

Estrogen Therapy in Menopausal Women: No Effect on Cognition?

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The majority of women experience some symptoms of menopause of varying severity, such as hot flashes, vaginal symptoms, night sweats and insomnia. For ameliorating menopausal symptoms hormone therapy (HT) is the most effective options. The early observational studies reported supplementary health gains with HT, such as decreased risk of cardiovascular disease and hip fracture.

Investigations of HT effect on cognition in menopausal women have produced many inconsistent findings since 1990. From one side, observational studies describing the effect of HT on cognition suggest that individual undergoing estrogenic treatment performed significantly better on tests of verbal memory [1], working memory [2-4] and visual memory [5] in comparison to non-HT users. Furthermore, observational studies suggested that HT offered a 50% reduction in Alzheimer's disease and protection against risk of dementia and the female gonadal steroids have a definite role during the brain development in generating neural circuits at the basis of the gender differences in behavior as evidenced by specific cognitive task performance [6-8]. Furthermore, cellular evidences have been reported to clarify the series of events leading to memory formation and storage, through slow genomic and fast non-genomic effects. E2 appears to enhance memory through epigenetic modifications, DNA methylation [9] and histone acetylation [10], processes that are critical for the basic memory formation. Cognitive impairment occurs when E2 concentrations are above or below an optimal level [11]. This inverted U-shaped dose-response of the estrogen effect on cognition may reflect the optimal level of estrogen receptors activation.

Observational studies paved the way for large-scale clinical investigations into the potential benefits of estrogen-based menopausal hormone therapies on cognition.

Contrary to all expectations, some years ago the reported neuro-protective effect of HT therapy was questioned by the two randomized controlled large-scale clinical trials: the Women's Health Initiative (WHI) and the Women's Health Initiative Memory study (WHIMS) [12-14]. WHI and WHIMS showed increased dementia risk and poorer cognitive outcomes in older postmenopausal women randomized to HT versus placebo with prolonged administration of estrogens, leading to trial withdrawal. However, animal models and clinical studies indicate a critical window for the therapeutic treatment such that the beneficial effects are lost with advanced age and/or with extended hormone deprivation.

Recently, it has been published the randomized large scale trial Women's Health Initiative Memory Study-Younger (WHIMS-Y) [15] an ancillary study to the WHI, to test whether an average of 5.4 years of HT during early menopause has longer term protective effects on

global cognitive function. Furthermore, the KEEPS Cognitive and Study Affective (KEEPS-Cog) [16], demonstrates that HT did not improve cognition when initiated in healthy recently postmenopausal women compared to placebo.

These data, taken together, strongly suggest that the underlying mechanisms that account for the effectiveness of HT to improve cognition in women are likely to be multifactorial and could be explained by possible variables known to influence cognitive abilities such as age, education and socio economic status, and by factors linked to HT therapy like types, doses and duration of hormones administered, route of treatment delivery, and the time of the initiation of treatment compared to proximity relative to menopause. In conclusion, the lack of cognitive benefit described in WHIMS-Y and KEEPS-Cog trials and the absence of short- and long-term harm to cognitive function should reassure healthy women who choose to use HT for treatment of menopausal symptoms but the problem of conflicting data between observational studies and large scale trials is still open. If from one side, studies to cellular level are clarifying the molecular mechanisms that trigger the estrogen effect on the central nervous system, more research efforts are needed and, in particular, large scale trials are needed to tackle this complex problem taking into account all variables in field.

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