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Research Report

The rationale, design, and baseline characteristics of the Women's Health Initiative Memory Study of Younger Women (WHIMS-Y)

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ARTICLE INFO

Article history:
Accepted 29 March 2013
Available online 8 April 2013

Keywords:
Postmenopausal hormone therapy
Cognitive function
Aging

ABSTRACT

The Women's Health Initiative Memory Study-Younger (WHIMS-Y) was designed to assess the effect of prior random assignment to hormone therapy (HT) (conjugated equine estrogen (CEE) alone or CEE plus medroxyprogesterone acetate (MPA)) on global cognitive function in younger middle-aged women relative to placebo. WHIMS-Y was an ancillary study to the Women's Health Initiative (WHI) HT trial and enrolled 1361 women who were aged 50–55 years and postmenopausal at WHI enrollment. WHIMS-Y will examine whether an average of 5.4 years of HT during early menopause has longer term protective effects on global cognitive function and if these effects vary by regimen, time between menopause and study initiation, and prior use of HT. We present the study rationale and design. We describe enrollment, adherence to assigned WHI therapy, and compare risk factor characteristics of the WHIMS-Y cohort at the time of WHI enrollment to similar aged women in the WHI HT who did not enroll in WHIMS-Y. Challenges of WHIMS-Y include lower than expected and differential enrollment. Strengths of WHIMS-Y include balance in baseline risk factors between treatment groups, standardized and masked data collection, and high rates of retention and on-trial adherence and exposure. In addition, the

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0006-8993/$ - see front matter
http://dx.doi.org/10.1016/j.brainres.2013.03.047

telephone-administered cognitive battery showed adequate construct validity. WHIMS-Y provided an unprecedented chance to examine the hypothesis that HT may have protective effects on cognition in younger postmenopausal women aged 50–55 years. Integrated into the WHI, WHIMS-Y optimized the experience of WHI investigators to ensure high retention and excellent quality assurance across sites.

This article is part of a Special Issue entitled Hormone Therapy.

1. Introduction

Although early termination and publication of the Women's Health Initiative Memory Study (WHIMS) primary results showed increased risk of probable dementia and no protection of global cognitive function following initiation of postmenopausal hormone therapy (HT) (Espeland et al., 2004; Rapp et al., 2003; Shumaker et al., 2003, 2004), there is continued speculation that HT may still protect cognitive function in women if initiated during the peri-menopausal or recent postmenopausal period (Craig et al., 2005; Joffe et al., 2006). This speculation has led to recent calls for studies that examine the possible protective effects of HT on cognitive function in peri-menopausal and recent postmenopausal women. (Henderson and Sherwin, 2007; Lord et al., 2008; Resnick and Henderson, 2002). The WHIMS Study of Younger Women (WHIMS-Y) provides a unique and cost-effective opportunity to evaluate the impact of HT on cognitive function in younger postmenopausal women enrolled in the Women's Health Initiative (WHI) HT trials at ages 50–55 years. It will assess the long-term impact of randomized assignment to HT among these women, and thus will provide critical information regarding the clinical treatment of younger postmenopausal women and potential mechanisms for how HT may affect cognitive function.

1.1. *Objectives of WHIMS-Y*

The primary objective of WHIMS-Y is to test the hypothesis that conjugated equine estrogen (CEE)-based HT (CEE-Alone or CEE+MPA (medroxyprogesterone acetate)) in postmenopausal women aged 50–55 years has a long-term effect on women's global cognitive function. Specifically, WHIMS-Y tests whether randomized assignment to CEE+MPA and/or CEE-alone in younger postmenopausal women may confer the proposed protection relative to placebo.

Secondary objectives are to determine whether effects on cognitive function vary according to prescription of unopposed or opposed CEE, years between menopause and the initiation of study-prescribed therapy, and prior use of HT. WHIMS-Y will also identify incident cases of probable dementia (PD) and mild cognitive impairment (MCI); however it is not expected to provide sufficient statistical power to detect differences in the rates of these.

In this paper that focuses on the design of WHIMS-Y, we describe the enrollment of the cohort and compare selected characteristics of the cohort at the time of their WHI HT enrollment with characteristics of similar-aged women in the WHI HT who declined enrollment in WHIMS-Y. We also describe adherence to assigned WHI therapy, using pill counts and length of enrollment in the WHIMS-Y cohort.

2. Results

Here, we report on the design of WHIMS-Y, including enrollment of the cohort, the comparison of cognitive risk factors and adherence patterns of WHIMS-Y enrollees and non-enrollees and CEE and CEE/MPA groups at WHI enrollment, and baseline cognitive characteristics of WHIMS-Y women at the initiation of cognitive testing. In addition, we describe the results of factor analytic analyses of the cognitive battery. In year 1, $N=1732$ currently active participants of the WHI Extension Study agreed to initial contact by the WHIMS coordinating center, and $N=1361$ (78.6%) agreed to participate. Of these, $N=1264$ (93.1%) completed the test battery in year 1, with a small percentage lost to follow-up after eight attempts to contact. An additional $N=62$ participants included in the analyses completed the test battery for the first time in years 2 or 3.

In the comparison of WHIMS-Y enrollees and non-enrollees at the time of their WHI enrollment, a number of risk factors were examined, including age, age at last menstrual period, education, race and ethnicity, smoking status, alcohol intake, body-mass index (BMI), hypertension status, prior cardiovascular disease (CVD), hysterectomy, years since last regular menstrual period, prior HT at recruitment, and adherence. As seen in Table 1, at WHI enrollment there was no difference in the distributions of important potential confounds between women in the placebo and the HT groups. When we compared WHIMS-Y enrollees to non-enrollees, there were significant or marginal differences in several variables, including: age at last menstrual period, education, race and ethnicity, alcohol consumption, BMI, years since last regular menstrual period, prior HT at WHI recruitment, and adherence. Overall, WHIMS-Y enrollees reported being slightly older at their last menstrual period ($M=45.1$, $SD=6.2$) than non-enrollees ($M=44.4$, $SD=6.5$), $p=0.04$. Enrollees reported a lower percentage having only a high school education or less (15.9%) than non-enrollees (25.1%), $p<0.001$. A lower percentage of enrollees were African American (12.5%) than non-enrollees (20.1%), and Hispanic (4.4%) than non-enrollees (9.9%), $p=<0.001$ for race overall. A higher percentage of enrollees reported <1 drink per day (66.1%) than non-enrollees (59.7%), $p=0.008$. A higher percentage of enrollees (28.5%) than non-enrollees (23.3%) had BMI's of 20–25 kg/m^2, $p=0.06$ overall. For enrollees, years since last regular menstrual period for women with prior hysterectomy were somewhat fewer ($M=12.6$, $SD=6.1$) than non-enrollees ($M=13.6$, $SD=5.8$), $p=0.05$. There was a greater