Sleep and Brain Function at Menopause

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Around one-third of our life is spent asleep which is an internally regulated universal biological function of life. Sleep disturbances and cognitive difficulties, often termed as brain fog, are common complaints during menopause. Research reveals that these symptoms are intricately linked to neuroendocrine changes, particularly the decline in estrogen levels. Sleep is considered healthy for an adult if it is adequate, timely, regular, and without disturbances. There is a risk of adverse health outcomes if the duration of sleep is <7 h such as weight gain and obesity, diabetes, hypertension, heart disease, stroke, depression, impaired performance, and increased errors.

The prevalence of insomnia is 6%–10% and higher in women, older age, and lonely people. At least 6–7 h of sleep is considered a normal sleep duration, and the odds of associated diabetes and hypertension are 3 and 5, respectively, for the short sleep duration. Insomnia of menopause is the chronic insomnia disorder characterized by chronic sleep-onset or sleep-maintenance complaints with an associated daytime impairment that occurs at least three times a week persisting for at least 3 months and is not due to other morbid conditions.[1]

Insomnia at menopause is the disequilibrium due to the inadequacy of sex hormones. It has a cause–effect relationship. This hormonal imbalance produces multiorgan symptoms and may result in multiple symptomatic medical interventions.

Sleep disorders are hormone-specific concerning the phases of reproductive life like the luteal phase of menstruation, pregnancy, and menopause. Increasing nocturnal awakenings or wake-after-sleep onset are common. There is an increased risk for insomnia in the luteal phase; an increased risk of restless legs syndrome and sleep apnea in the third trimester of pregnancy; and a high prevalence of insomnia and sleep-disordered breathing in menopause.[2]

Sleep Disruption during Menopause

Sleep disturbances affect 40%–60% of menopausal women, with common complaints including insomnia, frequent awakenings, and nonrestorative sleep.[3] A key factor contributing to these disturbances is the decrease in estrogen and progesterone levels, both of which regulate sleep by modulating serotonin and gamma-aminobutyric acid (GABA).[4] menopausal women experience a 56% increase in the prevalence of insomnia compared to premenopausal women [Figure 1].[5]

The Neuroendocrine Changes in Menopause

Estrogen has far-reaching effects on brain function, supporting synaptic plasticity, neurotransmitter regulation, and neuroprotection. Estrogen deficiency during menopause can significantly impact cognitive performance, mood, and sleep. Synaptic plasticity in the hippocampus and prefrontal cortex, regions critical for memory and executive function are promoted by estrogen.[5] The decline in estrogen during menopause is associated with a reduction in synaptic density, leading to cognitive challenges such as brain fog, memory lapses, difficulty concentrating, and decreased mental clarity.[6]

Estrogen deficiency has been linked to decreased serotonin production, which plays a critical role in sleep–wake regulation.[4] Furthermore, progesterone, known for its sedative effects, diminishes during menopause, exacerbating sleep difficulties.[6]

Hot flashes, experienced by approximately 75% of menopausal women, are another significant contributor to sleep disruption. women who experienced frequent nocturnal hot flashes reported poorer sleep quality and more awakenings.[7] The physiological mechanism behind hot flashes involves dysregulation of the hypothalamus, driven by estrogen withdrawal.[6]

Brain Fog: Cognitive Challenges in Menopause

Brain fog is a subjective experience often reported during menopause, encompassing memory lapses, difficulty concentrating, and mental fatigue. Women in the early stages of menopause were more likely to experience deficits in verbal memory, working memory, and executive function compared to premenopausal women.[8] Verbal memory and processing speed during menopause relies on the hippocampus, appears to be particularly affected, with studies showing that estrogen enhances synaptic connectivity in this region, supporting

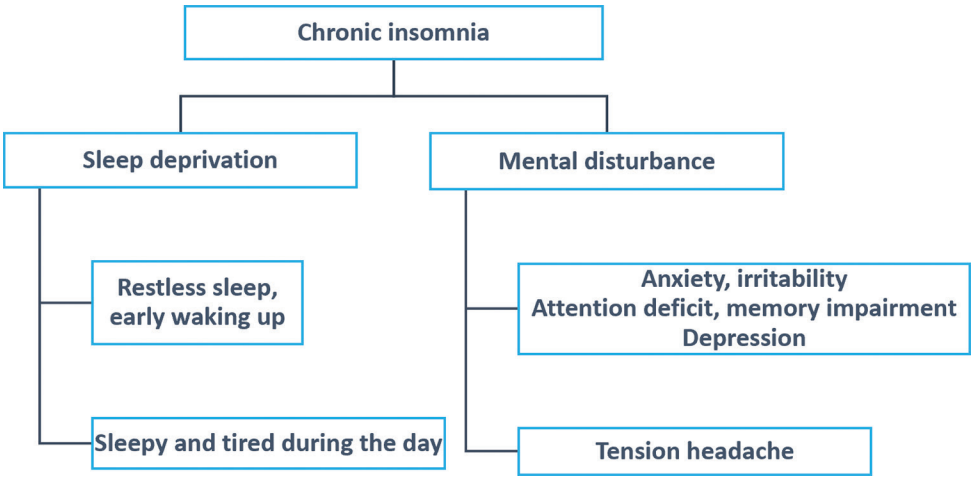

Figure 1: Presentation of chronic insomnia

memory retention.[9] However, these effects were found to be transient for many women, with cognitive function often stabilizing postmenopause.[10,11]

The Menopause-Alzheimer's Connection

Emerging research suggests a potential link between menopause and an increased risk of Alzheimer's disease, the most common form of dementia. One hypothesis is that the dramatic decline in estrogen during menopause may accelerate the accumulation of amyloid beta plaques and tau tangles, both hallmarks of Alzheimer's pathology.[12] Women are disproportionately affected by Alzheimer's disease, accounting for nearly two-thirds of all cases.[13]

Women who entered menopause earlier or experienced surgical menopause had a higher risk of developing Alzheimer's disease.[12] Genetic factors also play a role in this connection. The APOE ε4 allele, a known risk factor for Alzheimer's disease, appears to interact with estrogen deficiency to further increase the risk of cognitive decline in women.[13]

Variations in sleep stages occur in other conditions like *Narcolepsy* (rapid eye-movement (REM) sleep is reached much more quickly than usual; *Sleep apnoea* (Pauses in breathing during sleep especially interrupt REM sleep); *Depression* (Less time appears to be spent in non-rapid eye-movement (NREM) sleep 3, and REM sleep may be reached earlier than is typical);[14] and *Schizophrenia* (less time appears to be spent in NREM phases, especially NREM 3. REM sleep may be reached earlier than is typical, but this could be due to the high rates of depression in people with schizophrenia.[15]

Managing Sleep and Cognitive Symptoms during Menopause

Addressing the cognitive and sleep-related symptoms of menopause requires a multifaceted approach. Hormone replacement therapy (HRT), lifestyle modifications, and cognitive interventions have all been explored as potential strategies for improving brain function and sleep quality during this transition. sleep hygiene education, behavioral sleep scheduling interventions such as sleep restriction and stimulus control procedures, cognitive restructuring therapy, and relaxation-based interventions. Pharmacological therapy as a second-line intervention includes benzodiazepines and other GABA-A receptor agonists (zolpidem, eszopiclone, zopiclone), sedating antidepressants, orexin antagonists, antihistamines, antipsychotics, melatonin receptor agonists, and phytotherapeutic substances (valerian, medicinal cannabis). For adults with primary insomnia treated for any duration or secondary insomnia in which underlying comorbidities are managed, the antipsychotics should be stopped without tapering.[16]

Short-acting medications work for sleep-onset insomnia but may not help with sleep-maintenance insomnia. Triazolam has a short duration of action but is associated with significant rebound insomnia and is no longer considered a first-line agent for insomnia. Zaleplon has a very short duration of action and may be useful as a "rescue medication" for middle-of-the-night dosing (as long as 4–6 h of potential sleep remains).

European guidelines detail the diagnostic procedure for insomnia, and its comorbidities, such as a clinical sleep history, questionnaires, and diaries; psychosomatic history; physical examination and diagnostic tests such as blood tests, electrocardiogram, and electroencephalogram. If there is clinically significant nocturnal and diurnal sleep impairment with maintained synchrony but having sleep affecting substance intake, then, a change of medication is advised. If it is associated with comorbid somatic or mental disorders, then, the respective treatment is advised; but in its absence, the first-line treatment option

is cognitive-behavioral therapy (CBT)- I or short-term medications such as benzodiazipines, or sedating antidepressants. If there is no clinically significant sleep impairment and sleep synchrony is maintained, then psychoeducation would be sufficient.[17]

Insomnia of menopause is managed by HRT especially estrogen which helps treat anxiety, depression, insomnia, mood swings, and hot flashes. It has beneficial effects on skin and bone health as well as lipid metabolism. Progesterone can help to minimize sleep apnea as well. HRT helps to minimize menopause-related insomnia but other conditions leading to insomnia should be dealt with simultaneously.

Therefore, treating the cause is the first line of intervention and the remaining symptoms are to be managed accordingly. Causal intervention would be either HRT or hormone modulator-rich foodstuff. Promotive lifestyle modification interventions will be supportive of the quality of life.

Preventive measures to deal with menopausal insomnia are: optimizing weight; following a sleep schedule; minimizing hot flashes by avoiding large evening meals, and spicy or acidic foods; stopping drinking before bedtime; preserving sleep quality by avoiding nicotine, caffeine, and alcohol in the late afternoon and early evening; use the restroom before going to bed; lower stress by massage, exercise, yoga and evening bath; meditation or deep breathing; minimize daytime nap and bedtime, and maximize sleep time; and keeping room temperature at reasonably cool and wear light night dress.

There is significant sleep electrical activity in the brain of women on HRT with increased frequency of REM sleep and reduced awake time. Combining both estrogen and progesterone yields improved sleep quality and cognitive function, lesser sleep latency and wake-up frequency, and increased REM sleep. Obstructive sleep apnea (OSA) occurs in 2% of women and its annual increased risk is 4% per annum from perimenopausal age. However, it will be less if HRT is begun earlier. This is because progesterone acts as a respiratory stimulant to prevent both central and OSA by preventing the relaxation of the upper airways.[18]

Hormone replacement therapy

HRT remains one of the most effective treatments for alleviating menopausal symptoms, including sleep disturbances and cognitive difficulties. Early initiation of HRT improved memory and attention in menopausal women, particularly those who started therapy before the age of 60 years.[10] However, the benefits of HRT must be weighed against potential risks, including an increased risk of cardiovascular events and breast cancer.[11,12]

HRT significantly reduces the frequency of hot flashes and improved sleep quality, particularly when used in combination with progesterone.[5] For cognitive function, the timing of HRT initiation appears to be crucial, with the "critical window hypothesis" suggesting that starting HRT closer to the onset of menopause offers more cognitive benefits than starting later in life.[10]

Lifestyle modifications

Lifestyle interventions play a pivotal role in managing menopausal symptoms. Regular physical activity has been shown to improve both sleep quality and cognitive function in menopausal women. Aerobic exercises significantly reduces sleep latency and improved overall sleep efficiency in menopausal women.[4] Exercise also enhances neuroplasticity and reduce inflammation, both of which support cognitive health.[12]

Dietary factors also influence brain health during menopause. A diet rich in antioxidants, omega-3 fatty acids, and phytoestrogens can help mitigate oxidative stress and support hormonal balance.[8]

Cognitive interventions

Cognitive interventions such as memory training and cognitive-behavioral therapy (CBT) offer promising avenues for managing brain fog during menopause. A randomized trial published in psychological medicine found that memory training significantly improved verbal memory and executive function in menopausal women.[9] These programs often focus on teaching strategies for organizing information, enhancing recall, and improving mental flexibility.[9]

CBT has also been shown to be effective in addressing sleep problems and anxiety during menopause. A study in *The Journal of Sleep Research* found that CBT for insomnia improved sleep quality and reduced anxiety in menopausal women, leading to subsequent improvements in cognitive function.[5] Engaging in mentally stimulating activities, such as puzzles, learning new skills, and reading, can also help maintain cognitive function during menopause.[12] These activities promote synaptic plasticity and cognitive resilience, reducing the risk of long-term cognitive decline[12] These findings underscore the importance of monitoring cognitive health during menopause, particularly in women with a family history of Alzheimer's disease.[19]

Conclusion

Menopause presents a unique challenge for brain health, with the decline in estrogen contributing to sleep disturbances, brain fog, and an increased risk of

neurodegenerative diseases such as Alzheimer's disease. However, emerging research offers hope for managing these symptoms through a combination of hormone therapy, lifestyle changes, and cognitive interventions. There is a risk of adverse health outcomes if the duration of sleep is less than seven hours such as weight gain and obesity, diabetes, hypertension, heart disease, stroke, depression, impaired performance, and increased errors.

Healthcare providers should adopt a holistic approach to menopause management, addressing both the physical and cognitive aspects of this transition. By supporting sleep health, promoting cognitive resilience, and offering tailored interventions, we can help women navigate menopause with confidence and maintain their quality of life during this critical stage.

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