Age Modulated the Tamoxifen-Cholinergic Interaction Effects on Cognition in Healthy Postmenopausal Women: Evidence for a Critical Period Effect.

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Tamoxifen (TAM) is a selective estrogen receptor modulator used for treatment and prevention of breast cancer. Whether TAM has antagonist activities in the human brain is less clear and its effects on cognitive function have not been carefully explored. Prior research suggests that estradiol reverses the anticholinergic impairment of younger postmenopausal women compared to older women, supporting the critical period hypothesis for an estrogen benefit on cognition after menopause. This study compares the effects of TAM on cognitive performance in younger postmenopausal women aged 50 to 59 and older postmenopausal women aged 60 to 74. A total of 21 postmenopausal women participated in this study. Each woman was administered 20 mg oral dose of TAM or placebo for three months, then completed five drug challenge days using the anti-cholinergic drugs mecamylamine (MECA) and scopolamine (SCOP) and were then cognitively assessed. After a three month period of placebo washout, they were then switched to the other drug or placebo for an additional three months, followed by another five cholinergic challenge days. The cognitive data suggest that younger postmenopausal women were more responsive to TAM treatment during MECA challenge compared to the older postmenopausal women. Specifically this effect was observed on the Buschke Selective Reminding test which is a measure of verbal episodic memory. Since episodic memory is hippocampally driven, these data suggest that TAM works through estrogen receptors on the hippocampus to affect cognition after menopause. Additionally, similar to the critical period effect we have previously shown for the estrogen-cholinergic interaction (Dumas et al. 2008), there also appears to be a similar critical period effect the tamoxifen-cholinergic interaction effect on cognition in postmenopausal women.