Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women

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Abstract

Objective—To investigate possible differential effects of the coadministration of conjugated equine estrogen (CEE) and a placebo (CEE + PL), CEE and medroxyprogesterone acetate (CEE + MPA), or CEE and micronized P (CEE + MP) on aspects of cognitive functioning in naturally postmenopausal women.

Design—Double-blind, randomized, controlled trial.

Setting—Gynecologic screening occurred at a university hospital, and neuropsychological testing took place in a university laboratory.

Patient(s)—Twenty-four naturally menopausal women with an intact uterus who had never used hormone therapy were recruited by means of newspaper advertisements. All completed the study.

Intervention(s)—A battery of mood and neuropsychological tests was administered. Women were randomly assigned to receive CEE + PL (n = 7), CEE + MPA (n = 9), or CEE + MP (n = 8). The tests were readministered 12 weeks later.

Main Outcome Measure(s)—Standardized tests of mood, verbal memory, working memory, spatial abilities, and visual–spatial sequencing, and assays of serum sex hormone levels.

Result(s)—Mood improved after treatment in all groups. No changes in scores occurred over time in any cognitive test in the group that received CEE + PL. Only the CEE + MP group had a significant decrease in their delayed verbal memory scores from baseline to after treatment. The CEE + MP-treated women performed significantly better on a test of working memory than women in the other two groups.

Conclusion(s)—Coadministration of CEE with MPA or MP caused differential effects on aspects of memory in postmenopausal women. These findings need to be replicated with a larger sample size before their potential clinical implications can be determined.

Keywords

Postmenopause; micronized progesterone; medroxyprogesterone acetate; estrogen; cognition; mood

Although there is substantial evidence that estrogen (E)-alone therapy administered to postmenopausal women at the time of menopause may protect aspects of memory function, there is reason to believe that the coadministration of P or synthetic progestins may attenuate the beneficial effect of E on cognition or even cause harm (1). In the Women's Health Initiative Memory Study (WHIMS), the largest randomized controlled trial of its kind, women whose average age was 72 years at the time of the initiation of treatment with either continuous conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA), a synthetic 17 α -hydroxyprogesterone derivative, or placebo found an increased risk of probable, all-cause dementia in the combined hormone group (CEE + MPA) compared with placebo (2). Because there was no heightened incidence of dementia in 72-year-old hysterectomized women treated with CEE alone (3), one interpretation of the WHIMS findings is that, in older women, the addition of MPA to E-alone therapy caused the excess risk of all-cause dementia. Because only a single test of global cognitive function was used in the WHIMS, it was not possible to examine specific effects of CEE or MPA on aspects of memory function in their sample. An earlier prospective observational study of women over the age of 65 years had also found that whereas treatment with unopposed CEE was associated with modest beneficial effects on a test of global cognitive function over time, treatment with CEE + MPA was associated with a modest detrimental effect with increasing age (4).

Because of the evidence that beneficial effects of hormone therapy on cognition may accrue only to younger women in whom hormone treatment is initiated closely in time to the occurrence of menopause (the so-called *critical period hypothesis* or *window of opportunity hypothesis*) (1), it is important to investigate whether the negative effects of CEE + MPA on cognition documented in older women in the WHIMS (2) also applies to younger, naturally postmenopausal women treated between the ages of 50 and 60 years. When 52-year-old postmenopausal women with cognitive complaints randomly received either CEE 0.626 mg + 2.5 mg MPA or CEE alone daily for 4 months, a trend toward poorer performance on tests of long- and short-term verbal memory was observed in the E + P group ($P < .10$) (5), suggesting that treatment with CEE + MPA may have a similarly negative effect on aspects of cognition in middle-aged women as it does in older women.

Because P has different physiological effects on aspects of central nervous system function than synthetic progestins (6), there has been much speculation that micronized P (MP), a natural P, may have different effects on cognitive functions when coadministered with CEE to postmenopausal women compared with the coadministration of CEE with MPA. If that is true, it would suggest that the results of the WHIMS should not be generalized to E-alone therapy that is coadministered with other P drugs. However, to our knowledge, no head-to-head studies of the hypothesis that MPA and MP may have differential effects on aspects of cognitive functioning in middle-aged women have been undertaken. The goal of this randomized, controlled clinical trial was to determine whether differential changes in aspects of cognitive function occurred in middle-aged postmenopausal women treated with either CEE alone, CEE + MP, or CEE + MPA. On the basis of the limited clinical evidence available, it was hypothesized that women who randomly received CEE alone would perform better compared with their pretreatment baseline on tests of verbal memory than

those given either of the combined hormone regimens; however, there was insufficient extant evidence to predict the possible effect of either of the two combined CEE + P regimens on aspects of cognition.

MATERIALS AND METHODS

Participants

Between 2002 and 2006, 24 naturally menopausal women with an intact uterus who had never used hormone therapy were recruited by means of newspaper advertisements. They were required to be between the ages of 50 and 55 years with the absence of menstrual cycles for the previous 6 months, to have at least 9 years of formal education, and be fluent in either English or French. Exclusion criteria were history of acute or chronic medical illness, history of gynecologic or breast cancer, use of psychotropic medications, contraindications to hormone therapy, and use of hormone therapy during the 3 months before their recruitment.

Materials

Mood measures—The Beck Depression Inventory (BDI-II) (7) was used to measure mood before and after treatment.

Menopausal symptoms—Menopausal symptoms were assessed with the Menopausal Index (8). This questionnaire measures, on 7-point Likert scales, the frequency and severity of six somatic symptoms (hot flushes, cold sweats, weight gain, breast pain, tired feelings, and trouble sleeping) and eight psychological symptoms (irritable and nervous, feel blue and depressed, forgetfulness, inability to concentrate, crying spells, loss of interest in most things, feeling tense or wound-up, worry needlessly) that have been associated with menopause. Women were required to circle the number that best indicated the degree to which they were experiencing each symptom.

Neuropsychological tests—Verbal memory was tested using the Logical Memory test (Immediate and Delayed) and the Paired Associates Test (Immediate and Delayed). The Digit Span Forward Test measured attention, whereas the Digit Span Backward is taken to be a measure of working memory. All of these are subtests of the Wechsler Memory Scale (9). Spatial abilities were tested using the Mental Rotations Test (10), and the Trails Making Test–Form B measured visual–spatial sequencing and cognitive set-shifting abilities (9).

Drug Groups

Drug groups were as follows: group 1 (CEE + PL): 0.625 mg CEE daily for 28 days (Premarin, Wyeth-Ayerst) plus a placebo (PL) daily from days 1 to 14 of each treatment cycle for 12 weeks; group 2 (CEE + MPA): 0.625 mg CEE for 28 days plus 10 mg MPA daily (Provera, Pfizer) from days 1 to 14 of each treatment cycle for 12 weeks; group 3 (CEE + MP): 0.625 mg CEE daily for 28 days plus 200 mg MP (Prometrium, Schering-Plough) from days 1 to 14 of each cycle for 12 weeks.

Procedure

Women who answered the newspaper advertisement were screened over the telephone to determine that they met the inclusion and exclusion criteria and then given an appointment to visit the laboratory. They signed a consent form that had been approved by the Ethics Review Board, Faculty of Medicine, McGill University, Montreal, Canada. The battery of mood, symptom, and neuropsychological tests was administered, and women were then scheduled for an appointment with a gynecologist at the Royal Victoria Hospital, McGill University Health Center, Montreal, Canada, to ensure that they had no contraindications to hormone therapy.

After the gynecologist approved her participation (which occurred in every case), each woman was assigned a study number. The hospital pharmacy generated a random assignment list of which they were sole custodians, and a hospital pharmacist dispensed a 12-week supply of drugs to each woman in accordance with the random assignment list. The women were instructed to take the pills daily at bedtime. Each woman was given an appointment to return to the laboratory for the readministration of the mood and neuropsychological battery of tests between days 9 and 12 of the 12th week of treatment when women in group 1 were taking CEE + PL and those in groups 2 and 3 were taking CEE + MPA or CEE + MP, respectively.

RESULTS

Statistical analyses were conducted using the SPSS statistical software package (version 18.0). Repeated-measures analyses of variance (ANOVAs) were performed with hormonal treatment (Group) as the between-subject factor and the pre- and posttreatment testing times (Time) as the within-subject factor.

The demographic characteristics of all participants appear in Table 1. The 24 women had a mean age of 55 years and were fairly well educated. A one-way ANOVA failed to find significant differences between the treatment groups in terms of age, years of education, or estimated general intelligence (based on standard scores on the Vocabulary subtest). Levels of FSH and LH were in the postmenopausal range and did not differ among groups. Therefore, these demographic and biological variables were not used as covariates in the analyses of group scores on the neuropsychological tests. Although the mean body mass index (BMI) was significantly higher for women in the E + MPA group compared with the other two groups ($P < .03$), as a group, their BMI mean fell below the obese range ($\text{BMI} < 30 \text{ kg/m}^2$).

The ANOVA analyzed main effects for differences between the three groups, main effects for Time (before treatment and after treatment), and possible interaction effects between Group and Time. A significant main effect for Time [$F(2,21) = 7.27$, $P = .017$] was found on the BDI-II such that mean mood scores were improved at time 2 compared with time 1 in all three treatment groups (Table 2). However, both the pre- and posttreatment BDI-II scores of the participants fell within the normal range on this measure of mood at both test times. On the Menopausal Index, there was a trend for a decrease in somatic symptom scores ($P < .089$).

and the psychological symptom scores ($P<.087$) in all three groups after treatment, but no Group $\times$ Time interaction was evident.

Results of the neuropsychological tests that found significant within- and between-group differences appear in Table 3. In no case did any score change on any of the cognitive tests throughout the study in the group that had randomly received E + PL. Although no significant changes were evident on short-term verbal memory scores (PAL Immediate), there was a significant Group $\times$ Time interaction for long-term verbal memory (PAL Delayed Recall) score [$F(2,21) = 4.56$; $P=.042$]. Post hoc tests revealed that women randomly treated with E + MP had a significant decrease in their delayed verbal memory scores from baseline to after treatment [$t(1, 8) = 2.82$, $P=.022$], whereas scores of those treated with E + PL and E + MPA did not change from before to after treatment on this test of verbal memory.

The analysis of Digit Span Forward scores failed to find changes in any group over time. However, there was a significant main effect for Time [$F(2,21) = 4.85$, $P=.018$] on the Digit Span Backward test such that women treated with E + MP experienced a significant increase in their scores on the Digit Span Backward test from before to after treatment [$t(1, 8) = -3.507$, $P=.008$]. No changes in performance on this task of working memory occurred in either of the other groups from before to after treatment.

Although there were no significant interactions between the Group and Time factors on the Trails Making Test Form B, there was a significant main effect for Time such that it took the women less time to complete this test that measures visual-spatial sequencing after treatment regardless of treatment group [$F(2,21) = 9.98$, $P=.032$].

No within- or between-group differences occurred in either the Paragraph Recall Immediate or Delayed tests of verbal memory or in the Mental Rotations Test (a test of spatial ability) in any treatment group throughout the study.

DISCUSSION

In contradistinction to our hypothesis, the 55-year-old naturally postmenopausal women in this study who received E + PL did not experience any changes in cognitive function after 12 weeks of treatment. Although we have previously demonstrated that E-alone therapy helps to maintain verbal memory in premenopausal women who underwent bilateral oophorectomy (11, 12), others have also failed to find a beneficial effect of unopposed E-alone therapy when given to postmenopausal women several years after their natural menopause (13, 14).

Women in all three groups performed significantly better on the Trails B, a test of visual-spatial sequencing, after 12 weeks of treatment. Because the improvement in performance on this test occurred in all three treatment groups, it is not possible to conclude whether the beneficial effect was due to treatment with CEE or due to practice effects resulting from prior exposure to the test stimuli during the pretreatment baseline test session.

On the other hand, several differential effects of the coadministration of E + MPA or E + MP on aspects of cognitive functioning were evident. Whereas treatment with E + MP caused a significant decrease in scores on a test of delayed verbal memory, women who randomly received 12 weeks of treatment with E + MPA experienced no change in scores on the same test. However, the magnitude of the effect of E + MP on delayed verbal memory is very small and unlikely to be clinically meaningful. In contrast, women who were randomly treated with E + MP experienced a significant increase in their scores on a test of working memory, whose effect size suggests that the increase would be clinically meaningful. Whereas verbal memory is primarily hippocampally dependent, working memory, the ability to hold in mind and manipulate information to make a response, involves mainly the prefrontal cortex (15). Our findings therefore suggest that E + MP, but not E + MPA, has a salutary effect on the prefrontal cortex, whose function declines with normal aging (16). The fact that no changes occurred from before to after treatment in the E + PL group on any of the cognitive tests lends support to the interpretation that the improvement in working memory was, in fact, due to the coadministration of MP and not to CEE.

Among other brain areas, nuclear P receptors are found in both the hippocampus and in the prefrontal cortex (17), which implies that this hormone could affect both hippocampal (verbal) memory as well as cognitive abilities that rely heavily on the prefrontal cortex, such as working memory. Moreover, established differences in the neurochemical properties of MP and MPA (6) could have caused differential effects on aspects of cognition in the present study. For example, in contrast to MP, MPA is not converted to the γ -amino-butyric acid-A metabolite, allopregnanalone, and MPA but not MP has been shown to antagonize the neuroprotective effect of E on cultured hippocampal cells (18). Interestingly, premenopausal women performed better on a test of working memory during the early luteal phase of the menstrual cycle when P levels were at their highest (19).

Although mood scores decreased significantly in all three groups from before to after treatment, at all times they remained within the normal, euthymic range, so that the improvement in mood scores would likely not have clinical significance. Previous randomized controlled trials have also found that E-alone therapy decreased mood scores within the normal range in healthy surgically menopausal women (20) and that treatment with CEE + MP or CEE + MPA had no effect on mood in euthymic naturally postmenopausal women (21). The trends toward lower somatic and psychological symptom scores on the Menopausal Index after 12 weeks of treatment also indicate that the women were generally feeling better while taking E-alone therapy or hormone therapy.

In summary, this randomized, controlled trial found that healthy, naturally postmenopausal women exposed to any of the three regimens of hormone therapy experienced an increase in mood scores that was unlikely to be clinically meaningful. Although women treated with E + MP experienced a modest decrease in scores on a test of delayed verbal memory, they also experienced a significant increase in their scores on a test of working memory after 12 weeks of treatment. The strength of this study is that women with homogeneous demographic characteristics had been randomly assigned to treatments. The obvious limitation is that the study was very small. Although we had originally planned to recruit 25 women per treatment group, many women refused to take hormone therapy after the

publication of the Women's Health Initiative findings in 2003, and we ultimately had to terminate the study early. Clearly these findings need to be replicated with a much larger sample size before their clinical import can be ascertained.

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TABLE 1

Baseline means (SDs) for demographic characteristics of all participants.

Characteristic	CEE + PL (n = 7)	CEE + MP (n = 9)	CEE + MPA (n = 8)	P value
Age (y)	55.4 (3.7)	55.89 (6.5)	54.5 (3.25)	.74
Education (y)	11.3 (2.6)	11.9 (3.5)	12.4 (3.9)	.93
Vocabulary score	10.43 (1.71)	13.00 (3.07)	11.43 (3.0)	2.00
FSH (IU/L)	54.32 (20.7)	87.87 (32.16)	63.28 (15.3)	.13
LH (IU/L)	39.08 (1.14)	39.08 (5.08)	32.73 (8.04)	.189
BMI	23.01 (2.65)	24.04 (3.68)	27.46 (2.35)	.038

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TABLE 2

Means (SDs) for mood and menopausal symptom scores before and after treatment.

Test variable	Visit	CEE + PL (n = 7)	CEE + MP (n = 9)	CEE + MPA (n = 8)
BDI-II (normal range: 0–13)	Baseline	11.57 (9.7)	10.89 (6.5)	10.63 (11.1)
	Posttreatment	8.29 (7.6) ^a	5.89 (4.5) ^a	4.75 (4.1) ^a
Somatic symptoms (Menopausal Index)	Baseline	15.50 (7.23)	20.42 (8.73)	14.40 (5.89)
	Posttreatment	10.25 (2.06) ^b	17.71 (7.22) ^b	12.40 (6.22) ^b
Psychological symptoms (Menopausal Index)	Baseline	21.50 (15.15)	21.57 (15.15)	16.00 (5.56)
	Posttreatment	18.50 (14.46) ^c	18.42 (7.23) ^c	12.60 (7.09) ^c

^aWithin group difference ($P < .017$).

^bWithin-group difference ($P < .089$).

^cWithin-group difference ($P < .087$).

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TABLE 3

Means (SDs) for mood and neuropsychological tests scores.

Test variable	Visit	E + PL (n = 7)	E + MP (n = 9)	E + MPA (n = 8)
PAL–Delayed Recall, raw scores	Baseline	12.0 (1.3)	13.00 (2.6)	11.87 (1.6)
	Posttreatment	11.0 (3.3)	11.91 (1.7) ^a	12.88 (1.12)
Mental Rotations, correct responses	Baseline	2.67 (2.2)	3.44 (2.1)	3.25 (2.3)
	Posttreatment	3.83 (1.72)	3.11 (2.2)	3.13 (2.9)
Mental Rotations, time to complete (s)	Baseline	412.33 (108)	417.89 (83)	380.63 (107)
	Posttreatment	382.17 (131)	449.00 (65)	374.25 (93)
Trails Making B, time to complete (s)	Baseline	86.14 (24.5)	99.67 (51.3)	82.38 (28.6)
	Posttreatment	74.86 (25.0) ^b	85.56 (32.9) ^b	70.50 (19.5) ^b
Digit Span Backward, raw scores	Baseline	5.43 (0.98)	6.67 (1.73)	8.13 (3.441)
	Posttreatment	5.57 (0.81)	8.56 (1.33) ^c	8.50 (2.673)
Logical Memory, Immediate Recall	Baseline	15.25 (3.5)	14.94 (4.5)	12.57 (7.33)
	Posttreatment	15.67 (5.94)	15.27 (6.39)	15.07 (4.92)
Logical Memory, Delayed Recall	Baseline	11.91 (4.7)	12.33 (4.1)	10.21 (6.2)
	Posttreatment	11.5 (6.6)	12.94 (6.4)	14.57 (5.5)

Note: PAL = Paired Associates Learning.

^aWithin-group difference ($P=.022$).

^bWithin-group difference ($P=.008$).

^cWithin-group difference ($P=.032$).

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