formation in the temporal lobe of the brain that includes the hippocampus and the subiculum part of the hippocampal trinaptic circuit and is thought to contribute to the formation of new episodic memories. Estrogens trigger their function in many neurotransmitter systems including acetylcholine, serotonin, norepinephrine and glutamate. The cholinergic neurotransmitter system is relevant in memory processes. The method by which estrogen exerts its action on the brain includes neurotrophic and neuroprotective actions specifically, enhancing synaptic plasticity,

neuron growth and hippocampal neurogenesis and protecting against neural injury and apoptosis4, estrogen appears to enhance mitochondrial function, enhancing adenosine triphosphate production and mitochondrial respiration which is important in a site with high energy requirements such as the brain5. Other types of estrogen action in the brain include DNA repair and promoting an antioxidant effect6. Estrogen has also been associated with increased levels of C-reactive protein (an inflammatory marker), which has been linked to impaired cognitive function.

Similar to estrogen, P4 is a potent regulator of neurogenesis, cell survival, and bioenergetic systems. They do not have a synergistic action and their joint administration leads to a lower response than with the administration of a single compound. P4 acts both through the classical pathway that binds to its receptors (RPα and RPβ) and by regulating gene transcription and, together with allopregnanolone and dihydroprogesterone, through the non-classical pathway that activates different signaling cascades and transcription of several genes. The main effects of the two pathways are the promotion of antiapoptotic effects and cell survival, bioenergetic regulation, and a significant effect on neural cell proliferation. P4 exerts its action on glial cells, promoting the proliferation and action of oligodendrocytes. Oligodendrocytes produce P4 and transform circulatory P4 into DHP and allopregnanolone, which regulates myelination and modulates gamma-aminobutyric acid (GABA) receptors. P4, and especially allopregnanolone, promotes the GABAergic system drug or chemical compound that modulates the GABA system in the body or brain by inhibiting synaptic transmission, producing an anxiolytic effect similar to benzodiazepines, decreased levels of allopregnanolone are related to depression and antidepressants determine and increase this metabolite. The GABAergic role of P4 in the hippocampus explains why exogenous administration of progestins has a negative impact on the cognitive performance of healthy women in working memory tests. P4 and allopregnanolone influence dopaminergic systems, sensory motor functions are best observed during phases of the menstrual cycle when P4 is high. The positive modulation of allopregnanolone on dopamine release has an effect on drug abuse and depression. The brain is capable of locally producing the androgenic dihydrotestosterone independently of the gonads7; Androgens induce neurogenesis and spinal synapses in the hippocampus and like estrogens, androgens have neuroprotective effects. Considering the relationship between androgens and neurotransmitters, testosterone increases serotonergic tone (also through its conversion to E2) and the effect of noradrenergic antidepressant agents, dehydroepiandrosterone has antioxidant, neuroprotective and antiglucocorticoid effects8; through these mechanisms it can reduce anxiety and improve cognitive deficits, psychotic and depressive symptoms.

The impact of the menopausal transition (MT) and aging in midlife on women's health and well-being to determine whether TM-related changes during midlife are related to unfavorable health and well-being in early old age; sleep disturbances increase during the menopausal transition. During midlife, objectively measured sleep duration and deep sleep do not worsen and may improve. Black and Hispanic women have shorter sleep duration and less efficient sleep compared to white women; poor sleep has an adverse impact on cardiovascular health in women in midlife; or older during late perimenopause and postmenopause. Other factors, such as stressful life events, financial strain, low social support, sleep problems, and low physical activity are important contributors to symptomatic symptoms and anxiety, independent of TM.

The menopausal transition is associated with an increase in insomnia symptoms, especially difficulty staying asleep, which negatively impacts quality of life. Vasomotor symptoms are a key component of sleep disruption. Results of polysomnographic studies—a test that records certain bodily functions as one sleeps or tries to sleep; used to diagnose sleep disorders that involves recording brain activity, breathing, heart rate, muscle activity, and oxygen levels—are less consistent in showing sleep disruption in the menopausal transition independent of aging; more prospective studies are needed. Hormone therapy alleviates subjective sleep disturbances, particularly if vasomotor symptoms are present. However, because of contraindications, other options should be considered, including cognitive-behavioral therapy for insomnia. More work is needed to develop preventive and treatment strategies to alleviate sleep disturbances to ensure better health, quality of life, and productivity in midlife women 9-13

The Influence Of The Menopause Transition And Cognition

During the menopause transition, many women complain of memory problems, such as difficulty with words, forgetfulness, and mental confusion, due to hormonal changes related to menopause. Older women are at higher risk than men for age-related dementia, gender differences are not explained by longevity13, middle-aged women perform better on detailed memory tasks compared with men of the same age14; sex differences were attenuated in postmenopausal years; high plasma levels of E2 were associated with better performance; low cognitive impairment associated with higher levels of E2 was reported in women with cognitive impairment; other studies showed no relationship between cognitive problems and estrogen levels. The impact of the menopausal transition on memory and cognitive function; some report subtle declines in cognitive function; others showed no significant cognitive decline, with the exception of verbal fluency; cognitive performance deterioration was reported mainly in learning skills during the menopausal transition, with subsequent improvement from premenopausal levels and into the postmenopausal period this study will provide unique insight into the long-term effects of hormonal changes in middle-aged women; not only events occurring during the menopausal transition but also lifelong hormonal processes are significant for cognition; a longer fertile window (older age at natural or surgical menopause) was associated with better verbal memory 1,15, in another study, a longer fertile window was not associated with a lower risk of dementia.

Menopause Hormonal Therapy And Cognition

In women without dementia

Despite the medical literature highlighting the profound connection between estrogen and cognitive function, data on the relationship between menopausal hormone therapy (MHT) and its neuroprotective outcomes remain conflicting. Although several observational studies have demonstrated a positive effect of hormone therapy on Alzheimer's disease (AD) 16,17, MHT is associated with a 29% reduction in AD in meta-analyses such as the Women's Health Initiative (WHI) and the Women's Health Initiative Memory Study (WHIMS) did not support those findings 4,9.

WHIMS was a randomized, placebo-controlled clinical trial, and the first large long-term study to address the cognitive effects of MHT (0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate) in preventing AD, in 4532 postmenopausal women (aged 65 years or older) enrolled in the larger WHI study. Results showed that after a median follow-up of 4.2 years, MHT failed to reduce overall cognitive decline and was associated with a substantial and clinically important increase in Modified Mini-Mental State Examination (MMSE) total scores compared with placebo.

Post hoc analysis of 2947 women treated with WHIMS with estrogen alone (aged 65 to 79 years) showed that mean MMSE scores were significantly lower in the estrogen group compared with placebo. The adverse effect of estrogen was most pronounced in women with lower cognitive function at baseline. 9

In women aged 70 to 81 years, little difference in cognitive decline was found between current hormone users and those who had never used them. Long-term users (at least 5 to 10 years of use) of estrogen or estrogen plus progestin showed an increased risk of substantial decline on most cognitive tests. Decline was most evident in women starting hormones at an older age. Further analysis showed that MHT users with the apolipoprotein E4 allele (APOE 4) had worse cognitive decline. MHT (estrogen or progestin and estrogen therapy) in postmenopausal women (over age 60) concluded that MHT does not protect against decline in cognitive function in normal women. In the WHIMS study, women over 65 years of age were considered; they did not consider the so-called "time hypothesis." Indeed, other studies, similar to cardiovascular risk, have suggested that estrogen may be neuroprotective only if started soon after the onset of menopause. Supporting the "critical window hypothesis," some epidemiological studies have suggested that MHT in early menopause is linked to a lower risk of dementia, whereas later use is not. Other data revealed that women using MHT had a reduced risk of AD compared to non-MHT users only if treatment was started soon after menopause (within five years). Similarly, in postmenopausal women, MHT in midlife was associated with a protective effect against cognitive decline, whereas starting MHT later in life might have a negative effect. Other studies did not confirm that MHT use near the time of menopause was clearly associated with better cognitive performance later in life or a lower risk of dementia.13–16.

There have also been other limited clinical trials regarding early MHT and cognitive performance later in life. In postmenopausal women aged 50–55 years randomized to MHT with CEE with or without medroxyprogesterone acetate (MPA) 2.5 mg for a mean of 7.0 years or placebo. CEE-based therapies produced no sustained overall benefit or risk to cognitive function when administered to postmenopausal women aged 50–55 years. Cognitive assessment performed up to age 67 years showed no sustained benefit of MHT over placebo. Although they do not support the theory of cognitive enhancement in MHT users, these studies provide reassurance that hormone therapy does not negatively influence cognition in young postmenopausal women.

Cognitive decline and dementia are a growing public health problem. The inability to recall information, defined as impaired episodic memory, is a potentially alarming symptom of the early signs of AD or other forms of dementia. AD is the most common cause of dementia and arises more frequently in women than in men, with some authors implying sex-specific differences in the incidence of AD17,18. This condition is characterized by a progressive loss of episodic memory and cognitive function, which subsequently causes deterioration of language and visuospatial function, which is the ability to mentally represent, analyze, and manipulate objects; which is often accompanied by behavioral disorders such as apathy, aggression, and depression. Considering the importance of this disease, research in this field has attracted considerable scientific and public interest. The role of estrogen has been evaluated not only in maintaining cognitive function in non-demented women but also in preventing and/or treating AD.

Preliminary in vivo and in vitro data suggest that estrogen may play a role in preventing amyloid deposition. Estradiol has been shown to attenuate hyperphosphorylation resulting from the imbalance of the action of different kinases and phosphatases resulting from a disruption of the existing dynamic regulatory balance between protein phosphatases and protein kinases and the deposition of beta-amyloid and has also been shown to ameliorate the inflammatory sequelae of beta-amyloid, In a prospective study of incident dementia in men (mean age 73.2 years) and women (mean age 74.5 years), women using MHT had a reduced risk of AD compared with non-MHT users (adjusted hazard ratio 0.59), whereas there was no apparent benefit with current use of MHT unless used for more than 10 years. Other epidemiological studies have addressed the role of exogenous estrogens and dementia risk. A reduced risk of dementia was reported in MHT users, another did not associate MHT and all-cause dementia and AD19. Transdermal 17-beta estradiol therapy was associated with a decrease in beta-amyloid deposition in neuroimaging studies, particularly in carriers of APOE, a plasma protein constituent of lipoproteins, which functions to maintain the structure and regulate the metabolism of several of them; it plays a central role in the metabolism of plasma lipoproteins and in the transport of lipids within tissues. APOE shows a genetic polymorphism determined by three common alleles20, APOE 2, APOE 3, APOE 4.

More recently, it was shown that systemic hormone therapy users have an increased risk of AD compared with vaginal estradiol users and that long-term use of systemic hormone therapy might be affected by an overall increased risk of AD, regardless of age at initiation of systemic hormone therapy. 18 The risk of AD was similar between estradiol-only and estrogen-progestogen users; the risk was not associated with specific progestogens (norethisterone acetate, MPA, or other progestogens). It should be noted that for shorter treatment, the risk of AD was not increased among those who had started estrogen therapy or estrogen plus progestin therapy before age 60; the possibility of estrogen treatment in women with Alzheimer's has been considered. In women, one year of estrogen administration (CEE 0.625mg or 1.25mg versus placebo) did not delay disease progression or improve global, cognitive, or functional outcomes; the studies should not alter our current clinical practice in decision making regarding MHT; several studies supported the safety profile of MHT on cognition in early menopause. Overall, young menopausal women with no contraindication to MHT and impaired quality of life due to night sweats, vasomotor symptoms, or sleep disruption may benefit from MHT with several studies assuring that MHT does not negatively affect cognition in these women. On the other hand, it should be noted that according to the guidelines, MHT should not be prescribed for the sole purpose of preventing AD or memory loss in women without these symptoms or in those who are unwilling to begin hormonal treatment. Despite the amount of data already available on this topic, future research should focus on the long-term risks of MHT on cognition and AD and on the different effects on cognitive outcomes of various types of molecules9,13-16.

The Influence Of The Menopause Transition And Menopause Hormonal Therapy On Mood

Mood Disorders During The Menopause Transition

During the menopausal transition, women are at increased risk of developing depression, stress, anxiety, and emotional distress 21-23; women are more likely to be more susceptible to depression at certain stages throughout their life; we can describe precise periods of biological vulnerability in women's lives, such as the phases of the menstrual cycle, pregnancy, postpartum, and the menopause transition; There are windows of vulnerability for depressive episodes related to reproduction, such as the increased sensitivity experienced by some women to changes in hormonal levels that characterize the luteal phase of cycles, the postpartum period, and the transition to

menopause. 24 Depressed mood and sleep problems (insomnia, waking during the night, or rising early) are likely related and should be specifically treated. 25 Other factors influence mood, including demographic, psychosocial, and health-related characteristics such as unemployment, low educational attainment, race, poor social support, smoking, chronic medical conditions, history of anxiety, postpartum depressive symptoms, nulliparity, vasomotor symptoms (VMS), stressful life events, death of a partner, body mass index (BMI), and self-esteem. Body dissatisfaction may be common in middle-aged women. There is evidence that age and BMI are positively related to the intensity of menopausal symptoms, as well as to changes in lifestyle factors (physical activity), which influence women's mood. Self-esteem is directly associated with depression and anxiety, low self-esteem predicts the occurrence of distress related to menopausal symptoms, such as hot flashes, and is related to women's health, stress and perceived mood during this period of their life.

The association between depression and hysterectomy with or without bilateral salpingo-oophorectomy (BSO), the results are mixed 26,27, an elevated risk of depressive symptoms was detected, 20% or more in women with hysterectomy without BSO and 44% higher in women with hysterectomy with BSO compared to controls (women without hysterectomy) 28.

The role of estrogens should be considered, even if the link of E2 (either decreasing levels or low levels) in the precipitation of perimenopausal depression (PMD) is still controversial 29. E2 regulates the synthesis, metabolism and receptor activity of the classical neurotransmitters involved in depression (serotonin, dopamine and noradrenaline)30; the presence of wide distribution of ER in the brain has been demonstrated. The activity of estrogen found in regions known to be involved in mood and cognitive regulation (prefrontal cortex, hippocampus), contributes to the evidence for the concept of mediating effects (and therapeutic effects) of this hormone on mood, the effects of E2 on serotonin (5-hydroxytryptamine (5-HT) can be described as favorable for mood, with an increase in the synthesis and availability of 5-HT24, with reduction of monoamine oxidases (MAO) A and B activity after E2 has been documented, with a limitation of 5-HT degradation. This also promotes the increase of both isoforms of tryptophan hydroxylase, the rate-limiting enzyme for serotonin production. Estrogens also improve mitochondrial respiratory efficiency, helping to prevent the formation of oxygen free radicals that negatively affect mitochondrial energetics in depression. The effects of estrogen also promote norepinephrine (NE) availability through a reduction of MAO and an increase in the activity of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis. Acute administration of E2 stimulates the transcription of the dopamine b-hydroxylase gene, catalyzing the hydroxylation of dopamine to form NE17, estrogen plays a role as an antidepressant, due to its stimulating effect on brain-derived neurotrophic factor, an important neuroprotective agent and growth factor, which is deficient in depression 30; About 30% of those who developed depression during follow-up experienced a worsening of the persistence or recurrence of depressed mood and was confirmed in those with new cases of depression 31,32, a parallel trend towards an increased risk of depressive symptoms in the menopausal transition has been observed 33, however, the risk of higher depressive symptoms increased in the years before menopause and decreased in the years after menopause, in relation to the date of the last menstrual period (LMP). The risk of depressive symptoms was higher in women in the transition to menopause, before LMP with a lower risk after LMP 34.

The existence of depression associated with menopause is controversial, despite the undeniable evidence of a high increase in major depressive disorder (MDD) during the menopausal transition. However, it is not possible to define an "estradiol withdrawal hypothesis", notable methodological differences include menopausal status (perimenopausal versus postmenopausal), ascertainment of status, baseline symptomatology (asymptomatic versus depressive symptoms versus syndromic depression), route of hormone administration (transdermal versus oral), and symptom or syndrome measurement, much of the literature on women's mental health analyses the menopausal transition in terms of disease risk; it is not absolute hormone levels that make the difference in the onset of MDD, but rather individual variability and sensitivity to reproductive hormonal change 35.

Hormonal Therapy For Menopause And Mood

In non-depressed women

In perimenopausal, non-depressed women, MHT for six months with CEE for two weeks followed by two weeks of CEE plus MPA. No significant effects on mood were seen 36. Estrogens in preventing depressive symptoms in the menopausal and early postmenopausal transition with transdermal E2 (0.1 mg/day) plus intermittent oral micronized P4 (200 mg/day for 12 days every three months) or placebo; women receiving estrogen plus P4 were less likely to have depressive symptoms compared with placebo (32.3 versus 17.3%), mainly in early perimenopause 35; In contrast, when used in non-depressed postmenopausal women, there is no effect on mood with oral E2 (1 or 2 mg); neither with MHT (CEE 0.625 mg/AMP, 10 mg/day) nor with oral E2 versus placebo. Only oral CEE versus transdermal E2 has a positive impact reported; MHT should not be proposed to asymptomatic non-depressed perimenopausal women to prevent or alleviate mood symptoms. Estrogen appears to have a potential role among specific subpopulations at risk for depressive symptoms during the menopausal transition 10,18,37-49.

In depressed women

MHT has a potential antidepressant effect similar to classical antidepressants when administered to depressed premenopausal women31; the antidepressant properties of E2, the acceptance of estrogen therapy is restricted by the diverse clinical effects of MHT on mood in pre- or postmenopausal women and, in particular, if these women had already been suffering from depressive disorders 24; the beneficial effects of E2 are observed only if it is administered close to the cessation of ovarian activity and estrogen is ineffective for depressive disorders in postmenopausal women 31; women who initiated MHT soon after menopause, suggesting that it has a neutral or beneficial effect on mood43 the use of MHT (estradiol valerianate 2 mg plus dienogest 2 mg, estradiol 1 mg/day plus medroxyprogesterone 10 mg/day for 2 weeks and transdermal 17-estradiol 0.05 mg/day) in postmenopausal women with depressive disorders showed improvement or no change in mood]; in women with MMD compared with those without previous depression29, transdermal E2 (100 mg/day) in women with previous PMD, who previously responded to hormone therapy, had a higher risk of recurrence of depressive symptoms during hormone withdrawal than those who remained on E2 therapy and continued to be asymptomatic, indicating that normal changes in ovarian E2 secretion trigger a dysfunctional behavioral state in susceptible women. Although estrogen increases the response to antidepressants in middle-aged and older women, its use should still be suggested when indicated for other concurrent conditions such as SVM 31. Estrogen is not approved for mood disturbances, it is mandatory to accurately investigate the origin of depressive symptoms to detect those women who had a history of depression before the

menopausal transition and those who appeared during the menopausal transition. Antidepressants remain the first-line treatment for depression in patients with a history of depression 24. In women seeking improvement of mild mood disorder symptoms, clinicians should consider nonpharmacological strategies (i.e., exercise, balanced diet, and dietary supplements) and/or hormonal strategies.

Sleep Changes Associated With The Menopausal Transition

Sleep

Women in the menopausal transition typically complain of poor sleep quality, insufficient sleep, nighttime awakenings, and apnea. Sleep difficulties often begin during the menopausal transition and their prevalence increases in postmenopausal life with rates of self-reported sleep problems ranging from 40 to 56%, compared with premenopausal women in their late reproductive years. Lack of sleep is a known risk factor for cardiovascular disease, diabetes, obesity, and neurobehavioral dysfunction and can increase health care costs and reduce quality of life and work performance 10.

Sleep disturbances can be categorized into three groups: problems falling asleep, waking up multiple times, and waking up early; waking up during the night was the most common type of sleep problem50; the associations between E2, follicle-stimulating hormone (FSH), and sleep disturbances; only changes in hormone levels, but not baseline levels, are associated with sleep disturbances. In particular, reduced serum E2 was correlated with problems both falling and staying asleep, whereas increases in serum FSH levels were associated with reports of difficulty staying asleep; women who had a slower rate of change of FSH were shown to have significantly lower sleep efficiency, and in contrast to previously observed associations between changes in FSH and sleep, sleep measurements did not reflect changing levels of E2. High baseline E2 was associated with a moderate decrease in sleep quality, surgical menopause is associated with more severe sleep disturbances than natural menopause50, women undergoing SOB are at increased risk for more severe hot flashes than women in physiological menopause. The transition to menopause is accompanied by other typical risk factors for sleep disorders other than estrogen withdrawal. VMS are the most characteristic manifestations of menopause, with association with sleep disorders; they arise with the decrease in estrogen through a complex mechanism of actions, more complex than simple estrogen withdrawal, involving central noradrenergic activity, as well as serotonergic mechanisms and participation of hypothalamic kisspeptin, neurokinin B and dynorphin and neurons. Women with moderate to severe hot flashes (6–14 days in a two-week period) are almost three times more likely to suffer from frequent nocturnal awakenings compared with women without hot flashes. Other factors associated with the aging process are involved in the appearance of sleep problems during the menopausal transition, such as obesity, cardiovascular diseases, gastrointestinal, urinary, endocrine problems, chronic pain syndromes, the use of neuroactive medications, smoking, caffeine, selective serotonin reuptake inhibitors, bronchodilators, antiepileptic drugs, thyroid hormone preparations, among others 51, the aging process is characterized by changes in the sleep electroencephalogram and in the secretion of sleep-related hormones, which correlate with decreased sleep continuity, slow wave sleep (SWS) and increased nighttime wakefulness. Other factors related to sleep problems are restless legs syndrome (RLS) and obstructive sleep apnea (OSA). RLS is a common nervous system condition that causes an overwhelming irresistible urge to move the legs, which occurs during the night or at bedtime. Its prevalence is higher in women; the cause is unknown, they are associated with iron deficiency secondary to pregnancy or persistently high levels of estrogen during pregnancy or decreased estrogen and melatonin in menopause 51; estrogen in the etiopathogenesis of RLS influences the dopaminergic system and dopamine catabolism by inhibitory influence on the enzyme catechol O-methyltransferase which is one of several enzymes that degrade catecholamines (such as dopamine, adrenaline and noradrenaline) in humans; a recent study found no differences between genders 52. Menopausal women who previously suffered from RLS describe a worsening of severity after menopause, regardless of the use of menopausal hormone therapy (MHT). Between 47 and 67% of postmenopausal women have suffered from OSA. Physiological factors explaining this increased prevalence include higher BMI, larger neck circumference, higher waist-to-hip ratio, and changes in fat distribution, with an increase in central obesity. OSA causes a condition of nighttime apnea and hypopnea resulting in disrupted sleep patterns and worsening sleep quality, due to intermittent hypoxemia, arousals, and both rapid eye movement sleep and reduced SWS. These arousals rarely result in full awakening, but can have a significant negative effect on restorative sleep quality. Women may often suffer from excessive daytime sleepiness and insomnia or symptoms such as snoring, gasping, choking, and memory impairment.

Hormonal Therapy For Menopause And Sleep

Combined estrogen-only MHT for women who have undergone hysterectomy and combined with progestin for women with an intact uterus is the most effective treatment of VMS and its potential consequences (i.e., decreased sleep quality, irritability, and reduced quality of life) 53; methods for assessing sleep lack uniformity in defining the diagnosis of sleep disorders and variations in MHT preparations (formulation, dose, and type of administration), and improved sleep quality was the result of an improvement in vasomotor symptoms 10,45-54; MHT administered as low doses of estrogen or progestogen could improve chronic insomnia in menopausal women, a clear decrease in intermittent wakefulness after micronized P4 compared to placebo is reported, without affecting daytime cognitive functions, through a GABA agonist mechanism, or possible sedative effects of oral progesterone, on the etiology of menopausal sleep disorder is controversial and multifactorial in cause; more research is needed to determine whether self-reported sleep quality in menopause is affected by different molecules, formulations and pathways of MHT 54.

Conclusions

During the menopausal transition, women experience dramatic fluctuations in the levels of sex hormones with E2, P4 and androgens, responsible for modifications in behavior, cognition, mood and sleep; Despite the profound connection between estrogen and cognition, the relationship between MHT and neuroprotective outcomes is controversial; there is no cognitive benefit of estrogen or estrogen plus progestin in women over 65 years of age without underlying dementia. Young menopausal women with no contraindication to MHT and impaired quality of life due to night sweats, VMS, or sleep disruption benefit from MHT, but with no negative effect on cognition in these women; the etiology of menopausal sleep disorder is controversial. MHT improves sleep quality, by decreasing night sweats, or by other mechanisms independent of these. Further research is needed to determine whether self-reported sleep quality in menopause is affected by different molecules, formulations, and routes of administration of MHT. For example, the GABAergic sedative effects of P4 should be considered in women with sleep problems; some data support a beneficial effect of MHT on mood; but, not for non-depressed perimenopausal women; estrogen is considered in menopause with other concurrent conditions, such as VMS, increases the response to antidepressants.

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