

Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

Update #4: Preliminary Scan Report #2

June 2010

**The Agency for Healthcare Research and
Quality has not yet seen or approved this report**

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update Report:

Update #3 was completed in October 2007, with searches through March 2007.

Date of Last Update Scan:

Update #4 Scan #1: May 2009

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different estrogen preparations when used by perimenopausal and postmenopausal women for
 - Reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?
 - Preventing low bone density and fractures?
2. What is the comparative safety of different estrogen preparations when used by perimenopausal and postmenopausal women for
 - Short-term use (<5 years)?
 - Long-term use (5 or more years)?
3. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion criteria**Populations**

- Study participants include women recruited from any health care setting or a population-based sample experiencing menopause. When possible, data are considered separately for women with natural vs. surgical menopause (oophorectomy) and for women in peri vs. postmenopause.
- Perimenopausal women are those transitioning through natural menopause who had irregular menstrual periods within the last 12 months.
- Postmenopausal women are those with surgical or natural menopause and amenorrhea for more than 12 months.

Interventions

Interventions include oral and transdermal estrogens listed below for all symptoms, bone density, and fracture outcomes, and vaginal cream for urogenital atrophy, with or without concomitant use of progestin/progesterone administered as sequential or continuous regimens. Progestin/progesterone preparations will not be considered separately. These include:

- 17-beta estradiol (E2): oral, transdermal, vaginal cream
- Estradiol valerate (E2V): oral
- Conjugated equine estrogen (CEE): oral, vaginal cream
- Synthetic conjugated estrogen: oral
- Esterified estrogen (EE): oral
- Estropipate: oral

Effectiveness outcomes

- Hot flashes or flushes defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied. Studies will be included if they measured frequency, severity, presence versus absence, or a combination measure of frequency and severity as either primary or secondary outcomes at baseline, 3 months, and/or end of study.
- Other symptoms such as sleep disturbances/night sweats, mood changes (depression), sexual function, urogenital atrophy, and quality-of-life measures.
- Prevention of osteoporosis measured by improvement in bone density and fracture outcomes after at least 1 year of use.

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects

For short-term use

- Atypical bleeding; endometrial hypertrophy
- Nausea and vomiting
- Breast tenderness
- Headaches
- Weight changes
- Dizziness

- Thrombosis (including relationship to estradiol levels)
- Cardiovascular events
- Rash and pruritis
- Cholecystitis
- Effects on the liver

For long-term use

- Cardiovascular events
- Breast cancer
- Thrombosis
- Cholecystitis
- Ovarian cancer/endometrial cancer

Study Designs

- Symptoms: Double-blind, randomized controlled trials of at least 3 months duration of one hormone therapy preparation versus another hormone therapy preparation or versus placebo.
- Prevention of osteoporosis: Double-blind or open, randomized controlled trials of postmenopausal women who are treated for at least 1 year versus another hormone therapy preparation or versus placebo.
- Good quality systematic reviews and meta-analyses.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from May 2009 through May Week 1, 2010 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality (www.ahrq.gov) and the Canadian Agency for Drugs and Technologies in Health (www.CADTH.ca). We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis>) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X2) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

No comparative effectiveness reviews were identified through searches of the AHRQ and CADTH websites. Medline searches resulted in 69 citations. Of those, there are 11 new potentially relevant new trials. Table 1 summarizes the studies (see Appendix A for abstracts).

Table 1. Potentially relevant trials of hormone therapy

Study year	Comparison	N, duration	Focus
Bachmann 2009a	Conjugated estrogens vaginal cream vs placebo	423, 12 weeks	Atrophic vaginitis
Bachmann 2009b	Transdermal 17-beta estradiol (low dose or micro-dose) vs placebo	121, 12 weeks	Vulvovaginal symptoms
Baksu 2009	Oral conjugated estrogen vs intranasal estradiol hemihidrate vs no treatment	100, 1 year	Climacteric symptoms, anxiety and depression
Freedman 2009	Synthetic conjugated estrogens vaginal cream vs placebo	305, 12 weeks	Vulvovaginal atrophy
Gast 2009	Oral low-dose conjugated estrogens plus conjugated estrogens vaginal cream vs placebo cream and placebo tablet	285, 6 weeks	Sexual function and quality of life
Haines 2009	Micro-dose transdermal estradiol vs placebo	165, 12 weeks	Asian women, hot flashes
Honjo 2009	Low-dose oral estradiol vs placebo	211, 8 weeks	Japanese women, hot flashes
Huang 2009	CEE vs placebo	2763, 1 year	Secondary analysis from HERS study data, risk of coronary heart disease
Maki 2009	CEE vs black cohosh vs red clover vs placebo	66, 1 year	Cognition
Michael 2010	CEE vs placebo	1458, 6 years	Secondary analysis of WHI data, physical function in women ages 65 to 79 years at enrollment
Resnick 2009	CEE vs placebo	886, 3 years	Secondary analysis of WHI data, cognition in women age 65 years and older

Along with the 33 trials identified in the previous update scan, there are now 44 potentially relevant new trials for this drug class.

New Drugs

No new drugs were identified.

New Indications

December 2009: FDA approved a new 10 mcg dosage regimen of Vagifem[®] (estradiol) vaginal tablets for the treatment of atrophic vaginitis due to menopause.

New Safety Alerts

No new safety alerts were identified.

Appendix A. Abstracts of potentially relevant new trials of estrogens (N=11)

Bachmann, G., C. Bouchard, et al. (2009a). "Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally." *Menopause* **16**(4): 719-27.

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of low-dose conjugated estrogens (CE) cream for treatment of atrophic vaginitis. **METHODS:** Postmenopausal women (N = 423) with moderate-to-severe vaginal atrophy were randomized to CE cream 0.3 mg or placebo once daily (21 days on/7 days off) or twice weekly for 12 weeks, followed by open-label treatment with CE cream for 40 weeks consistent with their prior regimen. Primary endpoints were changes in vaginal maturation index (VMI; percentage of superficial cells), vaginal pH, and severity of participant-reported most bothersome symptom (vaginal dryness, itching, burning, or dyspareunia) at week 12. Endometrial safety was assessed by transvaginal ultrasound and endometrial biopsy for 52 weeks. **RESULTS:** At week 12, improvements in VMI with daily and twice-weekly use of low-dose CE cream (27.9% and 25.8%, respectively) were significantly greater compared with placebo (3.0% and 1.0%, respectively; $P < 0.001$). Improvements in vaginal pH with daily and twice-weekly CE cream (-1.6 for both) were also significantly greater relative to placebo (-0.4 and -0.3, respectively; $P < 0.001$). VMI and vaginal pH responses were sustained through 52 weeks. Both CE cream regimens significantly reduced most bothersome symptom scores compared with placebo ($P < 0.001$), including those for dyspareunia ($P < 0.01$). There was no report of endometrial hyperplasia or carcinoma. Adverse events occurred with similar frequency among the active and placebo groups during the double-blind phase. **CONCLUSIONS:** Daily and twice-weekly use of low-dose CE cream was equally effective in relieving symptoms of vulvovaginal atrophy. Both regimens showed endometrial safety and sustained efficacy during 1 year of therapy.

Bachmann, G. A., M. Schaefer, et al. (2009b). "Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women." *Menopause* **16**(5): 877-82.

OBJECTIVE: The aim of this study was to investigate the effectiveness of microdose transdermal 17beta-estradiol (E2) therapy in postmenopausal women with moderate to severe vulvovaginal symptoms. **METHODS:** This report is based on a subset of 121 women who reported most bothersome moderate or severe vulvovaginal symptoms at baseline, from a previous randomized, double-blind, placebo-controlled, multicenter study of 425 healthy, symptomatic, postmenopausal women. Recruits had experienced at least 7 moderate or severe hot flushes daily for at least 1 week or at least 50 moderate or severe hot flushes per week for at least 1 week. Effects on coprimary efficacy variables have been reported previously. Participants received low-dose transdermal E2 plus levonorgestrel (n = 43; nominal delivery 0.023 mg/d E2/0.0075 mg/d levonorgestrel), microdose E2 (n = 42; nominal delivery 0.014 mg/d), or placebo (n = 36) for 12 weeks. Secondary efficacy variables reported herein include mean change from baseline in vaginal pH and vaginal maturation index, the proportion of women with symptoms of vulvar and vaginal atrophy at baseline and week 12, and the proportion of women with moderate-to-severe symptoms of vulvar and vaginal atrophy. **RESULTS:** Microdose transdermal E2 treatment was associated with a consistent benefit versus placebo in women with vulvovaginal atrophy. There was a statistically significant difference between both E2 versus placebo for changes in vaginal pH and vaginal maturation index. **CONCLUSIONS:** Microdose transdermal E2 offers a useful addition to the therapeutic armamentarium for postmenopausal women in whom vulvovaginal symptoms are particularly troublesome.

Baksu, B., A. Baksu, et al. (2009). "Do different delivery systems of hormone therapy have different effects on psychological symptoms in surgically menopausal women? A randomized controlled trial." *Maturitas* **62**(2): 140-5.

OBJECTIVE: To compare the influence of different delivery forms of estrogen therapy on menopausal and psychological symptoms in surgically menopausal women. **STUDY DESIGN:** Surgically menopausal women were assigned to a 1-year-therapy with oral conjugated estrogen 0.625mg/day (n=35), intranasal 300microg/day estradiol hemihidrate (n=33), percutaneous gel 1.5mg/day estradiol hemihidrate (n=32) or no treatment (control group, n=32). Serum E(2) and FSH levels, Kupperman's Scale used to assess climacteric symptoms, Hamilton Depression Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) scores were assessed before and after 1-year-therapy. **RESULTS:** After 1 year, the greatest increase in E(2) was in the oral group, followed by the transdermal gel, and then the intranasal group (oral vs transdermal gel: $p=0.022$; oral vs intranasal: $p=0.0001$; transdermal gel vs intranasal: $p=0.0001$). All treatment groups improved significantly in total Kupperman index score and HARS ($p<0.05$) with no difference between the groups. With regard to HDRS, all treatment groups improved significantly ($p<0.05$) with the greatest improvement in the oral group, and no difference between transdermal gel and intranasal groups (oral vs transdermal gel: $p=0.015$; oral vs intranasal: $p=0.001$; transdermal gel vs intranasal: $p=0.735$). Control group scored worse in all tests after study ($p<0.05$). All scores correlated significantly with post-treatment serum E(2) and FSH levels ($p<0.001$). **CONCLUSION:** Oral, intranasal and percutaneous gel estradiol therapies significantly improve menopausal and psychological symptoms in surgically menopausal women with oral route better than transdermal gel and intranasal modalities against depressive mood.

Freedman, M., A. M. Kaunitz, et al. (2009). "Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy." *Menopause* **16**(4): 735-41.

OBJECTIVE: The aim of this study was to evaluate low-dose synthetic conjugated estrogens A (SCE-A) cream administered twice weekly for the treatment of moderate to severe vulvovaginal atrophy (VVA) in a symptomatic postmenopausal population. **METHODS:** In a multicenter, double-blind, randomized, placebo-controlled study, 305 women with symptoms of VVA were treated with either 1 g SCE-A cream (n = 150) or matching placebo (n = 155) for a period of up to 12 weeks. Participants had to have a vaginal pH of greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and at least one of five symptoms of VVA (dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse) that was moderate or severe in intensity. Women had to select one moderate or severe symptom as the most bothersome. **RESULTS:** Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). A statistically significant increase in the maturation index and significant decreases in pH and severity of the MBS were observed for those treated with SCE-A vaginal cream compared with placebo. **CONCLUSIONS:** A low dose (1 g = 0.625 mg) of SCE-A vaginal cream administered twice weekly was shown to be effective compared with placebo in treating VVA in postmenopausal women for the three coprimary efficacy measures of maturation index, pH, and severity of the MBS.

Gast, M. J., M. A. Freedman, et al. (2009). "A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women." *Menopause* **16**(2): 247-56.

OBJECTIVE: To evaluate the effects of combined vaginal and oral low-dose estrogen plus progestogen therapy (EPT) on the frequency and severity of dyspareunia, sexual function, and quality of life in recently postmenopausal women. **METHODS:** This outpatient, double-blind, randomized, placebo-controlled trial enrolled 285 healthy, sexually active postmenopausal women aged 45 to 65 years. Women received either one daily oral low-dose conjugated estrogens (0.45 mg)/medroxyprogesterone (1.5 mg) tablet for six 28-day cycles along with 1 g conjugated estrogens vaginal cream (0.625 mg), intravaginally for the first 6 weeks of the trial or a placebo cream and placebo tablet. Efficacy was evaluated using the McCoy Female Sexuality

Questionnaire, self-reported daily diary cards, the Brief Index of Sexual Functioning-Women (BISF-W), and the Women's Health Questionnaire. RESULTS: The EPT group had a significant decrease in the frequency of dyspareunia compared with baseline and placebo in an analysis of responses to the McCoy Female Sexuality Questionnaire. Also, EPT was associated with a significant improvement in a woman's level of sexual interest, frequency of orgasm, and pleasure of orgasm. There was no effect of EPT use on coital frequency. The EPT group had significant improvement in receptivity/initiation and relationship satisfaction, although not in other BISF-W domains, versus placebo (BISF-W analysis) and significant improvement versus placebo on most Women's Health Questionnaire responses. CONCLUSIONS: EPT provided a statistically significant improvement compared with placebo in dyspareunia, sexual experience, and quality of life as measured in this study. In general, EPT also improved self-reported sexual perception and enjoyment significantly compared with placebo.

Haines, C., S. L. Yu, et al. (2009). "Micro-dose transdermal estradiol for relief of hot flashes in postmenopausal Asian women: a randomized controlled trial." *Climacteric* 12(5): 419-26.

OBJECTIVES: To compare the effect of micro-dose transdermal estradiol and placebo on the incidence and severity of menopausal symptoms and well-being in postmenopausal Asian women with vasomotor symptoms. DESIGN: Multicenter, double-blind, randomized, placebo-controlled study. RESULTS: Of 165 subjects randomized to estradiol 0.014 mg/day or placebo for 12 weeks, 80 per group were included in the analysis. Groups were comparable at baseline, although time since menopause was slightly shorter in the estradiol group. There was a greater reduction in mean weekly hot flashes at week 12 in the estradiol group (55%) than the placebo group (40%; $p < 0.01$), which was evident by week 4. A similar pattern was seen for moderate and severe hot flashes (-58% vs. -39%, respectively). Reductions were statistically significant at weeks 4, 8, and 12. Vaginal pH fell significantly in the estradiol group by week 4 and then remained stable throughout the treatment period, but there were no significant changes in the placebo group. Vaginal maturation value increased more in the estradiol than the placebo group ($p < 0.001$). Few subjects had vaginal bleeding or spotting. Quality of life improved similarly in both groups. Urogenital symptoms improved considerably from baseline in both treatment groups, with no significant differences. Eight subjects experienced treatment-related adverse events (seven in the estradiol group). CONCLUSIONS: In Asian women, micro-dose estradiol was significantly superior to placebo in improving vasomotor symptoms. The bleeding profile was comparable with that of placebo. Micro-dose estradiol was safe and well tolerated in Asian women.

Honjo, H. and Y. Taketani (2009). "Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial." *Climacteric* 12(4): 319-28.

OBJECTIVES: To investigate two different doses of oral estradiol to reduce the number of hot flashes in Japanese women with climacteric symptoms. METHODS: Women ($n = 211$) aged 40-64 years who had experienced natural menopause or bilateral oophorectomy, with $> \text{ or } =$ three moderate/severe hot flashes per day in the week before study, were randomized to receive micronized estradiol (E2) 0.5 or 1.0 mg or placebo once daily for 8 weeks. The primary efficacy endpoint was percentage change in mean daily number of hot flashes over 7 days from baseline to final examination. RESULTS: Percentage change in mean daily number of hot flashes at final examination was similar for E2 0.5 mg and E2 1.0 mg (-79.58 +/- 28.29% vs. -82.49 +/- 25.31%, $p = 0.555$) but was significantly lower with placebo (-57.89 +/- 34.15%, $p < 0.001$ vs. E2, both doses). There was no significant difference in number of treatment-related adverse events occurring in the E2 0.5 and 1.0 mg groups (25% and 36.6%, respectively). The higher E2 dose showed more pronounced effects on symptom severity. CONCLUSIONS: The dose of 0.5 mg/day was effective as the oral E2 starting dose for treatment of hot flashes in Japanese women.

Huang, A. J., G. F. Sawaya, et al. (2009). "Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women." *Menopause* **16**(4): 639-43.

OBJECTIVE: The aim of this study was to examine interactions between hot flushes, estrogen plus progestogen therapy (EPT), and coronary heart disease (CHD) events in postmenopausal women with CHD. **METHODS:** We analyzed data from the Heart and Estrogen/Progestin Replacement Study, a randomized, placebo-controlled trial of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate in 2,763 postmenopausal women with CHD. Hot flushes were assessed at baseline using self-administered questionnaires; women reporting bothersome hot flushes "some" to "all" of the time were considered to have clinically significant flushing. Cox regression models were used to examine the effect of EPT on risk of CHD events among women with and without significant flushing at baseline. **RESULTS:** The mean age of participants was 66.7 +/- 6.8 years, and 89% (n = 2,448) were white. Sixteen percent (n = 434) of participants reported clinically significant hot flushes at baseline. Among women with baseline flushing, EPT increased risk of CHD events nine-fold in the first year compared with placebo (hazard ratio = 9.01; 95% CI, 1.15-70.35); among women without baseline flushing, treatment did not significantly affect CHD event risk in the first year (hazard ratio = 1.32; 95% CI, 0.86-2.03; P = 0.07 for interaction of hot flushes with treatment). The trend toward differential effects of EPT on risk for CHD among women with and without baseline flushing did not persist after the first year of treatment. **CONCLUSIONS:** Among older postmenopausal women with CHD, EPT may increase risk of CHD events substantially in the first year of treatment among women with clinically significant hot flushes but not among those without hot flushes.

Maki, P. M., L. H. Rubin, et al. (2009). "Effects of botanicals and combined hormone therapy on cognition in postmenopausal women." *Menopause* **16**(6): 1167-77.

OBJECTIVE: The aim of this study was to characterize the effects of red clover, black cohosh, and combined hormone therapy on cognitive function in comparison to placebo in women with moderate to severe vasomotor symptoms. **METHODS:** In a phase II randomized, double-blind, placebo-controlled study, 66 midlife women (of 89 from a parent study; mean age, 53 y) with 35 or more weekly hot flashes were randomized to receive red clover (120 mg), black cohosh (128 mg), 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (CEE/MPA), or placebo. Participants completed measures of verbal memory (primary outcome) and other cognitive measures (secondary outcomes) before and during the 12th treatment month. A subset of 19 women completed objective, physiological measures of hot flashes using ambulatory skin conductance monitors. **RESULTS:** Neither of the botanical treatments had an impact on any cognitive measure. Compared with placebo, CEE/MPA led to a greater decline in verbal learning (one of five verbal memory measures). This effect just missed statistical significance (P = 0.057) in unadjusted analyses but reached significance (P = 0.02) after adjusting for vasomotor symptoms. Neither of the botanical treatment groups showed a change in verbal memory that differed from the placebo group (Ps > 0.28), even after controlling for improvements in hot flashes. In secondary outcomes, CEE/MPA led to a decrease in immediate digit recall and an improvement in letter fluency. Only CEE/MPA significantly reduced objective hot flashes. **CONCLUSIONS:** Results indicate that a red clover (phytoestrogen) supplement or black cohosh has no effects on cognitive function. CEE/MPA reduces objective hot flashes but worsens some aspects of verbal memory.

Michael, Y. L., R. Gold, et al. (2010). "Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial." *Menopause* **17**(2): 295-302.

OBJECTIVE: Although estrogen may be linked to biological pathways that maintain higher physical function, the evidence is derived mostly from observational epidemiology and therefore has numerous limitations. We examined whether hormone therapy affected physical function in women 65 to 79 years of age at enrollment. **METHODS:** This study involves an analysis of the

Women's Health Initiative randomized controlled trials of hormone therapy in which 922 nondisabled women who had previous hysterectomies were randomized to receive estrogen therapy or a placebo and 1,458 nondisabled women with intact uteri were randomized to receive estrogen + progestin therapy or a placebo. Changes in physical function were analyzed for treatment effect, and subgroup differences were evaluated. All women completed performance-based measures of physical function (grip strength, chair stands, and timed walk) at baseline. These measures were repeated after 1, 3, and 6 years. **RESULTS:** Overall, participants' grip strength declined by 12.0%, chair stands declined by 3.5%, and walk pace slowed by 11.4% in the 6 years of follow-up (all P values <0.0001). Hormone therapy, as compared with placebo, was not associated with an increased or decreased risk of decline in physical function in either the intention-to-treat analyses or in analyses restricted to participants who were compliant in taking study pills. **CONCLUSIONS:** Hormone therapy provided no overall protection against functional decline in nondisabled postmenopausal women 65 years or older in 6 years of follow-up. This study did not address the influence of hormone therapy for women of younger ages.

Resnick, S. M., M. A. Espeland, et al. (2009). "Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy." Journal of Clinical Endocrinology & Metabolism **94**(11): 4152-61.

CONTEXT: Different menopausal hormone therapies may have varied effects on specific cognitive functions. We previously reported that conjugated equine estrogens (CEE) with medroxyprogesterone acetate had a negative impact on verbal memory but tended to impact figural memory positively over time in older postmenopausal women. **OBJECTIVE:** The objective of the study was to determine the effects of unopposed CEE on changes in domain-specific cognitive function and affect in older postmenopausal women with prior hysterectomy. **DESIGN:** This was a randomized, double blind, placebo-controlled clinical trial. **SETTING:** The study was conducted at 14 of 40 Women's Health Initiative (WHI) clinical centers. **PARTICIPANTS:** Participants were 886 postmenopausal women with prior hysterectomy, aged 65 yr and older (mean 74 yr), free of probable dementia, and enrolled in the WHI and WHI Memory Study (WHIMS) CEE-Alone trial for a mean of 3 yr and followed up for a mean of 2.70 yr. **INTERVENTION:** Intervention was 0.625 mg of CEE daily or placebo. **MAIN OUTCOME MEASURES:** Annual rates of change in specific cognitive functions and affect, adjusted for time since randomization, were measured. **RESULTS:** Compared with placebo, unopposed CEE was associated with lower spatial rotational ability (P < 0.01) at initial assessment (after 3 yr of treatment), a difference that diminished over 2.7 yr of continued treatment. CEE did not significantly influence change in other cognitive functions and affect. **CONCLUSIONS:** CEE did not improve cognitive functioning in postmenopausal women with prior hysterectomy. CEE was associated with lower spatial rotational performance after an average of 3 yr of treatment. Overall, CEE does not appear to have enduring effects on rates of domain-specific cognitive change in older postmenopausal women.