Alzheimer's
Drug Discovery
Foundation

Estrogen-Containing Hormone Therapy

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"Estrogens" refers to a broad range of natural and synthetic molecules that affect estrogen receptors. Estrogen-containing hormone therapy usually consists of estrogens alone or combined with a progestogen and can be used to treat symptoms of menopause. While estrogens demonstrate some potential benefits for the brain, including reduced oxidative stress and improved energy production, clinical studies have shown inconsistent and sometimes even negative results. For women over 65, in fact, estrogens may increase the risk of dementia. Experts do not recommend estrogen-containing hormone therapy to prevent or treat cognitive aging or dementia [1].

EVIDENCE AND POTENTIAL BENEFIT FOR BRAIN HEALTH
Rated 1/4 based on 4/4 evidence

Randomized controlled trials: Based on the evidence, it is unlikely that hormone therapy reduces the risk of dementia or improves cognitive function, even if it is initiated soon after menopause. In 2004, the Women's Health Initiative, a huge clinical trial, reported that an estrogen (CEE) plus progestin therapy slightly raised the risk of dementia while estrogen therapy alone had no effect [2].

The KEEPS-Cog trial monitored 662 recently menopausal women, with average age of 52.6 years, who were 1.4 years past their last menstrual cycle. Results published in 2015 showed that, over the course of four years, no cognitive benefits were obtained either with oral conjugated equine estrogens (CEE) with cyclic (12 days per month) micronized progesterone or transdermal estradiol with cyclic micronized progesterone [3]. Although this trial was too short to determine whether estrogen-containing therapy can protect from dementia, it showed that estrogens are unlikely to improve cognitive function even when taken shortly after menopause.

The Early vs Late Intervention Trial with Estradiol (ELITE) randomized controlled trial enrolled 567 healthy women to compare the effects of hormone therapy for people within six years versus those more than 10 years post-menopause. The study, published in 2016, concluded that treatment with 17β-estradiol (17βE) and cyclic micronized progesterone did not benefit or harm cognitive abilities such as verbal memory, executive functions, and global cognition, whether the treatment is initiated early (within six years) or late (after 10 years) [4].

A small prospective randomized clinical trial examined 45 women (mean age 58) with heightened risk for dementia who used hormone therapy for an average of 10 years to test the effects of continuing versus discontinuing the therapy for the subsequent 2 years. Women who continued hormone therapy relatively preserved their frontal and parietal cortical metabolism and demonstrated better verbal memory [5; 6]. Discontinuing 17βE therapy or continuing CEE-hormone therapy significantly reduced the metabolism of precuneus/posterior cingulate cortical area, which is known to significantly decline in the earliest stages of Alzheimer's disease. Women taking concurrent progestins with 17βE or CEE also experienced a significant decline in the metabolism of the posterior cingulate cortical area.

Other human research: Years ago, scientists observed that women who took hormone therapy reduced their risk of developing dementia by approximately 34 percent, although some problems with those observational studies were noted [7]. A few observational studies, including the KEEPS-Cog trial, have reported that postmenopausal women using transdermal 17βE instead of CEE/premarin have better memory abilities, but this evidence is limited and inconclusive [8; 9]. A recent systematic review of 15 epidemiologic studies reported that hormone therapy did not affect the risk of dementia [10]. This lack of benefit matches the recent clinical trial evidence discussed above [3].

Biology: Preclinical trials have suggested that estrogens protect the brain from a wide range of injuries and diseases. These same experiments suggest that while estrogen can protect healthy cells from new damage, it may also harm unhealthy neurons [11].

APOE4 carriers: APOE genotype can likely affect the response to estrogen-containing therapy. Indeed, a variety of laboratory experiments and genetic association research suggests that many of the beneficial effects of estrogens on the brain are dependent on APOE and specific APOE alleles [12; 13].

Clinical research on how estrogen therapy may affect the long-term brain health for people with or without the APOE4 allele is contradictory. Out of two high-quality studies that tracked participants over time, one showed that people using estrogen-containing therapy had a higher rate of cognitive decline [14] while the other showed the opposite (a lower rate of cognitive decline) [7]. In both studies, however, those who did not carry APOE4 responded better to hormone therapy [7; 14]. Estrogen alone or estrogen plus progestogen therapy similarly had a better association in APOE4 non-carriers than APOE4 carriers in a handful of other human studies [15; 16].

Other studies suggest that APOE4 carriers respond favorably to estrogens. One high-quality observational study that tracked participants over time suggested that hormone therapy protected APOE4 carriers from their typically increased risk of dementia [17]. Also,

in a randomized trial examining telomere shortening—a controversial marker of aging—APOE4 carriers who stopped using hormone therapy had a higher rate of shortening while non-carriers had a higher rate if they did not stop using hormone therapy [18]. In other words, hormone therapy appeared to slow aging in APOE4 carriers but to accelerate it in non-carriers.

For more information on what the APOE4 gene allele means for your health, read our APOE4 information page.

For Dementia Patients

Randomized controlled trials: In clinical trials, estrogen-containing hormone therapy has generally not improved cognition or function for Alzheimer's patients [19]. Some researchers argue that certain forms of estrogens, such as transdermal 17βE and cyclic progesterone treatment, could still be beneficial but this theory has not been adequately tested. Other researchers remain skeptical, largely because of the many failures of estrogen-related therapies in clinical trials.

SAFETY

Rated 2/4

Estrogen-containing hormone therapy poses some risks for long-term treatment, for older women, and for younger women with specific health risks. Some, though not all, mid-life women can safely use physician-supervised hormone therapy for several years to treat menopause symptoms [1]. For example, in the KEEPS clinical trial, four years of hormone therapy for healthy women between the ages of 42 and 58 provided some health benefits and no serious side effects. However, the risks are higher for long-term treatment, for older women, and for younger women with specific health risks. The Hormone Health Network offers a free "Menopause Map" and other resources to help individuals understand their possible risks and benefits.

A 2012 Cochrane meta-analysis of 23 randomized controlled studies (total 42,830 postmenopausal women) showed that combined continuous hormone therapy increased the risk of coronary events, venous thromboembolism, stroke, breast cancer, gallbladder disease, and death from lung cancer [20]. Treatment with estrogen alone increased venous thromboembolism, stroke, and gallbladder disease, but not breast cancer. Women taking hormone therapy had significantly decreased incidence of fractures with long-term use. For women between the ages of 50 and 59, combined continuous hormone therapy increased the risk for venous thromboembolism. Some types of hormone therapy, such as the bioidentical 17β-estradiol and cyclic progesterone may be safer than others, but the evidence is limited particularly for long-term use.

To reduce the risk of endometrial cancer, women with a uterus must not take estrogens without an effective progestogen. Hormone therapy can increase the risk of breast cancer and blood clots, which increases later in life. Either oral estrogen or estrogen plus progestogen therapy can increase the risk of stroke, an effect that probably disappears after hormone treatment is stopped [1]. This risk might be reduced by transdermal or intranasal delivery of the hormones instead of an oral pill [21]. Transdermal treatments should be used carefully to avoid accidentally exposing children and animals.

Clinical research and observational studies indicate that hormone therapy may lower the overall risk of death for women under the age of 60, while increasing it in women over 70 years of age [1]. A 2015 meta-analysis of 43 randomized controlled trials (of which 5 started within 10 years post-menopause) showed that hormone therapy had no effect on mortality regardless of type or history of preexisting heart disease [22]. Estrogen with progestogen use was associated with a likely increase in breast cancer mortality, but estrogen alone was not. Hormone therapy was not associated with mortality of other types of cancer. Meta-analysis of five randomized controlled trials where hormone replacement therapy was started at a younger age (below 60) showed a lower mortality rate [22].

HOW TO USE

Currently, the American Congress of Obstetricians and Gynecologists (ACOG) and other groups recommend that hormone therapy be supervised by a physician and used at the lowest dose and for the shortest possible duration to alleviate menopausal symptoms. The U.S. Preventive Services Task Force does not recommend hormone therapy to prevent or treat chronic conditions such as cognitive aging or dementia. The Hormone Health Network offers a free "Menopause Map" and other resources to help individuals understand their possible risks and benefits for treating menopausal symptoms

Bioidentical 17β-estradiol, which is derived from plants, is available as custom-made compounded hormones or as FDA-approved pills, patches, creams, gels, and vaginal tablets [23]. Compounded hormones have not been rigorously tested, particularly for long-term health, and their quality can vary [1; 23]. A small randomized clinical trial showed that compounded bioidentical hormones can yield lower levels of estrogen in the body compared to the standard estradiol patch [24].

Progestogens include a drug form of the molecule produced by the body (progesterone) and synthetic versions (progestins). Progesterone treatments are available as FDA-approved drugs or from compounding pharmacies. Progestins include medroxyprogesterone acetate (MPA), which was used in the Women's Health Initiative study. Some therapies try to mimic the natural hormone fluctuations of premenopausal women by giving progestogen only in the second half of the month. This cyclic treatment

can effectively protect against endometrial cancer risk from estrogen therapy and might be safer for breast cancer risk than continuous treatment [25; 26; 27].

When estrogens are absorbed through the gut, most of it never reaches the bloodstream and those that do are often converted by the liver from estradiol into estrone [28]. Unlike oral treatment, transdermal estrogens such as gels, creams, and sprays do not appear to increase the risk of stroke [21]. However, transdermal treatments should be used carefully to avoid accidentally exposing children and animals.

WHAT'S THE FUTURE?

Clinical trials have tested whether short-term treatment with either estrogens alone or with progesterone can minimize the damage of traumatic brain injury in both men and women (NCT00973674; NCT01809639). One trial was completed in 2014, but the results have not yet been published. The other trial is ongoing.

In addition, novel drugs and supplements related to hormone therapy are on the way. In 2015, researchers at the University of Southern California examined whether PhytoSERMS, a food supplement of three plant-based estrogens (phytoestrogens), can protect against age-associated memory decline in postmenopausal women (NCT01723917). Allopregnanolone, a natural byproduct of progesterone, is currently being tested in the clinic as a potential therapy to protect against cognitive decline for people with mild cognitive impairment or early-stage Alzheimer's disease (NCT02221622). This trial, developed in part with funding from the Alzheimer's Drug Discovery Foundation, is scheduled to finish in December 2016.

Many scientists are examining selective estrogen receptor modulators (SERMs), which mimic estrogens in some tissues while blocking their effects in other tissues. An observational study is currently underway to examine the effects of phytoestrogens and SERMs on mood and depression in perimenopausal women (NCT00001231).

Additionally, a phase 3 REPLENISH trial is testing the safety and efficacy of compounded bioidentical hormones (TX-001HR, composed of 17β-estradiol and progesterone) in treating menopausal symptoms like hot flashes (NCT01942668). It is scheduled to be completed in October 2016. However, the trial will not be examining any measures of cognitive function.

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