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Menopausal Hormone Therapy (MHT) and Dementia: What's the Truth?

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Introduction

There is extensive literature documenting that postmenopausal (PMP) estradiol (E2) therapy improves vasomotor symptoms,[1,2,3,4,5,6] the genitourinary syndrome of menopause (GSM),[5,6,7,8] bone mineral density,[9,10,11] breast cancer mortality,[12,13,14] and cardiovascular mortality.[15,16,17] However, the totality of the literature (RCTs and observational studies) on estradiol and cognition is inconsistent and confusing.

The reason for the inconsistent results is multifactorial. Reasons include different study populations using different E/E2 formulations and doses, different endpoints that are tested using different methodologies, and study duration. The latter is especially important since Alzheimer's disease (AD) develops over a long time and most studies are too short to really discern E2's protective effects.

Estradiol works synergistically with many biological systems to promote cognitive function. Basic science reveals that administering E2 (E2-alone or E2 + Oral Micronized Progesterone) results in increased antioxidants, decreased free radicals (ROS), and substantially lower mitochondrial DNA oxidative damage. Estradiol also regulates glucose and oxidative metabolism and mitochondrial function and promotes ATP generation. Decreases in these cognitive processes are characteristic of AD.[18,19] In addition, higher estrone (E1) levels have been associated with poorer cognition, specifically working memory performance. The latter supports transdermal/pellet E2's use with its physiologic estradiol (E2): estrone (E1) ratio (1:1) as compared to any oral-E/E2, which after hepatic and intestinal first-pass metabolism generates much higher E1 levels and thus a higher, less physiologic E1: E2 ratio.[20]

Despite E2's positive effects on cognition, E2's role in preventing AD continues to be controversial. Between 1999 and 2019 multiple published studies led to mixed results. For example, in 1999 and 2001, 2 small RCT pilot studies in females with Alzheimer's disease placed on a transdermal (TD) estradiol (E2) patch, Estraderm 0.025mg and 0.05mg respectively, demonstrated improved cognition only while prescribed the patches.[21,22] However, in 2003, the Women's Health Initiative Memory Study (WHIMS) assessed postmenopausal (PMP) females without dementia who were older than 65 and had received conjugated equine estrogen (CEE) plus medroxyprogesterone (MPA) and found a two-fold increase in dementia risk.[23,24]

In 2006, 2 small RCT's assessed PMP females without dementia. One study evaluated the TD E2 Climara 0.05mg/d patch[25] and the other assessed the no longer available 0.014mg/d Menostar patch,[26] both found no improvement in cognitive function. The Climara patch study did find improvement in executive functioning.[25] Then, between 2013 and 2016, three often cited, randomized, double-blind, placebo-controlled trials in females without dementia were published assessing whether MHT initiated soon after menopause (critical period hypothesis) influenced cognition years later. The first, WHIMS-Y (younger females), published in 2013, evaluated CEE and MPA and showed that in younger PMP females who initiated hormone therapy soon after menopause, MHT was neither beneficial nor harmful.[27] The second, published in 2015, Kronos Early Estrogen Prevention Study (KEEPS) Cognitive and Affective Sub study (KEEPS-Cog) assessed the transdermal estradiol Climara patch 0.05mg/d plus cyclic progesterone 200mg x 12 days each month or CEE 0.45mg/d plus cyclic progesterone 200mg x 12 days each month.[28] KEEPS-Cog found, like WHIMS-Y,[27] that there was neither cognitive harm nor benefit.[28]
Likewise, in 2016, Early versus Late Postmenopausal Treatment with Estradiol (ELITE)-Cog was published assessing oral estradiol (1.0mg/d) plus vaginal progesterone 45mg x 10 days each month and it too found no cognitive benefit or harm.[29]

Contrary to the 3 RCTs cited above, there was an often-cited observational study, Cache County, published in 2013,[30] and its follow-up published in 2019,[31] that suggested a positive association between MHT initiated soon after menopause and continued for > 10 years and cognitive status. The 2013 publication detected a

reduced AD risk if MHT was initiated within 5 years of menopause and continued for > 10 years.[30] The latter 2019 publication confirmed these findings.[31]

In June 2023, Pourhadi, et al.[32] published an observational, case-controlled study in the British Medical Journal (BMJ) that suggested an increased dementia risk with either short-term or long-term MHT use.[32] The study garnered a lot of attention by the lay press, including articles in the *New York Times* and *Fortune,* as well as coverage by CNN. Given MHT's mixed history and its relationship with dementia, providers and patients alike are asking about how to interpret this latest study.

Menopausal hormone therapy and dementia: nationwide, nested case-control study[32]
This study's objective was to evaluate the association between MHT and dementia development according to hormone therapy type, duration, and age at onset. Using the Danish national registries, 5589 incident dementia cases (dementia group) and 55,890 demographically-matched controls (control group) were identified between 2000 and 2018. The Danish females were aged 50-65 years old with no dementia history and no contraindications to MHT. Females with a previous hysterectomy were excluded. The primary exposure of interest was estradiol plus progestin. Oral estradiol and oral progestins were the most prescribed. The most common progestins utilized were norethisterone followed by medroxyprogesterone (MPA) and levonorgestrel. There was no information on progesterone. Females with dementia were identified based on diagnosis or treatment using dementia therapies. Late-onset dementia cases compromised 4436 (79.4%) among females with all cause dementia and 1458 cases (26.1%) were registered as AD. The median age at diagnosis was 70 years old and those diagnosed with dementia were more likely to have hypertension, diabetes, and thyroid disease when dementia was diagnosed.
In both groups, the median age and duration of MHT initiation was 53 and 3.8 years, respectively. Also in both groups, all estradiol-progestin users, 66.2% (11,879) were last treated more than 8 years before diagnosis and 8.7% (1,555) were still using MHT.

The authors found that MHT was associated with an increased dementia risk with either short-term or long-term use, even those using MHT for < 1 year. Females prescribed oral estradiol-progestin, systemic or vaginal estradiol-only, and perimenopausal progestin-only therapies were more likely to develop all cause dementia when compared to those who never used MHT. Interestingly, associations for progestin-only therapy did not reach statistical significance for all cause and Alzheimer's dementia and there was no association between vaginal estradiol-only therapy and all cause or Alzheimer's dementia. Pourhadi and coauthors concluded that MHT was positively associated with all cause and Alzheimer's disease risk even when MHT was initiated in younger females (< 55 years old) and used for < 1 year. They agreed that further studies were necessary to determine causality.[32]

Discussion
Pourhadi's[32] findings contradict the often-cited 3 RCTs noted above that documented when MHT was initiated early in menopause (age 50-55) cognitive function was not affected when compared with placebo.[27-29] In this Danish population, cofounding factors could, and probably did, contribute to the increased risk. Most notable was Pourhadi's findings that females using MHT for < 1 year had an increased dementia risk,[32] which is biologically implausible since AD develops over many years. Additional cofounding factors included hypertension and diabetes both vascular disease risk factors, which were found more commonly in the dementia group.[32]

Kantarci and Mason,[33] in an editorial commenting on Pourhadi's publication, noted additional cofounding factors. First, during the menopause transition, approximately two-thirds have subjective cognitive difficulties and may experience a temporary decline in cognitive processing speed. Also, females with vasomotor symptoms, especially during sleep, may develop a higher volume of white matter hyperintensity, which is a marker for poor brain vascular health. They concluded that Pourhadi's findings do not infer a causal relationship and should not be used to inform shared decision making about MHT initiation for menopausal symptoms. In addition, longer follow-up studies are necessary.[33]

Conclusion
Randomized controlled trials provide the strongest evidence for causation. The 3 RCTs, WHIMS-Y,[27] KEEPS-cog,[28] and ELITE-cog,[29] all document that MHT, prescribed to females without dementia has no effect on cognitive function. Surprisingly, the recent nationwide Danish study published in the BMJ found an association between both short- and long-term use of MHT and an increased risk of dementia. Unfortunately, it doesn't provide a conclusive answer on whether MHT contributes to dementia risk, But, because the study was observational, it cannot establish that the higher chance of dementia was actually caused by using the hormone therapy.

Like all observational studies, correlation does not equal causation and thus the results should be appropriately weighed. In fact, the Danish study adds little to the MHT and cognition story especially here in the US since the most prescribed MHT is transdermal estradiol (including pellet therapy) and oral micronized progesterone, not oral estradiol and progestins. Relevant long-term, randomized, double-blind, placebo controlled, prospective studies using currently prescribed MHT, transdermal/pellet estradiol and micronized progesterone, are necessary to answer the MHT and cognition question. Until these studies are done, when counseling patients regarding MHT and cognition, you can feel comfortable informing them that a causal link between MHT and dementia remains unlikely.[33]

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