

January 2012

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Effects of Hormone Therapy on Cognition in Post-menopausal Women

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Abstract

Menopause occurs as a result of decreased natural estrogen production by the body. A variety of short-term and long-term symptoms can occur during menopause, which may significantly impact a woman's daily life. Hormone therapy (HT) is commonly employed to alleviate these unwanted symptoms and to regain balance of hormone levels. Options include estrogen-only or estrogen-progestin combination therapy. While HT may help relieve symptoms such as cognitive decline caused by menopause, it also carries potential side effects. Although HT has shown a potential benefit in women with Alzheimer's disease (AD), overall outcomes measuring cognitive function improvement are inconclusive. Therefore, HT should not be initiated solely to improve cognition until further research is completed to support this indication. HT, however, is still an effective means to treat several other post-menopausal symptoms. It is imperative for pharmacists and physicians to stay updated on current research to appropriately assess the risks and benefits of HT treatment on an individual patient basis.

Introduction

Menopause results from decreased estrogen levels due to the loss of functioning ovarian follicles. It is defined as a physiologic event occurring after 12 months of amenorrhea and signifies the end of reproductive years.¹ The average woman goes through menopause around the age of 51 and experiences a variety of short-term symptoms, which may include problems with concentration and memory as well as an increased risk of developing long-term health issues such as osteoporosis and coronary artery disease. Both short-term and long-term menopausal effects can significantly impact a woman's quality of life, but with proper management, short-term symptoms can be effectively alleviated and long-term risks can be minimized.

Physiology of Menopause

There are a few possible mechanisms that are thought to contribute to physiologic changes in menopausal women. Prior to menopause, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which causes the pituitary gland to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Estradiol and progesterone, secreted by functioning ovarian follicles, decrease levels of FSH and LH via negative feedback. In menopausal women, ovarian follicles stop functioning and therefore do not secrete estradiol and progesterone; this allows levels of FSH and LH to rise, producing a state of hormonal imbalance. It is postulated that increased levels of LH contribute to a decline in cognitive function.² This theory is supported by evidence that LH receptors are highly expressed in the hippocampus and that down-regulation of these receptors leads to cognitive improvement even in the absence of estrogen. Another theory is that estrogen raises levels of acetylcholine, which is believed to improve cognitive functioning.³

Hormonal Therapy (HT)

Non-pharmacologic therapy can be used to alleviate menopausal symptoms; however, HT is frequently used in an attempt to correct the hormonal imbalance and relieve associated symptoms. The decision to initiate HT should be based on individual patient parameters including menopausal symptoms and risk factors for osteoporosis, cardiovascular disease, breast cancer and/or thromboembolism.¹ Each woman should also be thoroughly educated on the potential benefits and risks of HT before making a decision to initiate treatment (Table 1). There are two main types of systemic HT: estrogen-only and estrogen-progestin combination. Estrogen-only therapy is for women who have had a hysterectomy. Estrogen-progestin combination is used in women with an intact uterus to decrease the risk of endometrial cancer associated with estrogen use. In either situation, The North American Menopause Society recommends using the

Table 1. Potential Benefits, Risks and Side Effects of HT¹

Benefits	Risks*	Side effects of estrogen	Side effects of progestin
<ul style="list-style-type: none"> Decrease hot flashes and night sweats Improve vaginal atrophy Prevent and treat osteoporosis Reduce risk of colorectal cancer 	<ul style="list-style-type: none"> Ovarian cancer Endometrial cancer Breast cancer Venous thromboembolism Gallbladder disease Cardiovascular disease 	<ul style="list-style-type: none"> Nausea Headache Breast tenderness Heavy bleeding 	<ul style="list-style-type: none"> Irritability Depression Headache Mood swings Bloating Fluid retention Sleep disturbances
*Risks are influenced by type of HT along with patient-specific risk factors		To decrease use lower doses and/or transdermal estradiol	Vary with type of progestin and route of administration

lowest dose of HT necessary to relieve the patient's symptoms, as lower doses minimize risks.⁴ Both types of systemic HT have proven beneficial to alleviate vasomotor symptoms (hot flashes and night sweats), decrease vaginal atrophy, and prevent osteoporosis. However, there have been controversial studies regarding the effectiveness of HT to improve other menopausal symptoms, including cognitive decline.⁴

Cognition

Cognition includes a range of higher-level brain functions, especially those involved with the ability to learn and recall information. To evaluate cognition, subjects are tested in their ability to organize, plan, and solve problems with given information, as well as perform calculations. The ability to focus, maintain, and shift one's attention as necessary is also a major component. Other tests are given to show depth of understanding and usage of language, as well as the ability to perceive an environment in a correct manner.⁵ Cognitive decline is often associated with aging and the advancement of dementia or Alzheimer's disease (AD). Patients may begin noticing changes such as worsened memory, language barriers, thinking impairment, and reduced judgment as cognition begins to decline. These impairments may also be associated with feelings of depression, irritability and aggression, anxiety or apathy.⁶

Mental status tests are usually performed to assess the existence of cognitive decline. These tests are generally quick, involving tasks and questions. The Delayed Word Recall Test (DWR) tests verbal learning and short-term memory. Subjects are asked to remember 10 common nouns after a five-minute interval during which other tests are administered. To standardize results, respondents are to phrase sentences containing the 10 words and are then given a score based on the number of recalled words out of 10 (0-10).⁷ The Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (DSS/WAIS-R) test involves a timed translation of numbers (1-9) to symbols following a key. It is used to measure psychomotor performance and is unaffected by intelligence, memory or learning in most people. This test may be used to measure brain damage and scores are based on the number of correctly transcribed numbers to symbols in 90 seconds (high score of 93).⁷ The Word Fluency Test (WF) requires participants to list as many words as possible beginning with a certain letter of the alphabet within 60 seconds. The test is sensitive to linguistic impairment and early mental decline in older adults, usually involving three trials with three separate letters.⁷ The Vuschnke-Fuld Selective Reminding Test tests storage, retention and retrieval of spoken words; the subject is read 10 words and she must repeat as many as possible.⁸ Visual Reproduction Tests assess memory for geometric forms; in this test patients must reproduce three stimuli immediately and again after a half hour.⁸ A Blessed Information Memory Control Test assesses a subject's mental control; in these tests subjects must do things such as recite the months backwards and recall a name and address after a 10 minute delay.⁸

Clinical Trials

Patients have questioned how HT will affect their cognitive

function; whether it will cause a further decline, or serve to protect against additional deterioration. This is an important issue due to the fact that many more women are working into their menopausal and post-menopausal years. A survey of some available research on the topic has been conducted to determine the effects of HT on a woman's cognitive function.

A prospective cohort study enrolled 2,859 women who formerly used estrogen replacement therapy and tested them by the DWR, DSS/WAIS-R, and WF tests to analyze association of hormone replacement therapy with cognition in post-menopausal women.⁷ More participants were found to have surgically-induced menopause (69 percent) versus natural menopause (22 percent). Average users of HT were found to be younger, Caucasian, and more educated than nonusers of HT. This study found no association between estrogen replacement therapy and cognition, though evidence was found in animal models showing improved cognition decline. One possible confounder is the young age (mean age 56.6 years $SD \pm 5.5$) of many of the participants.

In a randomized, controlled trial, 64 postmenopausal participants (27 HT, 37 non-HT) were matched for age, level of education, and postmenopausal period.⁹ The HT group had to meet inclusion criteria of natural menopause and to have used HT for at least one year. Of the HT arm, 70.37 percent were given estrogenic treatment, either Premarin® (conjugated estrogens) or Estraderm® (estradiol), and 29.63 percent were given Livial® (tibolone), an estrogenic, progestogenic, and androgenic combination hormone. A group of 44 scored tests were used to measure cognitive functions, including immediate and delayed visual and verbal memory, visuospatial perception and orientation, prolonged attention/vigilance, visual search and scan, impulsivity and response speed, executive functions and general intelligence. Mental status tests used included Wechsler Memory Scale-Revised, Line Orientation Test, Cancellation Test and Raven Standard Progressive Matrices. After statistical analysis of the results, even though controlled techniques were applied, no relationship could be observed between HT and cognitive function.

A prospective cohort study of 83 women in Israel indicated no negative effect on cognitive function due to the use of HT.¹⁰ Inclusion and exclusion criteria for this study were strict. Women with surgically-induced menopause were specifically excluded, as were women with known dementia or who were being treated for cognitive decline, women using HT for <5 years, and women suffering from a few other known medical conditions. Inclusion in the study involved being aged 55-60, of Ashkenzai Jewish ethnicity, and a minimum of a university/college education. Of those participating in the study, 40 (48.2 percent) had never used HT. The remaining 43 users of HT included 87.5 percent of women treated with combination estrogen and progestin. A battery of computerized tests was run on each participant. This study demonstrated no significant difference between cognitive function in HT users and nonusers when measuring cognitive function via computerized cognitive battery.

A meta-analysis conducted by the American Medical Association (AMA) has categorized the research that has been performed on this topic.¹¹ The study compared the results from randomized controlled trials (RCTs) and cohort studies in the areas of verbal recall, visual memory, working memory, vigilance, concept formation and reasoning, motor speed, dementia screening measures and verbal function. It also compared the findings for the use of HT in the prevention of AD. Most results for each category were inconclusive; it seemed that each study came to a different conclusion. The area suggesting the most correlation with HT was in the prevention of AD, which showed no negative opposing results; however, this study area included no RCTs. The analysis also revealed that the use of estrogen-progestin combination was not shown to enhance the effects of estrogen in the possible improvement of cognitive function.

Conclusion and Pharmacy Implications

The majority of studies provided inconclusive results regarding the effects of HT on cognitive function in postmenopausal women. There may be a possible link between HT and the prevention of AD, but more research is needed before a definitive connection can be made. An AMA review found that progestin had no additional benefits to improve cognitive function when used with estrogen.¹¹ Some women choose not to use HT because they wish to stay medication free, want to avoid potential side effects such as breast tenderness or weight gain, question HT efficacy due to controversial findings or are concerned about the potential increased risk for developing certain types of cancer.¹²

Pharmacists and physicians can assist each woman to weigh the benefits and risks of HT and allow her to make an educated decision. The decision to initiate HT can be based on the severity of the symptoms the patient is experiencing. If symptoms are too problematic to manage with non-pharmacological treatment, HT therapy may be helpful if benefits outweigh potential side effects. A patient's fears should also be taken into consideration; if the patient feels her symptoms are only a minor disturbance to her daily living, risks of HT should be taken into account before a decision is reached. Ultimately, the decision to use HT should be the patient's choice and only made after evaluating all possible outcomes. Physicians should not regularly prescribe HT to prevent cognitive decline until further evidence demonstrates efficacy. Even though HT may not be beneficial for cognition, it may offer relief of other menopausal symptoms.

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