FEATURE: JOY M. HAMPTON, DMSc, MS, PA-C, DFAAPA

A Window of Opportunity: Estrogen Limits Cognitive Decline in Older Women

Starting estrogen hormone therapy near the onset of menopause may decrease all-cause mortality and possibly prevent cognitive decline.

Alzheimer disease affects more women than men.

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Alzheimer disease (AD) is a devastating neurodegenerative disorder. In the United States, approximately 6.5 million people aged 65 years and older are living with AD and nearly two-thirds of them are women.[1] It can have particularly overwhelming ripple effects on caregivers; in 2021, more than 11 million unpaid caregivers provided nearly 16 billion hours of care valued at $271.6 billion to individuals with AD.[1]

With no known cure for AD, many studies are examining preventive measures, such as the use of estrogen hormone therapy (EHT). Because estrogen facilitates cognitive function and declines during menopause,[2] researchers have investigated a possible causal relationship between estrogen deficiency and the onset of AD. Natural menopause is defined as 12 consecutive months of unintentional amenorrhea and has an average age of onset of 51 years.[2] Perimenopause describes the time leading up to menopause.[2] For most other hormone-deficient diseases, such as hypothyroidism, the treatment is hormone replacement.

When administered during menopause, EHT could improve cognitive function and potentially prevent the development of AD. This timing is important. The risks and benefits of postmenopausal EHT have been a controversial topic since the Women's Health Initiative (WHI) study was stopped prematurely because of the incidence of breast cancer and cardiovascular disease.[3] Unfortunately, because the publication was based on incomplete statistics, many of the findings of

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the study were presented as more substantial than the actual data support.[4]

Many of the risks associated with EHT reported in the WHI study are not seen if therapy is started early in menopause. The WHI study only evaluated synthetic conjugated equine estrogens[3] and participants were postmenopausal up to 15 years; therefore, they were without premenopausal levels of estrogen and progesterone for a long enough period of time to develop cardiovascular disease and osteoporosis, for example.[4] In recent studies, EHT started near the onset of menopause and/or at age 60 years or younger was safe and decreased all-cause mortality.[5] This time frame presents an opportunity to possibly prevent age-related cognitive decline in women.[6]

Alzheimer Disease

Epidemiology

As noted, AD disproportionately affects women. Because AD pathology precedes clinical manifestations by decades, this higher risk cannot be accounted for by the longer life span of women compared with men.[6] Early-onset AD, which occurs before age 65, is rare and has been associated with an autosomal dominant inheritance pattern. In people aged 65 years and older, AD is the fifth leading cause of death.[1] From 2000 to 2019, the mortality rate for AD increased by more than 145%, while the number of deaths from heart disease and stroke decreased.[1]

Pathophysiology

The exact etiology of AD is unknown. Certain risk factors have been identified, such as advancing age, female sex, and a first-degree relative who has had AD.[1] The presence of the e4 form of the apolipoprotein E (*APOE-e4*) gene has been associated with an increased risk for AD.[1] Studies have also suggested an inflammatory pathway in AD, which might be triggered by chronic fungal, bacterial, or viral infections.[7]

Physiologic changes in the brain that occur with AD include atrophy and abnormal deposition of beta-amyloid and tau proteins.[1] Beta-amyloid protein forms clumps outside the neurons (plaques), and tau protein forms clumps inside the neurons (neurofibrillary tangles).[1] These changes cause devastating neuronal dysfunction that manifests clinically as memory loss, progressive cognitive decline, and ultimately, death.[1]

Diagnosis

The diagnosis of AD is made via a detailed clinical assessment of the patient, including cognitive function, after alternative diagnoses have been excluded. Abnormal levels of beta-amyloid and tau proteins can be identified in the cerebrospinal fluid and by positron emission tomography imaging[1]; however, these studies are not routinely done because of their invasiveness and cost. A definitive diagnosis of AD can be made post-mortem at autopsy by identifying the hallmark brain changes of plaques and neurofibrillary tangles.

Estrogen

Role in Cognitive Function

The vast estrogen receptor network in the brain controls brain energy metabolism and many other systems.[6] Estradiol, the most physiologically important type of estrogen,[2] enhances brain function in several ways such as by improving neuronal growth and protecting neurons from injury.[8] Several brain areas that are essential for memory and learning such as the prefrontal cortex and amygdala have a significant number of estrogen receptors and rely on estrogen availability for proper functioning.[6]

Deficiency

During perimenopause, estrogen levels fluctuate unpredictably; in menopause, they decline steadily. When estradiol levels decrease, fundamental cellular changes occur in the brain. These include reductions in dendritic spines, synaptic density, and the number of synapses present.[2] The regulation of brain glucose metabolism by estrogen dissipates, creating a hypometabolic state.[6] These physiologic changes result in "brain fog" characterized by poor concentration and memory problems.[9] Although these transformations typically reverse with menopause,[9] they illustrate the undesirable effects of estrogen deficiency on cognition. The duration of time without estrogen also matters. Studies have shown that a woman who enters surgical menopause at a younger age has a higher rate of cognitive decline and AD-related pathology.[2]

Estrogen Hormone Therapy

Cognitive Benefits

The beneficial effects of EHT on the brain have been well documented. Boyle et al described increased gray and white matter volume in women who had a history of oral estrogen use, including synthetic conjugated equine estrogens, as measured using structural magnetic resonance imaging.[10] The Cache County Study found that women using EHT had a decreased incidence of AD compared with those who did not use EHT, and the longest use of EHT (>10 years) reduced the risk for AD the most.[11]

In contrast, other studies have shown that EHT does not decrease the risk for AD. For example, no cognitive benefits were observed in patients taking EHT despite neuroimaging

Several brain areas essential for memory and learning have a number of estrogen receptors and rely on estrogen for proper functioning.

results showing reductions in both biomarkers for brain aging and the deposition of the beta-amyloid protein.[9] Although patients with the *APOE-e4* gene are at increased risk for AD, one study suggests that this population has the fastest cognitive decline when taking EHT.[9]

Timing

Many pathologic changes that occur with AD begin years before the patient develops clinical symptoms.[2] Studies have suggested that the most beneficial time to start EHT is at or near the onset of menopause.[6] EHT also has protective effects against cardiovascular disease when started during this time frame.[12]

Considerations

Despite the relationship between estrogen and cognitive function, data for the role of EHT in neuroprotection are inconclusive.[9] The American College of Obstetricians and Gynecologists and the Menopause Society (formerly the North American Menopause Society) do not support its use as primary prevention of cognitive dysfunction,[13,14] and the International Menopause Society guidelines cite a lack of evidence to support its use.[15] One of the limitations of previous studies, such as the landmark WHI Memory Study,[16] is that they included postmenopausal women older than 65 years of age. The studies also did not consider the window of opportunity to begin estrogen replacement at or near the onset of menopause.

Risks

The decision to start EHT should be individualized for each patient. Alzheimer disease has a greater incidence in women; therefore, studies have focused on the beneficial role of estrogen in cognition and the potential of EHT to prevent AD. Hormone therapy should be avoided in those patients with contraindications, such as a history of estrogen-dependent cancer, thromboembolic events, or a blood clotting disorder. A progestin or progesterone should be given with estrogen if the patient has not had a hysterectomy, as unopposed estrogen can cause endometrial hyperplasia and potentially endometrial cancer.[14] Further research is needed to determine factors such as efficacy, dosing, route of administration, and duration of treatment. ■

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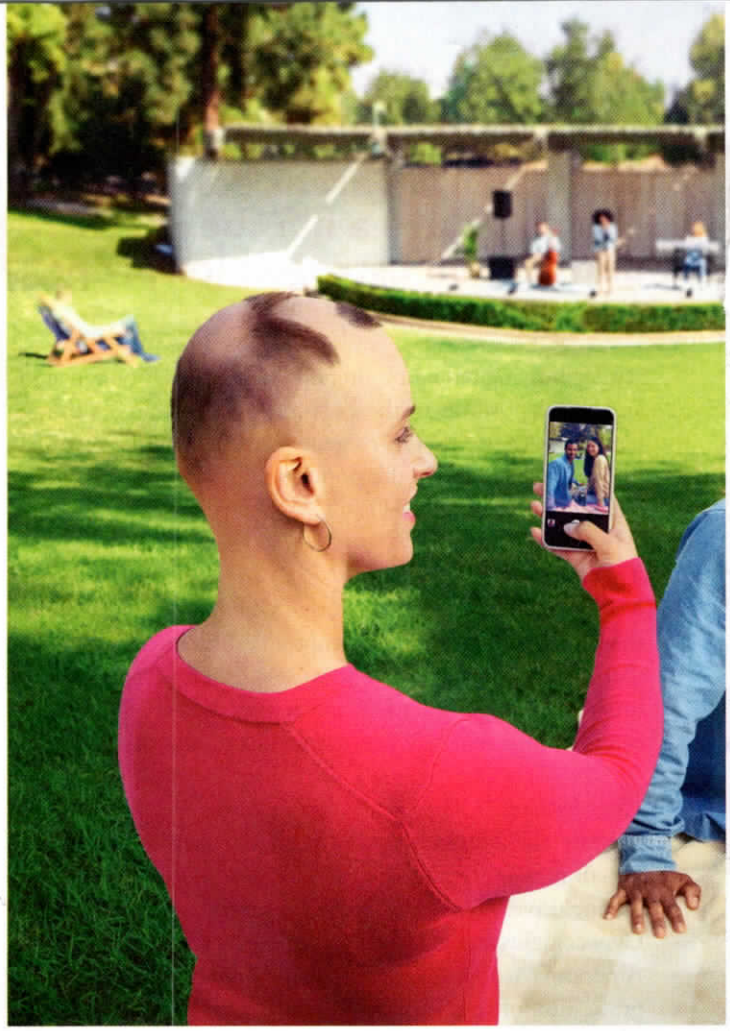

The **first and only** FDA-approved treatment for severe alopecia areata **in both adults and adolescents as young as 12.**[1,2]

INDICATION

LITFULO is a kinase inhibitor indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older.

Limitations of Use: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with LITFULO are at increased risk of serious bacterial, fungal, viral and opportunistic infections that may lead to hospitalization or death, including tuberculosis (TB). The most frequent serious infections reported with LITFULO have been appendicitis, COVID-19 infection (including pneumonia), and sepsis. Among opportunistic infections, multi-dermatomal herpes zoster was reported with LITFULO.

Avoid use of LITFULO in patients with an active, serious infection. Consider the risks and benefits of treatment prior to initiating LITFULO in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis (TB)
- with a history of serious infection or an opportunistic infection
- who have resided or traveled in areas of endemic TB or mycoses, or
- with underlying conditions that may predispose them to infection

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with LITFULO. Interrupt treatment if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with LITFULO should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. LITFULO may be resumed once the infection is controlled.

Tuberculosis

LITFULO should not be given to patients with active TB. Screen patients for TB before starting and monitor during therapy. Anti-TB therapy should be started prior to initiating therapy with LITFULO in patients with a new diagnosis of latent TB or previously untreated latent TB. In patients with a negative latent TB test, consider anti-TB therapy before initiating treatment with LITFULO in those at high risk and consider screening patients at high risk for TB during treatment with LITFULO.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (eg, herpes zoster), was reported in clinical trials. If a patient develops herpes zoster, consider interrupting treatment until the episode resolves. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with LITFULO. Patients with evidence of HIV infection or hepatitis B or C infection were excluded from clinical trials.

MORTALITY

In a large, randomized, postmarketing safety study of another Janus kinase (JAK) inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with