

# **Drug Class Review on Estrogens**

**Update #4: Preliminary Scan Report**

May 2009

**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.**

Oregon Evidence-based Practice Center  
Oregon Health & Science University  
Mark Helfand, MD, MPH, Director  
Marian S McDonagh, Principal Investigator,  
Drug Effectiveness Review Project

Scan prepared by Nancy Lee, PharmD, BCPS



## 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

Update #3, October 2007 (searches through March 2007)

## 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

**METHODS****Literature Search**

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from March 2007 through April 20, 2009 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. 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**

Searches resulted in 164 citations. Of those, there are 33 new potentially relevant trials and table 1 summarizes the studies (see Appendix A for abstracts).

**Table 1. Potentially relevant trials of drugs on estrogens**

<b>Study year</b>	<b>Comparison</b>	<b>N, duration</b>	<b>Focus</b>
Bachmann 2008	Vaginal estradiol (E2) vs. placebo	230, 12 weeks	Atrophic vaginitis
Bachmann 2008	Transdermal 17-beta-estradiol/levonorgestrel vs. placebo	425, 12 weeks	Moderate-severe vasomotor symptoms
Buster 2008	Transdermal estradiol spray vs. placebo	454, 12 weeks	Moderate-severe vasomotor symptoms
Cameron 2006	Continuous transdermal estradiol/levonorgestrel vs. interrupted estradiol patch x 4 days followed by estradiol/levonorgestrel patch	59, 6 months	Incidence of amenorrhea and relief of vasomotor symptoms
Cieraad 2006	17-beta estradiol/dydrogesterone vs. conjugated equine	169, 6 months	Lipids, vasomotor symptoms, bleeding, tolerability

<b>Study year</b>	<b>Comparison</b>	<b>N, duration</b>	<b>Focus</b>
	estrogen/norgestrel		
De Franciscis 2007	17-beta estradiol/dydrogesterone vs. dydrogesterone	120, 4 weeks	Vasomotor symptoms, bleeding
Endrikat 2007	Estradiol valerate/dienogest vs. placebo	324, 12 weeks	Moderate-severe vasomotor symptoms
Fonseca 2007	17-beta estradiol/norethisterone vs. placebo	40, cross over at 6 months	Sexual function and vasomotor symptoms
Hachul 2008	Estrogen/progesterone vs. placebo	24, 12 weeks	Sleep and cognition
Hedrick 2009	Various doses of estradiol gel 0.1% vs. placebo	488, 12 weeks	Vasomotor symptoms, vaginal atrophy
Heiss 2008	Conjugated equine estrogen/medroxyprogesterone	Mean 2.4 years of follow-up	To report health outcomes at 3yrs after intervention was stopped (WHI)
Huang 2007	Transdermal estradiol vs. placebo	382, 12 months	Bone turnover and BMD (appears to be post-hoc analysis from ULTRA trial)
Kalleinen 2008	Cyclic estrogen-progestin vs. placebo	25, 6 months (before-after)	Sleep
Lee 2007	Estradiol/drospirenone vs. placebo	90, 4 months	Vasomotor symptoms
Limpaphayom 2006	Various doses of conjugated estrogen/medroxyprogesterone	1028, 24 weeks	Quality of life in 9 ethnic groups of Asian women
Long 2006	Oral vs. vaginal conjugated equine estrogen	57, 3 months	Sexual function
Maki 2007	Conjugated equine estrogen/medroxyprogesterone vs. placebo	180, 4 months	Cognition, sexual function, quality of life, sleep
Marinho 2008	17-beta estradiol vs. placebo	74, NR	Cognitive function, depression
Mattsson 2007	Various doses of oral estradiol valerate/medroxyprogesterone (continuous HRT)	459, 12 months	Moderate-severe vasomotor symptoms
Moriyama 2008	Estradiol valerate vs. exercise	44, 6 months	Health-related quality of life, vasomotor symptoms
Odabasi 2007	Intranasal vs. transdermal 17-beta estradiol+vaginal progesterone	80, 12 weeks	Vasomotor symptoms
Panay 2007	Various doses of low dose 17-beta estradiol/norethisterone vs. placebo	577, 6 months	Vasomotor symptoms
Pefanco 2007	Micronized 17-beta estradiol vs. placebo	57, 3 years	Cognitive function including depression
Pitkin	Various doses of continuous	NR, 12 months	Health related quality of life

Study year	Comparison	N, duration	Focus
2007	combined HRT consisting of estradiol valerate/medroxyprogesterone		
Prior 2007	Conjugated equine estrogen vs. medroxyprogesterone	41, 12 months	Vasomotor symptoms
Samsioe 2007	Transdermal vs. oral estradiol/norethisterone	677, 1 year	Harms (safety), tolerability
Simon 2007	Transdermal estradiol gel vs. placebo	484, 12 weeks	Vasomotor symptoms, vaginal atrophy
Simon 2006	Topical micellar nanoparticle estradiol emulsion vs. placebo	200, 12 weeks	Moderate-severe vasomotor symptoms
Simon 2008	Synthetic conjugated estrogen vs. placebo	42, 12 weeks	Vulvovaginal atrophy
Veerus 2008	Continuous combined HRT vs. no treatment, or hormone therapy vs. placebo	1823, mean follow-up 3.6 yrs	Vasomotor symptoms, quality of life
Welton 2008	Conjugated equine estrogen/medroxyprogesterone vs. placebo	3721, 12 months	Health related quality of life, emotional and physical symptoms using scales
Yang 2007	Various doses of transdermal 17-beta estradiol gel vs. estriol	120, 12 months	Bone mass
Zaborowska 2007	Transdermal placebo vs. estrogen, or estrogen, acupuncture, or placebo	102, 12 weeks	Vasomotor symptoms

### New Drugs or Indications

Three estrogen products were approved since the last update of the report and the results are listed in Table 2. There is also a new indication and dose for Premarin® vaginal cream.

**Table 2. List of new drugs or indications for estrogen products**

Drug	Approval date	Indications
Estradiol (EvaMist®) transdermal spray	July 27, 2007	Treatment of moderate to severe vasomotor symptoms due to menopause
Estradiol 0.1% gel (Divigel®)	June 4, 2007	Treatment of moderate to severe vasomotor symptoms due to menopause
Conjugated estrogen (Premarin®)	New or modified indication, November 7, 2008	This supplemental new drug application provides for the use of Premarin (conjugated estrogens) Vaginal Cream for (1) a new indication, the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause and (2) a new dosing regimen for this indication, 0.5 g Premarin

Drug	Approval date	Indications
		(conjugated estrogens) Vaginal Cream intravaginally twice weekly
Synthetic conjugated estrogens A, vaginal cream	November 28, 2008	Treatment of moderate-severe vaginal dryness and moderate-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

### New Safety Alerts

#### *Postmarketing Experience with Climara® (transdermal system)*

The following adverse reactions have been identified during post approval use of Climara: a few cases in which there was a combination of the symptoms of generalized hives or rash with swelling of the throat or eyelid edema. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### *Postmarketing Experience with Estring® (estradiol vaginal ring)*

A few cases of toxic shock syndrome (TSS) have been reported. A few cases of ring adherence to the vaginal wall, making ring removal difficult, have been reported and a few cases of bowel obstruction have been reported. Patients who have or had liver problems should not use this product.

## Appendix A. Abstracts of potentially relevant new trials of estrogens (N=33)

Bachmann, G., R. A. Lobo, et al. (2008). "Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial." *Obstetrics & Gynecology* **111**(1): 67-76.

**OBJECTIVE:** To evaluate the efficacy of two vaginal doses of estradiol (E2) compared with placebo in the treatment of atrophic vaginitis. **METHODS:** In a multi-center, randomized, double-blind, parallel-group study, 230 postmenopausal women received treatment with 25 mcg or 10 mcg E2 or placebo for 12 weeks. Efficacy was measured through composite score of three vaginal symptoms and grading of vaginal health. Additional analyses included maturation of vaginal and urethral mucosa. Safety assessments included endometrial biopsy, adverse events, changes in laboratory tests, and physical examinations. After 12 weeks of treatment, all patients were switched to the open-label extension and received treatment with 25 mcg E2 up to week 52. **RESULTS:** Vaginal tablets with 25 mcg and 10 mcg E2 showed significant ( $P<.001$ ) improvement in composite score of vaginal health. Other results with 10 mcg E2 were not entirely consistent with those for 25 mcg E2. Over 12 weeks, both active treatments resulted in greater decreases in vaginal pH than placebo. There were no significant differences between the 25 mcg and 10 mcg E2 groups in terms of improvements in maturation value or composite score of three vaginal symptoms. The efficacy was maintained to week 52 with 25 mcg E2. **CONCLUSION:** Vaginal tablets with 25 mcg and 10 mcg E2 provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and increased maturation of the vaginal and urethral epithelium. Those improvements were greater with 25 mcg than with 10 mcg E2. Both doses were effective in the treatment of atrophic vaginitis. **CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00465192 and NCT00464971 **LEVEL OF EVIDENCE:** I.

Bachmann, G. A., M. Schaefer, et al. (2007). "Lowest effective transdermal 17beta-estradiol dose for relief of hot flashes in postmenopausal women: a randomized controlled trial.[see comment]." *Obstetrics & Gynecology* **110**(4): 771-9.

**OBJECTIVE:** To investigate the efficacy of micro-dose transdermal estrogen in relieving menopausal vasomotor symptoms. **METHODS:** A randomized, double-blind, placebo-controlled, multi-center trial. Healthy postmenopausal women with at least seven moderate or severe hot flashes per day for at least 1 week, or at least 50 per week, applied transdermal patches with a nominal delivery of 0.023 mg/d 17beta-estradiol and 0.0075 mg/d levonorgestrel (low-dose E2/levonorgestrel; n=145), 0.014 mg/d E2 (micro-dose; n=147), or placebo (n=133) for 12 weeks. The coprimary efficacy variables were the mean changes from baseline in frequency and severity of moderate and severe hot flashes at the week 4 and 12 endpoints. **RESULTS:** At the week 12 endpoint, mean weekly frequencies of moderate and severe hot flashes were significantly reduced compared with placebo with low-dose E2/levonorgestrel (-51.80;  $P<.001$ ) and micro-dose E2 (-38.46;  $P<.001$ ). Severity scores were also significantly reduced with both treatments compared with placebo. At week 12 endpoint, 41.3% of women receiving micro-dose E2 were treatment responders (75% or more reduction from baseline in hot flush frequency;  $P=.003$  compared with 24.2% placebo). In this group, the mean reduction in moderate and severe hot flashes from baseline was approximately 50% after 2, 70% after 4, 90% after 8, and 95% after 12 weeks. There were no differences between active treatments and placebo regarding adverse events. **CONCLUSION:** Micro-dose E2 (0.014 mg/d) was clinically

and statistically significantly more effective than placebo in reducing the number of moderate and severe hot flushes, with a 41% responder rate, supporting the concept of the lowest effective dose. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00206622

Buster, J. E., W. D. Koltun, et al. (2008). "Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial." *Obstetrics & Gynecology* **111**(6): 1343-51.

**OBJECTIVE:** To investigate the safety and efficacy of a transdermal estradiol (E2) spray in women with postmenopausal vasomotor symptoms. **METHOD:** A randomized, double-blind, placebo-controlled, multicenter, parallel-group clinical trial was conducted. Postmenopausal women (N=454) with at least eight moderate-to-severe hot flushes per day applied daily, one, two, or three E2 (90 microliter spray contains 1.53 mg E2) or matching placebo sprays. The primary efficacy endpoints were mean change from baseline in frequency and severity of moderate-to-severe hot flushes at weeks 4 and 12. **RESULTS:** All three E2 groups showed a significant decrease in hot flushes at weeks 4 and 12 compared with their placebo groups (P<.010). The mean change in frequency at week 12 was eight fewer flushes per day for women in the E2 groups and between four and six fewer flushes for women in the placebo groups. Women in the three- and two-E2 spray groups demonstrated significant (P<.050) reductions in severity score at weeks 4 and 12; women in the one-spray group showed significant reductions at week 5. At week 12, the majority (74-85%) of women on E2 showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic E2 delivery rates at week 12 were approximately 0.021 mg/d, 0.029 mg/d, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively. Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate was similar to placebo (1.3% compared with 1.8%). **CONCLUSION:** The three dose levels of E2 spray achieved efficacy at 0.021-0.040 mg/d delivery rates. The spray is a well-tolerated, new, convenient method of delivering low-dose E2 transdermally. Clinical Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00122200. **LEVEL OF EVIDENCE:** I.

Cameron, S. T., A. F. Glasier, et al. (2006). "Comparison of a transdermal continuous combined and an interrupted progestogen HRT." *Maturitas* **53**(1): 19-26.

**OBJECTIVES:** Pilot study to compare the effects of a continuous combined hormone replacement therapy (HRT) regimen with an interrupted progestogen regimen administered transdermally, upon the endometrium of postmenopausal women, the incidence of amenorrhoea and relief of menopausal symptoms. **METHODS:** Fifty-nine postmenopausal women aged 50-63 years were randomised to either (i) continuous combined regimen: combined oestrogen/progestogen skin patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) or (ii) interrupted regimen: oestrogen-only patches (releasing 80 microg estradiol/day) for 4 days followed by combined oestrogen/progestogen patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) for 3 days, for 6 months. An endometrial biopsy was performed at end of treatment for histological analysis. **RESULTS:** Thirty-three women (56%) completed the study. Significantly higher rates of amenorrhoea were observed with the interrupted than continuous combined regimen (P<0.0001; 25% versus 7% at 6 months). The interrupted regimen was also associated with fewer days of bleeding overall (total 20 versus 44 days during months 4-6; P=0.001). Both regimens improved vasomotor symptoms. No endometrial hyperplasia or atypical changes were observed in endometrial biopsies. **CONCLUSIONS:** Although significantly less bleeding was observed with the

interrupted regimen, it did not have a sufficiently high incidence of amenorrhoea to render it clinically useful.

Cieraad, D., C. Conradt, et al. (2006). "Clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms." Archives of Gynecology & Obstetrics **274**(2): 74-80.

A clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms. **OBJECTIVE:** The objective of the study was to compare the effects of sequential 17beta-oestradiol/dydrogesterone and conjugated equine oestrogens (CEE)/norgestrel on lipid parameters, climacteric symptoms, bleeding patterns and tolerability. **STUDY DESIGN:** This double-blind study was conducted in 193 peri- and post-menopausal women randomised to receive six, 28-day cycles of oral sequential oestradiol 1 mg/dydrogesterone 10 mg or CEE 0.625 mg/norgestrel 0.15 mg. The change from baseline in serum lipids and hot flushes was analysed using a two-way analysis of variance. **RESULTS:** After 24 weeks there was a statistically significant increase in high-density lipoprotein (HDL) cholesterol in the oestradiol/dydrogesterone group and a significant reduction in the CEE/norgestrel group. The difference between the groups was significant (P=0.001). The number of hot flushes was reduced by 86% in both groups; this improvement was supported by the Greene Climacteric Symptom Scale score, the patients' opinion and quality of life assessments. The percentage of women experiencing cyclic bleeding was greater with CEE/norgestrel, as was the mean duration and severity of bleeding. Both treatments were well tolerated. **CONCLUSION:** Oestradiol/dydrogesterone and CEE/norgestrel were equally effective in treating climacteric symptoms, but oestradiol/dydrogesterone showed some advantages in terms of lipid profile and incidence of bleeding.

De Franciscis, P., L. Cobellis, et al. (2007). "Low-dose hormone therapy in the perimenopause." International Journal of Gynaecology & Obstetrics **98**(2): 138-42.

**OBJECTIVE:** To evaluate the effects of low-dose hormone therapy (LD-HT) on bleeding pattern and vasomotor symptoms in perimenopausal women. **METHODS:** In a prospective, open-label study at an University clinic, 120 perimenopausal women suffering from irregular menstrual cycles and hot flushes were randomized to micronized 17beta-estradiol 1 mg plus dydrogesterone 10 mg sequential added (LD-HT; group A: 60 subjects) or dydrogesterone 10 mg from day 15 to 28 (group B: 60 subjects). Number and severity of hot flushes and bleeding pattern were assessed throughout the study. **RESULTS:** Women in group A experienced a significant reduction in number of hot flushes while no significant variation was observed in group B. The incidence of cyclic bleeding was 86% in group A and 76% in group B, the mean duration was significantly lower in group A than in group B. **CONCLUSIONS:** LD-HT may control both irregular bleeding and hot flushes in perimenopausal women.

Endrikat, J., T. Graeser, et al. (2007). "A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined hormone therapy preparation containing 1mg estradiol valerate/2mg dienogest on hot flushes in postmenopausal women." Maturitas **58**(2): 201-7.

**OBJECTIVES:** To evaluate the effects of an estrogen-reduced, continuous-combined hormone therapy preparation (HT) containing 1mg estradiol valerate (1EV) and 2mg dienogest

(2DNG) on the number of moderate and severe hot flashes. **METHODS:** This study compared the effects of an oral continuous-combined HT containing 1mg EV and 2mg DNG (1EV/2DNG) with those of placebo. The planned treatment duration was 12 weeks. Data were obtained from 324 postmenopausal women. The primary efficacy variable was the individual relative change of the mean number of moderate and severe hot flashes per week. Weeks 5-12 of treatment were compared with the 2 weeks preceding the treatment phase. **RESULTS:** Moderate and severe hot flashes were reduced by 80.8+/-30.9% in the 1EV/2DNG group and by 41.5+/-39.4% in the placebo group. This difference was statistically significant ( $p<0.0001$ ; Wilcoxon's rank sum test). The incidence of all types of hot flashes (mild+moderate+severe) was reduced by 75.2+/-30.2% under 1EV/2DNG and by 35.3+/-37.0% under placebo. In the subset of non-hysterectomized women, exposure to 1EV/2DNG led to 2.4+/-6.2 days with bleeding in the reference period of 84 days of treatment, versus 0.3+/-1.3 days in the placebo group. The safety profile of 1EV/2DNG was very similar to that of placebo. **CONCLUSIONS:** Continuous-combined HT preparation with 1mg EV and 2mg DNG induced a significant reduction of moderate and severe hot flashes compared to placebo ( $p<0.0001$ ). Thus, this low-estrogen preparation is an effective and safe option for HT.

Fonseca, A. M., V. R. Bagnoli, et al. (2007). "Monophasic estrogen-progestogen therapy and sexuality in postmenopausal women." Clinical Drug Investigation **27**(2): 131-7.

**OBJECTIVE:** This study aimed to evaluate the effects of monophasic estrogen-progestogen therapy on the sexuality and climacteric symptoms of postmenopausal women. **PATIENTS AND METHODS:** A prospective, randomised, double-blind, crossover, placebo-controlled, single-centre study was carried out over a total of 12 consecutive months in 40 postmenopausal women with an intact uterus who had no contraindications to hormone therapy. Patients received 17beta-estradiol 2mg in combination with norethisterone acetate 1mg (Cliane) daily for 6 months or one placebo tablet daily for 6 months. The tablets were identical in appearance. After 6 months, the groups were crossed over and the patients were followed up for another 6 months. The groups were homogenous with respect to age, height, bodyweight, body mass index and race. For the statistical analysis, the group receiving hormone therapy was referred to as group A and the placebo group was designated group B, irrespective of the placebo/hormone therapy sequence. **RESULTS:** In group A there were fewer hot flashes ( $F=22.85$ ,  $p<0.01$ ) and an improvement in sexual interest ( $F=5.55$ ,  $p<0.05$ ). The sequence in which the medication was received resulted in a statistically significant difference with respect to dyspareunia ( $F=9.65$ ,  $p<0.01$ ) and satisfaction with the duration of penetration ( $F=6.58$ ,  $p<0.05$ ). In the inpatient analysis of variation with respect to orgasmic capability and the presence of dialogue with partner regarding the couple's sexual life, whether the placebo was taken prior to or following hormone therapy was significant ( $F=17.12$ ,  $p<0.001$  and  $F=7.10$ ,  $p<0.05$ , respectively). **CONCLUSIONS:** Monophasic estrogen-progestogen therapy has a beneficial effect on sexuality and on hot flashes in postmenopausal women.

Hachul, H., L. R. A. Bittencourt, et al. (2008). "Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women." International Journal of Gynaecology & Obstetrics **103**(3): 207-12.

**OBJECTIVE:** To investigate the effects of estrogen and progesterone on sleep in postmenopausal women. **METHOD:** The 33 participants were randomly assigned to an estrogen or placebo group after undergoing clinical and hormonal assessments and a polysomnogram, and they underwent the same tests again after 12 weeks. Then, while still taking estrogen or placebo,

they all received progesterone for another 12 weeks and underwent a final polysomnogram. **RESULTS:** Estrogen plus progesterone was more effective than estrogen alone in decreasing the prevalence of periodic limb movement (PLM) (8.1% vs 2.8%), hot flashes (14.2% vs 0%), and bruxism (11.1% vs 0%) at night, or somnolence and attention difficulty during the day. The prevalences of breathing irregularities, arousal from sleep, anxiety, and memory impairment were decreased in both groups following progesterone treatment. **CONCLUSION:** While not significantly affecting sleep quality, hormone therapy decreased the prevalence of arousal in both groups and that of PLM in the group treated with estrogen plus progesterone.

Hedrick, R. E., R. T. Ackerman, et al. (2009). "Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women." *Menopause* **16**(1): 132-40.

**OBJECTIVE:** The objective of this study was to evaluate the efficacy and safety of three doses of estradiol gel 0.1% (Divigel, a novel formulation consisting of 1 mg estradiol per 1 g transdermal gel) to reduce the frequency and severity of vasomotor symptoms and signs of vulvar and vaginal atrophy associated with menopause. **DESIGN:** A total of 488 postmenopausal women were evaluated in a 12-week study comparing placebo with estradiol gel 0.1% at doses of 1.0, 0.5, and 0.25 mg/day, with estimated daily deliveries of 0.027, 0.009, and 0.003 mg of estradiol, respectively. Primary endpoints were the change from baseline in daily frequency and severity of moderate to severe vasomotor symptoms. Change from baseline in the signs of vulvar and vaginal atrophy (vaginal pH and percentage of superficial cells) was also assessed. **RESULTS:** Treatment with estradiol gel 0.1% showed statistically significant reductions in frequency and severity of vasomotor symptoms from baseline compared with placebo as early as Week 2 that were maintained throughout treatment. Signs of vulvar and vaginal atrophy were also significantly improved from baseline with all three doses of estradiol gel 0.1% compared with placebo. **CONCLUSIONS:** Low-dose transdermal estradiol gel 0.1% is an effective treatment for relief of vasomotor symptoms, as well as signs of vulvar and vaginal atrophy, associated with menopause. Estradiol gel 0.1% offers multiple dosing options to individualize patient therapy, including the lowest available effective dose (0.25 mg estradiol, delivering 0.003 mg/d estradiol) to treat the vasomotor symptoms of menopause.

Heiss, G., R. Wallace, et al. (2008). "Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin.[see comment]." *JAMA* **299**(9): 1036-45.

**CONTEXT:** The Women's Health Initiative (WHI) trial of estrogen plus progestin vs placebo was stopped early, after a mean 5.6 years of follow-up, because the overall health risks of hormone therapy exceeded its benefits. **OBJECTIVE:** To report health outcomes at 3 years (mean 2.4 years of follow-up) after the intervention was stopped. **DESIGN, SETTING, AND PARTICIPANTS:** The intervention phase was a double-blind, placebo-controlled, randomized trial of conjugated equine estrogens (CEE) 0.625 mg daily plus medroxyprogesterone acetate (MPA) 2.5 mg daily, in 16,608 women aged 50 through 79 years, recruited by 40 centers from 1993 to 1998. The postintervention phase commenced July 8, 2002, and included 15 730 women. **MAIN OUTCOME MEASURES:** Semi-annual monitoring and outcomes ascertainment continued per trial protocol. The primary end points were coronary heart disease and invasive breast cancer. A global index summarizing the balance of risks and benefits included the 2 primary end points plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. **RESULTS:** The risk of cardiovascular events after the

intervention was comparable by initial randomized assignments, 1.97% (annualized rate) in the CEE plus MPA (343 events) and 1.91% in the placebo group (323 events). A greater risk of malignancies occurred in the CEE plus MPA than in the placebo group (1.56% [n = 281] vs 1.26% [n = 218]; hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.04-1.48). More breast cancers were diagnosed in women who had been randomly assigned to receive CEE plus MPA vs placebo (0.42% [n = 79] vs 0.33% [n = 60]; HR, 1.27; 95% CI, 0.91-1.78) with a modest trend toward a lower HR during the follow-up after the intervention. All-cause mortality was somewhat higher in the CEE plus MPA than in the placebo group (1.20% [n = 233] vs 1.06% [n = 196]; HR, 1.15; 95% CI, 0.95-1.39). The global index of risks and benefits was unchanged from randomization through March 31, 2005 (HR, 1.12; 95% CI, 1.03-1.21), indicating that the risks of CEE plus MPA exceed the benefits for chronic disease prevention. **CONCLUSIONS:** The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal and nonfatal malignancies occurred after the intervention in the CEE plus MPA group and the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00000611.

Huang, A. J., B. Ettinger, et al. (2007). "Endogenous estrogen levels and the effects of ultra-low-dose transdermal estradiol therapy on bone turnover and BMD in postmenopausal women." Journal of Bone & Mineral Research **22**(11): 1791-7.

In a randomized controlled trial of a 0.014 mg/d transdermal estradiol patch, serum bone turnover markers decreased to a greater degree in postmenopausal women with lower versus higher endogenous estradiol levels. This suggests that the protective effects of ultra-low-dose estrogen therapy on the postmenopausal skeletal health may depend critically on women's endogenous estrogen levels before treatment. **INTRODUCTION:** Postmenopausal women with very low or undetectable estradiol levels have lower BMD, increased bone turnover, and increased risk of hip and vertebral fracture. We assessed whether the effects of ultra-low-dose 0.014 mg/d transdermal estradiol (Menostar; Berlex, Montvale, NJ, USA) on bone turnover and BMD are influenced by endogenous estradiol levels. **MATERIALS AND METHODS:** We analyzed data from postmenopausal women (mean age, 66 yr) randomized to an 0.014-mg/d transdermal estradiol patch or placebo in the ultra-low-dose transdermal estrogen (ULTRA) trial. The free estradiol index (FEI), calculated as the ratio of total estradiol (by mass spectrometry) to sex hormone-binding globulin (SHBG; by immunoradiometric assay) x 100, was used to estimate bioavailable estradiol at baseline. Among the 382 women who adhered to  $\geq 80\%$  of study medication, we examined change in serum osteocalcin and bone-specific alkaline phosphatase levels at 12 mo and total hip and lumbar spine BMD at 24 mo in each quintile of FEI. **RESULTS:** Compared with women in the highest quintile of FEI, those in the lowest quintile of FEI had a 26% greater reduction in bone-specific alkaline phosphatase and 15% greater reduction in osteocalcin in response to ultra-low estradiol treatment (p for trend across quintiles < 0.05). There was a trend toward greater improvement in total hip BMD (p = 0.06) but not spine BMD (p = 0.90) in those with lower versus higher FEI levels. **CONCLUSIONS:** The beneficial effects of ultra-low-dose 0.014-mg/d transdermal estrogen therapy on skeletal health may depend critically on women's endogenous estrogen levels before treatment.

Kalleinen, N., O. Polo, et al. (2008). "The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women." Climacteric **11**(3): 233-43.

**OBJECTIVE:** In this prospective randomized, placebo-controlled and double-blind study, the objective was to investigate the effects of estrogen-progestin treatment (EPT) on sleep in pre- and postmenopausal women. **DESIGN:** Seventeen premenopausal (aged 45-51 years) and 18 postmenopausal (aged 58-70 years) women were studied in a sleep laboratory for two nights (one night for adaptation and one study night) before and after 6 months of treatment with EPT or placebo. During the treatment period, premenopausal women received cyclic EPT or placebo and the postmenopausal women continuous EPT or placebo. Polysomnography and questionnaires were used to evaluate sleep and well-being. **RESULTS:** At the end of the treatment period, premenopausal women receiving EPT had more awakenings from stage 1 sleep ( $p = 0.047$ ) and postmenopausal women with EPT had a greater total number of awakenings ( $p = 0.031$ ) than the corresponding placebo group. Further, sleepiness decreased less in the premenopausal EPT group than in the placebo group ( $p = 0.031$ ). In postmenopausal women, EPT decreased and placebo slightly increased slow wave activity during the second non-rapid eye movement sleep episode ( $p = 0.046$ ). **CONCLUSIONS:** In premenopausal and late postmenopausal women, EPT had only random and marginal effects on sleep. Although the limited findings were mostly unfavorable for EPT, one cannot conclude that EPT deteriorates sleep. Further, neither middle-aged cycling premenopausal women nor older postmenopausal women benefit from estrogen-progestin treatment in terms of their sleep quality.

Lee, B. S., B. M. Kang, et al. (2007). "Efficacy and tolerability of estradiol 1 mg and drospirenone 2 mg in postmenopausal Korean women: a double-blind, randomized, placebo-controlled, multicenter study." *Maturitas* **57**(4): 361-9.

**OBJECTIVES:** The aim of this study was to demonstrate that the therapeutic efficacy of an estradiol 1mg/drospirenone 2mg (E2/DRSP) preparation is superior to a placebo in postmenopausal Korean women with hot flushes and other climacteric symptoms, and to demonstrate that this treatment is both safe and tolerable. **METHODS:** This was a double-blind, randomized, placebo-controlled, multicenter study over four 28-day treatment cycles. A total of 158 subjects were screened and 90 women were randomized into two treatment groups (E2/DRSP group,  $n=45$ ; placebo group,  $n=45$ ). The primary efficacy parameter was the individual relative change of hot flushes. The secondary efficacy parameters such as other climacteric, urogenital symptoms and vaginal bleeding patterns were also evaluated, and the occurrence of any adverse events was noted. In addition, physical, gynecological examinations and laboratory analyses were performed at the beginning and end of the study. **RESULTS:** The mean number of hot flushes per week during treatment weeks 3-16 decreased by 48.1% during treatment with placebo, and by 84.4% during treatment with E2/DRSP ( $p<0.001$ ). The E2/DRSP combination also reduced the incidence and intensity of menopausal symptoms in postmenopausal women. Most of adverse events was mild or moderate degree of intensity. None of the parameters measured in the study, including laboratory analyses, physical and gynecological examinations, vital signs, and weight, led to any concerns of safety. **CONCLUSIONS:** The E2 1mg/DRSP 2mg combination tested in the study was efficacious and safe in the treatment of hot flushes and other climacteric symptoms in postmenopausal Korean women.

Limpaphayom, K. K., M. S. Darmasetiawan, et al. (2006). "Differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study." *Climacteric* **9**(3): 204-14.

**OBJECTIVES:** To assess the prevalence of four categories (domains) of menopausal symptoms as markers for quality of life in nine ethnic groups of Asian women. To evaluate changes in quality of life (MENQOL scores) in Asian women following hormone therapy.

**METHODS:** A prospective, randomized, double-blind, multinational clinical trial in 1028 healthy postmenopausal women of nine ethnic groups from 11 Asian countries/regions. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5. At baseline and at the end of weeks 4, 12 and 24 following the start of therapy, the study participants were asked to record, on a menopause-specific quality of life (MENQOL) questionnaire, 29 menopausal symptoms, as experienced during the preceding month. The symptoms were categorized into four domains: vasomotor, psychosocial, physical and sexual.

**RESULTS:** The baseline (pretreatment) symptom scores in each of the four domains varied substantially among the different ethnic groups, ranging from 2.21 to 5.71 in the vasomotor, 2.37-5.96 in the psychosocial, 2.66-5.39 in the physical, and 2.11-6.55 in the sexual domain. Overall, Vietnamese and Pakistani women had the highest baseline scores, i.e. were most afflicted by each set of symptoms in a given domain, and Indonesian, Malay, Taiwanese and Thai women were least afflicted. In the overall population, intervention resulted in statistically significant decreases in the scores of all four domains within 4 weeks of intervention. The beneficial effects were similar in the three dose groups.

**CONCLUSIONS:** The prevalence of four domains of menopausal symptoms, representative of quality of life as recorded on a MENQOL questionnaire, varies considerably among ethnic groups of Asian women. The MENQOL scores in the overall population were significantly lowered in the course of the study, indicating an improvement in quality of life. In the absence of a placebo group, the relative contribution of hormones and placebo in our intervention is unknown.

Long, C.-Y., C.-M. Liu, et al. (2006). "A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women.[see comment]." *Menopause* **13**(5): 737-43.

**OBJECTIVE:** To compare the effects of oral and vaginal estrogen therapy (ET) on the vaginal blood flow and sexual function in postmenopausal women with previous hysterectomy.

**DESIGN:** Fifty-seven women were randomized to receive either oral (0.625 mg of conjugated equine estrogens per tablet; n = 27) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 30) estrogen administered once daily. All women underwent estradiol measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire before and 3 months after ET.

**RESULTS:** A higher serum level of estradiol was noted in the oral group compared with the topical group after 3 months of ET. There were significant increases in the number of vaginal vessels and the minimum diastole ( $P < 0.01$ ), and marked decreases of pulsatility index values ( $P < 0.01$ ) in both groups after ET. Regarding the systolic peak, we found a significant decrease only in the topical group ( $P < 0.05$ ). Although the post-ET prevalence of anorgasmia decreased significantly in both groups ( $P < 0.05$ ), changes in other domains, including the rates of low libido and coital frequency, were not statistically significant ( $P > 0.05$ ). In the topical group, ET improved sexual function on the vaginal dryness and dyspareunia domains in a statistically significant manner ( $P < 0.05$ ), but this was not the case in the oral group ( $P > 0.05$ ). However, the efficacy of oral ET for vaginal dryness and dyspareunia reached 80% and 70.6%, respectively. The corresponding figures of the topical ET were 79.2% and 75%.

**CONCLUSIONS:** The results of our study suggest that ET alone in hysterectomized

postmenopausal women increases the vaginal blood flow and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol.

Maki, P. M., M. J. Gast, et al. (2007). "Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial." *Neurology* **69**(13): 1322-30.

**OBJECTIVE:** To evaluate the effects of hormone therapy (HT) on cognition and subjective quality of life (QoL) in recently postmenopausal women with cognitive complaints. **METHODS:** Cognitive Complaints in Early Menopause Trial (COGENT) was a randomized, double-blind, placebo-controlled, multicenter, pilot study of 180 healthy postmenopausal women aged 45 to 55 years, randomly assigned to receive either placebo or conjugated equine estrogen 0.625 mg/medroxyprogesterone acetate 2.5 mg for 4 months. Outcome measures included memory, subjective cognition, QoL, sexuality, and sleep, which were assessed at baseline and month 4. **RESULTS:** The study was terminated before the expected final sample size of 275 due to a decrease in enrollment coinciding with the publication of findings from the Women's Health Initiative. There were no differences between groups on any cognitive or QoL measures, except for an increase in sexual interest and thoughts with HT. Modest negative effects on short- and long-term verbal memory approached significance ( $p < 0.10$ ). Women with baseline vasomotor symptoms (VMS) showed a decrease in VMS and an improvement in general QoL, but no cognitive benefit vs placebo. **CONCLUSIONS:** With the power to detect an effect size of  $\geq 0.45$ , this study suggests potential modest negative effects on verbal memory that are consistent with previous hormone therapy trials in older women.

Marinho, R. M., J. M. Soares, Jr., et al. (2008). "Effects of estradiol on the cognitive function of postmenopausal women." *Maturitas* **60**(3-4): 230-4.

**OBJECTIVE:** To analyze the effect of estrogen on the cognitive function of postmenopausal women through psychometric tests. **METHODS:** Seventy-four postmenopausal women were divided into two groups: (G1) estrogen group ( $n = 34$ ), treated with 2 mg 17 beta-estradiol; (G2) placebo group ( $n = 31$ ), treated with inactive substance. All the participants were submitted, before and after treatment, to psychometric tests, Greene's Scale of Climacteric Symptoms and the Hamilton Scale for depression. Statistical analysis was performed using the Mann-Whitney test and Student's t-test. In order to evaluate the degree of improvement of symptoms or depression after estrogen treatment, Spearman's correlation coefficient was calculated. **RESULTS:** A few psychometric tests (immediate and late recall of story, Trailmaking A and B, FAS, Stroop, Bells tests) showed post-intervention improvement, but these were not significant when compared to the placebo group's data. The estrogen group's climacteric symptoms were mitigated in comparison to placebo's, but there was no significant difference between the two groups on the Hamilton Scale. Reduction in climacteric symptoms was associated with improvement in executive function performance as evaluated by the Stroop test. **CONCLUSION:** Our results suggest estrogen improves the cognitive function, possibly due to a decrease in vasomotor symptoms.

Mattsson, L. A., S. Skouby, et al. (2007). "Efficacy and tolerability of continuous combined hormone replacement therapy in early postmenopausal women." *Menopause International* **13**(3): 124-31.

**OBJECTIVE:** Continuous combined hormone replacement therapy (ccHRT) based on estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) is effective for relief of menopausal symptoms three years or more after the menopause. This study was undertaken to examine the efficacy and tolerability of ccHRT in early postmenopausal women (last menstrual period 1.3 years before study entry). **STUDY DESIGN:** This was a 52-week, randomized, double-blind, multinational study of ccHRT comprising three different dose combinations of E2V/MPA in 459 early postmenopausal non-hysterectomized women experiencing 30 or more moderate to severe hot flushes a week and/or vasomotor symptoms requiring treatment. **MAIN OUTCOMES MEASURES:** The primary endpoint was change in frequency and severity of moderate to severe hot flushes at 12 weeks. Secondary outcome measures included number of bleeding days and evaluation of tolerability. **RESULTS:** The frequency of hot flushes was reduced by  $\geq 70\%$  after one month ( $P < 0.001$  for all doses at week 2 onwards), with little evidence of statistically different dose effects. Severity of flushing was also attenuated by ccHRT. Mean number of bleeding days fell to  $< 1$  per 28-day cycle at 52 weeks. Rates of amenorrhoea approached 80-90% at the end of the study, but were significantly lower at several time points with the highest-dose regimen (2 mg E2V + 5 mg MPA) than with the lower-dose options (1 mg E2V + 2.5 mg MPA and 1 mg E2V + 5 mg MPA;  $P < 0.05$ ). Adverse events declined in frequency over time with all regimens but throughout the study were more numerous with the highest-dose regimen than with lower doses ( $P = 0.0002$ ). **CONCLUSIONS:** Continuous combined HRT was effective for the relief of climacteric symptoms in early postmenopausal women and was well tolerated.

Moriyama, C. K., B. Oneda, et al. (2008). "A randomized, placebo-controlled trial of the effects of physical exercises and estrogen therapy on health-related quality of life in postmenopausal women.[see comment]." *Menopause* **15**(4 Pt 1): 613-8.

**OBJECTIVE:** The purpose of this study was to evaluate the isolated and associated effects of estrogen therapy (estradiol valerate 1 mg/d orally) and physical exercise (moderate aerobic exercise, 3 h/wk) on health-related quality of life (HRQOL) and menopausal symptoms among women who had undergone hysterectomy. **DESIGN:** A 6-month, randomized, double-blind, placebo-controlled clinical trial with 44 postmenopausal women who had undergone hysterectomy. The interventions were physical exercise and hormone therapy ( $n = 9$ ), being sedentary and hormone therapy ( $n = 14$ ), physical exercise and placebo ( $n = 11$ ), and being sedentary and placebo ( $n = 10$ ). HRQOL was assessed by a Brazilian standard version of the Medical Outcome Study Short-Form Health Survey and symptoms by Kupperman Index at baseline and after 6 months. **RESULTS:** There was a decrease in symptoms in all groups, but only groups who performed physical exercise showed an increase in quality of life. Analysis of variance showed that changes in physical functioning ( $P = 0.001$ ) and bodily pain ( $P = 0.012$ ) scores over the 6-month period differed significantly between women who exercised and women who were sedentary, regardless of hormone therapy. Hormone therapy had no effect, and there was also no significant association between physical exercise and hormone therapy in HRQOL. **CONCLUSIONS:** Physical exercises can reduce menopausal symptoms and enhance HRQOL, independent of whether hormone therapy is taken.

Odabasi, A. R., H. Yuksel, et al. (2007). "A prospective randomized comparative study of the effects of intranasal and transdermal 17 beta-estradiol on postmenopausal symptoms and vaginal cytology." *Journal of Postgraduate Medicine* **53**(4): 221-7.

**CONTEXT:** Investigating the adverse effects of oral hormone replacement therapy (HRT), the clinical effectiveness of alternative combinations and route of administrations. **AIM:** To compare the effects of intranasal and transdermal 17 beta-estradiol combined with vaginal progesterone on vasomotor symptoms and vaginal cytology. **SETTINGS AND DESIGN:** A 12-week, prospective, randomized comparative study was conducted between July 2005 and September 2006. **MATERIALS AND METHODS:** Eighty postmenopausal women aged between 42-57 years, who had scores of  $>$  or  $=1.7$  on the menopause rating scale-I (MRS-I) items "1-6", were randomly assigned to receive intranasal (300 microg/day, n =40) or transdermal (50 microg/day, n =40) 17 beta-estradiol continuously. All patients also received a vaginal progesterone gel twice weekly. Vasomotor symptoms were evaluated at weeks 0, 4, 8 and 12. Vaginal maturation index (VMI) was evaluated at weeks 0 and 12 of the study. **STATISTICAL ANALYSES:** The Mann-Whitney U and the Wilcoxon tests were used.  $P < 0.05$  was regarded as significant. **RESULTS:** Thirty-two women in the intranasal and 29 women in the transdermal group completed the study. The total score of the MRS, the sum-scores of Factor 1 "HOT FLUSHES" and Factor 2 "PSYCHE" significantly decreased in both groups at week 4. Factor 3 "ATROPHY" scores significantly decreased only in the transdermal group at week 12. The VMI showed no changes within and between the two groups at the end of the study. **CONCLUSION:** Intranasal and transdermal 17beta-estradiol combined with vaginal progesterone gel as a continuous HRT caused a similar decrease in vasomotor symptoms but did not have any significant effect on VMI after 12 weeks of treatment in this study population.

Panay, N., O. Ylikorkala, et al. (2007). "Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief." *Climacteric* **10**(2): 120-31.

**OBJECTIVE:** To evaluate the efficacy of two ultra-low-dose 17beta-estradiol plus norethisterone acetate (NETA) treatment regimens for relieving menopausal symptoms. **DESIGN:** A total of 577 postmenopausal women were enrolled, in three treatment groups in a double-blind, randomized, placebo-controlled study of 0.5 mg 17beta-estradiol + 0.1 mg NETA or 0.5 mg 17beta-estradiol + 0.25 mg NETA or placebo. Participants returned at weeks 4, 8, 12 and 24 for climacteric complaint evaluation based on a daily diary vasomotor symptom record. Patients were assessed by the Greene Climacteric Scale and urogenital symptoms were also evaluated. **RESULTS:** Treatment with ultra-low-dose 0.5 mg 17beta-estradiol + 0.1 mg NETA (0.1 Group) or 0.5 mg 17beta-estradiol + 0.25 mg NETA (0.25 Group) effectively reduced the severity and number of hot flushes within the initial weeks of therapy. Compared to placebo, a rapid, statistically significant decrease in the frequency and severity of hot flushes was achieved by week 3, followed by further improvement which continued throughout the study. There were no statistically significant differences between the active treatment arms. **CONCLUSIONS:** The data show that both ultra-low-dose regimens are effective in reducing the severity and number of hot flushes compared to placebo, with good safety profiles.

Pefanco, M. A., A. M. Kenny, et al. (2007). "The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women." *Journal of the American Geriatrics Society* **55**(3): 426-31.

**OBJECTIVES:** To evaluate the effect of ultra-low-dose (0.25 mg/d) micronized 17beta-estradiol on cognitive function in older postmenopausal women. **DESIGN:** Randomized, placebo-controlled trial conducted for 3 years. **SETTING:** Academic health center in greater Hartford, Connecticut. **PARTICIPANTS:** Fifty-seven healthy, community-dwelling, older postmenopausal women. **INTERVENTION:** Women received 0.25 mg/d of micronized 17beta-

estradiol (estrogen therapy (ET), n=32) or placebo (n=25); all women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months. MEASUREMENTS: Neuropsychological measures of memory, language, mood, and executive function were collected at baseline, 3 months, and 36 months. Measures of executive function included the Controlled Oral Word Association Test, the Trail Making Test, and the Wisconsin Card Sorting Test. The Boston Naming Test was used to measure language skills. The Symbol Digit Modalities Test was used as a measure of sustained attention. Measures of memory included the Complex Figure Test, Fuld Object Memory Test, and a selected subtest from the Wechsler Memory Scale. Scores from the Geriatric Depression Scale and the Beck Anxiety Inventory were used to assess symptoms of depression. RESULTS: No differences were found between ET and placebo on any of the neurocognitive measures or depression instruments, nor were there any differences when the groups were stratified according to age. CONCLUSION: This small study, which had adequate power to detect change in some but not all domains of cognition tested, revealed that low-dose estrogen neither benefits nor harms cognitive function in older women after 3 years of treatment, but confirmation is needed from larger trials.

Pitkin, J., V. P. Smetnik, et al. (2007). "Continuous combined hormone replacement therapy relieves climacteric symptoms and improves health-related quality of life in early postmenopausal women." Menopause International **13**(3): 116-23.

OBJECTIVE: Hormone replacement therapy (HRT) relieves menopausal symptoms but its effect on health related quality of life (HRQoL) is uncertain. The aim of this study was to assess the effect of three dose regimens of continuous combined HRT, consisting of estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) on HRQoL in early postmenopausal women (last menstrual period 1-3 years before study entry). STUDY DESIGN: This was a 52-week, randomized, double-blind, multinational study comparing E2V (1 mg or 2 mg) plus MPA (2.5 mg or 5 mg) in different dose combinations. The intention-to-treat population comprised 459 women (average age 51.5 years). MAIN OUTCOME MEASURES: HRQoL was assessed by the Women's Health Questionnaire (WHQ), the 15D Questionnaire and a visual analogue scale (VAS). RESULTS: There were improvements on eight of the nine domains of the WHQ with all dose regimens during the first 12 weeks ( $P < 0.0001$ ) and an improvement in the remaining domain (menstrual symptoms) with the lower-dose regimens ( $P < 0.05$ ). These initial improvements in HRQoL were then maintained or augmented over the remainder of the study ( $P < 0.0001$  for change from baseline at 52 weeks for all domains and dose regimens). Mean 15D total score had improved meaningfully and significantly by 12 weeks ( $P < 0.0001$  versus baseline) in all treatment groups and this improvement was maintained thereafter. This improvement in 15D total score was most marked among previous non-users of HRT ( $P < 0.05$  versus previous users). VAS scores recorded significant ( $P < 0.05$ ) reductions in hot flushes, sweating and sleep disturbances in all groups after week 1 and highly significant ( $P < 0.0001$ ) relief of all climacteric symptoms at week 52. CONCLUSION: Continuous combined HRT was associated with pronounced improvement of vasomotor symptoms and HRQoL in this population of early postmenopausal women.

Prior, J. C., J. D. Nielsen, et al. (2007). "Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy." Clinical Science **112**(10): 517-25.

Oestrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and oestrogen/progestin are not suitable for all women. MPA (medroxyprogesterone acetate) reduces

hot flushes, but its effectiveness compared with oestrogen is unknown. In the present study, oral oestrogen [CEE (conjugated equine oestrogen)] and MPA were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-year randomized double-blind parallel group controlled trial in an urban academic medical centre. Participants were healthy menstruating women prior to hysterectomy/ovariectomy for benign disease. A total of 41 women {age, 45 (5) years [value is mean (S.D.)]} were enrolled; 38 women were included in this analysis of daily identical capsules containing CEE (0.6 mg/day) or MPA (10 mg/day). Demographic variables did not differ at baseline. Daily data provided the number of night and day flushes compared by group. The vasomotor symptom day-to-day intensity change was assessed by therapy assignment. Hot flushes/night sweats were well controlled in both groups, one occurred on average every third day and every fourth night. Mean/day daytime occurrences were 0.363 and 0.187 with CEE and MPA respectively, but were not significantly different ( $P=0.156$ ). Night sweats also did not differ significantly ( $P=0.766$ ). Therapies were statistically equivalent (within one event/24 h) in the control of vasomotor symptoms. Day-to-day hot flush intensity decreased with MPA and tended to remain stable with CEE ( $P<0.001$ ). In conclusion, this analysis demonstrates that MPA and CEE are equivalent and effective in the control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

Samsioe, G., V. Dvorak, et al. (2007). "One-year endometrial safety evaluation of a continuous combined transdermal matrix patch delivering low-dose estradiol-norethisterone acetate in postmenopausal women." *Maturitas* **57**(2): 171-81.

**OBJECTIVE:** To evaluate the safety and endometrial protection of low-dose transdermal estradiol (E2)/norethisterone acetate (NETA) patches (Estalis 25/125) in terms of post-treatment incidence of endometrial hyperplasia/cancer after 1 year of treatment in postmenopausal women with intact uteri. **METHODS:** Patients were randomized to receive either transdermal E2/NETA (delivering daily doses of E2 25 microg and NETA 125 microg; applied every 3-4 days) or oral E2/NETA (E2 1mg and NETA 0.5 mg; given daily) in this open-label study. The primary variable was the incidence of endometrial hyperplasia/cancer based on endometrial biopsies; secondary variables included vaginal bleeding/spotting patterns, patch adhesion, safety and tolerability. **RESULTS:** Six hundred and seventy-seven patients were randomized (507 in the transdermal group and 169 in the oral group; one did not receive study drug) and >80% completed the study. There were no cases of endometrial hyperplasia or cancer in either group and the upper limit of the one-sided 95% confidence interval in the transdermal group was 0.85%. Over time, both treatments were associated with a decreasing frequency of spotting/bleeding days. The overall incidence of adverse events (AEs) was comparable in both groups, and the majority was mild-to-moderate in intensity. Breast tenderness was the most frequently reported AE (transdermal 19.9% versus oral 28.4%). AEs related to the gastrointestinal system were more frequent with oral E2/NETA, and episodes of spotting and bleeding were more frequent with transdermal E2/NETA. Local skin tolerability of the transdermal matrix system was good. **CONCLUSIONS:** Transdermal E2/NETA (25 and 125 microg) provided adequate endometrial protection in postmenopausal women when evaluated according to CPMP/CHMP criteria, achieved a high rate of amenorrhea, and was well tolerated.

Simon, J. A., C. Bouchard, et al. (2007). "Low dose of transdermal estradiol gel for treatment of symptomatic postmenopausal women: a randomized controlled trial.[see comment]." *Obstetrics & Gynecology* **109**(3): 588-96.

**OBJECTIVE:** To investigate safety and efficacy and identify the lowest effective dose of a new transdermal estradiol (E2) gel for relief of menopausal symptoms in a population of postmenopausal women. **METHODS:** This study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Postmenopausal women with at least 60 hot flushes per week applied 0.87 g/d (n=136), 1.7 g/d (n=142), or 2.6 g/d (n=69) E2 gel or placebo gel (n=137) topically for 12 weeks. The changes from baseline in hot flush frequency and severity at 4 and 12 weeks and changes from baseline in vaginal atrophy symptoms at 12 weeks were examined. **RESULTS:** With increasing E2 doses, mean trough serum E2 increased from 17 to 29 pg/mL. By weeks 3-5, E2 gel reduced moderate-to-severe hot flush rate by at least seven hot flushes per day ( $P<.001$ ) and reduced the severity score ( $P<.01$ ). The numbers needed to treat for benefit for an 80% and 100% decrease in hot flush number were 3.2 and 6.3 for the 0.87-g/d group and 1.3 and 2.3 for the 2.6-g/d group. At week 12, vaginal pH was more acidic and vaginal maturation index more mature compared with placebo ( $P<.001$ ). The lowest dose improved most bothersome vulvovaginal atrophy symptoms ( $P<.05$ ). Estradiol gel was well tolerated at the site of application and produced no unexpected adverse effects. The 0.87 g/d dose produced fewest adverse events. **CONCLUSION:** The 0.87 g/d dose of this new transdermal E2 gel, which delivers an estimated 0.0125 mg E2 daily, delivered the lowest effective dose for treatment of vasomotor symptoms and vulvovaginal atrophy in a population of postmenopausal women. **CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00391417. **LEVEL OF EVIDENCE:** I.

Simon, J. A. and E. S. Group (2006). "Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms." *Menopause* **13**(2): 222-31.

**OBJECTIVE:** To assess the efficacy and safety of topical micellar nanoparticle estradiol emulsion (MNPEE; Estrasorb; Novavax, Inc., Malvern, PA) in postmenopausal women with moderate to severe vasomotor symptoms. **DESIGN:** A multicenter, randomized, double-blind, placebo-controlled study was conducted in 200 postmenopausal women with seven or more moderate to severe hot flushes per day. The study consisted of a 3-week screening period followed by a 1-week placebo emulsion run-in period and a 12-week active or placebo treatment period. Women were randomized (1:1) to receive MNPEE (3.45 g daily dose of emulsion containing 8.6 mg estradiol) or matching placebo emulsion. The primary efficacy variable was the change from baseline in the frequency of moderate and severe hot flushes at weeks 4 and 12. Adverse events were monitored throughout the trial. **RESULTS:** Topical micellar nanoparticle estradiol emulsion was statistically significantly superior to placebo emulsion in reducing the mean frequency of moderate to severe vasomotor symptoms by week 3 ( $P = 0.003$ ), with superiority to placebo maintained from weeks 4 to 12 ( $P < 0.001$ ). At week 12 (peak benefit), MNPEE reduced mean daily frequency of hot flush count by 11.1 ( $P < 0.001$  vs placebo). MNPEE significantly reduced mean symptom severity from weeks 4 to 12 ( $P < 0.001$ ) compared with placebo. At endpoint, mean serum concentrations of estradiol and estrone were 63 and 89 pg/mL, respectively, in the MNPEE group. The mean endpoint ratio of estradiol to estrone in these patients was 0.774. MNPEE was safe and well tolerated. **CONCLUSION:** Once-daily application of 3.45 g of micellar nanoparticle estradiol emulsion containing 8.6 mg of estradiol was safe and effective in providing significant relief of vasomotor symptom frequency and severity in postmenopausal women.

Simon, J. A., K. Z. Reape, et al. (2008). "Randomized, multicenter, double-blind, placebo-controlled trial to evaluate the efficacy and safety of synthetic conjugated estrogens B for the treatment of vulvovaginal atrophy in healthy postmenopausal women." Fertility & Sterility **90**(4): 1132-8.

**OBJECTIVE:** To evaluate the safety and efficacy of synthetic conjugated estrogens B (SCE-B; 0.3 mg/d) for 12 weeks in the treatment of vulvovaginal atrophy in symptomatic, postmenopausal women. **DESIGN:** Prospective, randomized, multicenter, double-blind, placebo-controlled trial. **SETTING:** Forty-two participating sites in the United States. **PATIENT(S):** Postmenopausal women with at least one moderate to severe symptom of vaginal atrophy. **INTERVENTION(S):** Daily oral administration, in a randomized, placebo-controlled setting, of SCE-B (0.3 mg) or of placebo for 12 weeks. **MAIN OUTCOME MEASURE(S):** Mean changes in vaginal maturation index, percentage of parabasal and superficial cells, vaginal pH, and severity of the most bothersome symptom (MBS) between baseline and predetermined time points were assessed. Safety and tolerability were evaluated. **RESULT(S):** A total of 310 women (mean age, 58.6 y) were enrolled. Synthetic conjugated estrogens B yielded statistically significantly greater differences in vaginal maturation index and vaginal pH from baseline to the end of treatment. Vaginal dryness (44.4%) and pain during intercourse (30.2%) were the symptoms most commonly identified as the MBS. A statistically significant mean reduction in the severity of the MBS was noted for SCE-B. There were no clinically significant differences observed between the two groups for findings related to safety. **CONCLUSION(S):** Synthetic conjugated estrogens B (0.3 mg/d) was effective in treating vulvovaginal atrophy in symptomatic postmenopausal women. Significant improvement was seen in vaginal maturation index, vaginal pH, and severity of MBS from baseline to the end of treatment.

Veerus, P., K. Fischer, et al. (2008). "Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial." BMC Women's Health **8**: 5.

**BACKGROUND:** The aim of the study was to determine the effect of postmenopausal hormone therapy on women's symptom reporting and quality of life in a randomized trial. **METHODS:** 1823 women participated in the Estonian Postmenopausal Hormone Therapy (EPHT) Trial between 1999 and 2004. Women were randomized to open-label continuous combined hormone therapy or no treatment, or to blind hormone therapy or placebo. The average follow-up period was 3.6 years. Prevalence of symptoms and quality of life according to EQ-5D were assessed by annually mailed questionnaires. **RESULTS:** In the hormone therapy arms, less women reported hot flushes (OR 0.20; 95% CI: 0.14-0.28), sweating (OR 0.56; 95% CI: 0.44-0.72), and sleeping problems (OR 0.66; 95% CI: 0.52-0.84), but more women reported episodes of vaginal bleeding (OR 19.65; 95% CI: 12.15-31.79). There was no difference between the trial arms in the prevalence of other symptoms over time. Quality of life did not depend on hormone therapy use. **CONCLUSION:** Postmenopausal hormone therapy decreased vasomotor symptoms and sleeping problems, but increased episodes of vaginal bleeding, and had no effect on quality of life. **TRIAL REGISTRATION NUMBER:** ISRCTN35338757.

Welton, A. J., M. R. Vickers, et al. (2008). "Health related quality of life after combined hormone replacement therapy: randomised controlled trial.[see comment]." BMJ **337**: a1190.

**OBJECTIVE:** To assess the effect of combined hormone replacement therapy (HRT) on health related quality of life. **DESIGN:** Randomised placebo controlled double blind trial. **SETTING:** General practices in United Kingdom (384), Australia (94), and New Zealand (24). **PARTICIPANTS:** Postmenopausal women aged 50-69 at randomisation; 3721 women with a

uterus were randomised to combined oestrogen and progestogen (n=1862) or placebo (n=1859). Data on health related quality of life at one year were available from 1043 and 1087 women, respectively. INTERVENTIONS: Conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5/5.0 mg or matched placebo orally daily for one year. MAIN OUTCOME MEASURES: Health related quality of life and psychological wellbeing as measured by the women's health questionnaire. Changes in emotional and physical menopausal symptoms as measured by a symptoms questionnaire and depression by the Centre for Epidemiological Studies depression scale (CES-D). Overall health related quality of life and overall quality of life as measured by the European quality of life instrument (EuroQol) and visual analogue scale, respectively. RESULTS: After one year small but significant improvements were observed in three of nine components of the women's health questionnaire for those taking combined HRT compared with those taking placebo: vasomotor symptoms (P<0.001), sexual functioning (P<0.001), and sleep problems (P<0.001). Significantly fewer women in the combined HRT group reported hot flushes (P<0.001), night sweats (P<0.001), aching joints and muscles (P=0.001), insomnia (P<0.001), and vaginal dryness (P<0.001) than in the placebo group, but greater proportions reported breast tenderness (P<0.001) or vaginal discharge (P<0.001). Hot flushes were experienced in the combined HRT and placebo groups by 30% and 29% at trial entry and 9% and 25% at one year, respectively. No significant differences in other menopausal symptoms, depression, or overall quality of life were observed at one year. CONCLUSIONS: Combined HRT started many years after the menopause can improve health related quality of life. TRIAL REGISTRATION: ISRCTN 63718836.

Yang, T.-S., Y.-J. Chen, et al. (2007). "A clinical trial of 3 doses of transdermal 17beta-estradiol for preventing postmenopausal bone loss: a preliminary study.[see comment]." Journal of the Chinese Medical Association: JCMA **70**(5): 200-6.

BACKGROUND: It is well documented that a daily oral dose of 0.625 mg of conjugated equine estrogen or 1-2 mg of 17beta-estradiol is needed to prevent postmenopausal bone loss. Recent studies have indicated that a lower dose of estrogen maybe as effective in maintaining bone mass. The purpose of this study was to evaluate the effects of 3 dosages of transdermally administered 17beta-estradiol gel in postmenopausal women stratified by oophorectomy and natural menopause. METHODS: One hundred and twenty postmenopausal women were randomly selected to form 4 groups. Three groups of women were treated with a transdermal administration of estradiol gel at a daily dosage of 1.25, 2.5 and 5.0 g (containing 0.75, 1.5, and 3 mg of 17beta-estradiol/day), respectively. The 4th group of women, receiving estradiol 2 mg/day p.o., was studied concurrently as a control. Bone mineral density was measured by quantitative computed tomography of the vertebrae from T12 to L3 at baseline, then at 6-month intervals for 1 year. RESULTS: Women in all groups receiving 17beta-estradiol gel obtained a significant increase in bone mass, with the exception of the 1.25 g/day group, which showed a minimal increment at the 6-month period, compared with the control group. Comparisons of the increments in bone mass after estrogen therapy for both natural and surgical menopausal subjects found that there was a more prominent response in surgical menopausal women receiving a dosage of 2.5 g/day. CONCLUSION: Estradiol gel at the dosage of 1.25 g/day, equivalent to 17beta-estradiol 0.75 mg/day, effectively prevented bone loss in postmenopausal women after a 12-month treatment period. The therapeutic effect of estradiol gel on bone mass was more prominent in the surgical menopausal groups at the dosage of 2.5 g/day. The atrophic ovaries may therefore play a crucial role in the subsequent decades of postmenopausal women.

Zaborowska, E., J. Brynhildsen, et al. (2007). "Effects of acupuncture, applied relaxation, estrogens and placebo on hot flushes in postmenopausal women: an analysis of two prospective, parallel, randomized studies.[see comment]." *Climacteric* **10**(1): 38-45.

**OBJECTIVE:** To assess if transdermal or oral estrogens, acupuncture and applied relaxation decrease the number of menopausal hot flushes/24 h and improve climacteric symptoms, as assessed by the Kupperman index, more than transdermal placebo treatment. **SETTING:** An outpatient clinic at a Swedish university hospital. **METHODS:** A total of 102 postmenopausal women were recruited to two studies performed in parallel. In Study I, the women were randomized between transdermal placebo or estrogen treatment and, in Study II, between oral estrogens, acupuncture or applied relaxation for 12 weeks. Climacteric symptoms were measured with daily logbooks on hot flushes. Women completed the assessment questionnaire for the Kupperman index at baseline and after 12 weeks. **RESULTS:** The number of flushes/24 h decreased significantly after 4 and 12 weeks in all groups except the placebo group. Both at 4 and 12 weeks, acupuncture decreased the number of flushes more ( $p < 0.05$ ;  $p < 0.01$ , respectively) than placebo. At 12 weeks, applied relaxation decreased the number of flushes more ( $p < 0.05$ ) than placebo. The Kupperman index score decreased in all groups except the placebo group. The decrease in score was significantly greater in all treatment groups than in the placebo group ( $p < 0.01$ ). **CONCLUSION:** Acupuncture and applied relaxation both reduced the number of hot flushes significantly better than placebo and should be further evaluated as alternatives to hormone therapy in women with menopausal vasomotor complaints.