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

Preliminary Scan Report #4

September 2013

Last Report Update #3 (October 2007)

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 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 Previous Update Scans:

Scan #1: May 2009
Scan #2: June 2010
Scan #3: November 2011

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 hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?

2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for preventing low bone density and fractures?

3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?

4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?

5. Are there subgroups of patients based on demographics, other medications, co-morbidities, length of use, or initiation of use relative to onset of menopause, 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 versus surgical menopause (oophorectomy) and for postmenopausal women versus women in the menopausal transition stage.
- Women in the menopausal transition stage are those transitioning through natural menopause who have 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 estrogen monotherapy or estrogen plus progestin/progesterone preparations listed below for all symptoms, bone density and fracture outcomes, and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens. Included products are shown in Table 1.

Table 1. Included estrogen products

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Oral estrogens			
17b Estradiol	Gynodiol (generic) Estradiol (generic) Estrace	0.5, 1, 1.5, 2 mg 0.5, 1, 2 mg 0.5, 1, 2 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar or vaginal atrophy, topical vaginal products should be considered. 3. Treatment of Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen dependant carcinoma of the prostrate (for palliation only). 6. Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Estradiol acetate	Femtrace	0.45, 0.9, 1.8 mg	Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Esterified estrogens	Menest Neo-Estrone	0.3, 0.625, 1.25, 2.5 mg 0.3, 0.625, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Atrophic vaginitis. 3. Kraurosis Vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. 7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 8. Prostatic carcinoma-palliative therapy of advanced disease.
Estropipate	Estropipate (generic) Ogen Ortho-est	0.75, 1.5, 3 mg 0.75, 1.5, 3 mg 0.75, 1.5 mg	1. Signs and symptoms of naturally occurring or surgically induced estrogen deficiency states associated with menopausal and post-menopausal symptoms, e.g., hot flashes, sleep disturbances and urogenital atrophy. 2. Osteoporosis induced by estrogen deficiency states in conjunction with other pertinent measures.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Conjugated equine estrogens (CEE)	Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). 6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Synthetic conjugated estrogens	Cenestin Enjuvia C.E.S Congest PMS-Conjugated	0.3, 0.45, 0.625, 0.9, 1.25 mg 0.625, 1.25 mg 0.3, 0.625, 0.9, 1.25 0.3, 0.625, 0.9, 1.25, 2.5 mg 0.3, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause: 0.45mg, 0.625mg, 0.9mg, 1.25mg 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 0.3 mg
Estrogen-progestin combinations			
CEE, medroxyprogesterone	Prempro Premplus Premphase	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg 2.5/0.625 mg, 5/0.625 mg 0.625 mg CEE, 5.0 mg progesterone	1. Treatment of moderate to severe symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
17b-estradiol, norgestimate	Ortho-Prefest	1 mg estradiol/0.9 mg norgestimate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17-b estradiol, norethindrone acetate	Activella	1 mg estradiol/0.5 mg norethindrone acetate	1.0 mg/0.5mg and 0.5mg/0.1mg 1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. 1.0mg/0.5mg 3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
17b-estradiol, drospirenone	Angeliq	1.0 mg estradiol, 0.5 mg drospirenone	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Ethinyl estradiol, norethindrone acetate	FemHRT	5 mcg ethinyl estradiol/1 mg norethindrone acetate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Transdermal estrogens			
17b-estradiol matrix patch	Alora Climara Esclim Vivelle Vivelle-Dot Menostar Estradot Oesclim 17-b estradiol (generic)	0.025, 0.05, 0.075, 0.1 mg/d 0.025, 0.05, 0.06, 0.075, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 0.05, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 14 mcg/d 25, 37.5, 50, 75, 100 µg/d 25, 50 µg/day 25, 50, 100 µg/d 0.1, 0.05 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol reservoir patch	Estraderm	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risks of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol, norethindrone acetate patch	Combi-Patch Estalis Estalis Sequi Estracomb	0.05 mg estradiol/0.14 mg norethindrone, 0.05/0.25 mg 140 µg norethindrone acetate/50 µg estradiol-17β per day, 250/50 µg/day 0.05 mg estrogen twice/week (Vivelle 50 patch) for 2 weeks, then 9 or 16 cm^2 Estalis patch twice/week for 2 weeks 0.05 mg estrogen twice/week for 2 weeks, then 0.05 mg estrogen +	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
		0.25 mg progesterone for 2 weeks	
17b-estradiol, levonorgestrel patch	Climara Pro	0.045 mg estradiol/0.015 mg levonorgestrel	Treatment of moderate to severe vasomotor symptoms associated with menopause
17b-estradiol transdermal gel	EstroGel Elestrin Divigel	1.25 g (0.75 mg estradiol) 0.87 g (0.52 mg estradiol) 0.25, 0.5, 1.0 g (0.25, 0.5, 1.0 mg estradiol)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate topical emulsion	Estrasorb	1.74 g (0.5 mg estradiol)	Estrasorb is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause**.**
Topical products			
17b-estradiol vaginal cream	Estrace vaginal cream	0.1 mg estrogen/g	Treatment of vulvar and vaginal atrophy.
CEE cream	Premarin vaginal cream	0.625 mg estrogen/g	Treatment of atrophic vaginitis and kraurosis vulvae.
Esterified estrogen cream	Neo-Estrone vaginal cream	1 mg estrogen/g	1. Treatment of menopausal and post menopausal symptoms. 2. Should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.
17-b estradiol intravaginal ring	Femring Estring	0.05 mg estradiol, 0.1 mg/d 2 mg (7.5 µg estradiol/day)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate vaginal tablet	Vagifem	25 µg	Treatment of atrophic vaginitis.

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 the end of the study.
- 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.

Harms 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 pruritus
- Cholecystitis
- Effects on the liver

For long-term use

- Cardiovascular events
- Breast cancer
- Thrombosis
- Cholecystitis
- Ovarian cancer
- Endometrial cancer

Study Designs

1. 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.
2. 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.
3. 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 2010 through August 14, 2013 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) website for identification of new drugs, indications, and safety alerts.

Study Selection

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

RESULTS

New Drugs

No new drugs were identified.

New Indications

No new indications for included drugs were identified.

New Safety Alerts

Premarin: 10/28/2011 (oral); 02/14/2012 (topical); 04/11/2012 (injectable)
Prempro, Premphase: 02/02/2012 (oral)

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. (See **WARNINGS, Malignant Neoplasms, Endometrial cancer**.)

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast cancer**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Comparative Effectiveness Reviews

No new comparative effectiveness reviews were identified through searches of the AHRQ and CADTH websites. An AHRQ comparative effectiveness review of therapies for menopausal symptoms is currently in progress with amendments made to the protocol in May 2013. The Key Questions for this review are available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1022&pageaction=displayproduct#5120

Randomized Controlled Trials

Medline searches resulted in 57 citations. Of those, there are 11 potentially relevant new trials. Table 1 summarizes the studies (see Appendix A for abstracts of new studies, Appendix B for abstracts of previously identified studies). There were no new head-to-head studies, four active-controlled studies, and seven placebo or no treatment-controlled studies.

Table 1. Potentially relevant trials of hormone therapy

Study Year	Comparison	N Duration	Focus
Alhola 2010	Estrogen + progestin Placebo	32 6 months	Cognitive function
Bachmann 2008a	Vaginal estradiol (E2) vs. placebo	230 12 weeks	Atrophic vaginitis
Bachmann 2008b	Transdermal 17-beta-estradiol/levonorgestrel vs. placebo	425 12 weeks	Moderate-severe vasomotor symptoms
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
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
Carmignani 2010	Estradiol 1 mg/0.5 mg norethisterone vs	60 16 weeks	Psychological, somatic, and urogenital menopausal

Study Year	Comparison	N Duration	Focus
	Soy isoflavone 90 mg vs Placebo		symptoms
Chlebowski, 2010 WHI	CEE 0.625 mg + medroxyprogesterone acetate 2.5 mg Placebo	16,608 Intervention 5.6 years Followup 7.9 years	Breast cancer incidence and breast cancer mortality
Cieraad 2006	17-beta estradiol/dydrogesterone vs. conjugated equine estrogen/norgestrel	169 6 months	Lipids, vasomotor symptoms, bleeding, tolerability
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
Fahlen 2011	Estradiol+Progestogen No treatment control	75 1 year	Quality of life in breast cancer survivors
Fonseca 2007	17-beta estradiol/norethisterone vs. placebo	40 cross over at 6 months	Sexual function and vasomotor symptoms
Freedman 2009	Synthetic conjugated estrogens vaginal cream vs placebo	305 12 weeks	Vulvovaginal atrophy
Gambacciani, 2011	17-estradiol 1 mg + drospirenone 2 mg Calcium	70 3 months	Quality of life
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
Genazzani, 2011a	DHEA 10 mg Estradiol 1 mg + dihydrogesterone 5 mg Tibolone 2.5 mg	48 12 months	Sexual function
Hachul 2008	Estrogen/progesterone vs. placebo	24 12 weeks	Sleep and cognition
Haines 2009	Micro-dose transdermal estradiol vs placebo	165 12 weeks	Asian women, hot flashes
Hassa 2010	Conjugated equine estrogen 0.625 mg vs Transdermal 17 beta-estradiol patch 3.9 mg every other week vs Placebo	N not reported in abstract 6 months	Vasomotor symptoms
Hayashi 2011	All initially taking Estriol + medroxyprogesterone then randomized to same or to raloxifene 60 mg	32 52 weeks	Bone-mineral density

Study Year	Comparison	N Duration	Focus
Hedrick 2009	Various doses of estradiol gel 0.1% vs. placebo	488 12 weeks	Vasomotor symptoms, vaginal atrophy
Heiss 2008	Conjugated equine estrogen/medroxyprogesterone vs Calcium	16,608 Mean 2.4 years of follow-up	To report health outcomes at 3yrs after intervention was stopped (WHI)
Honjo 2009	Low-dose oral estradiol vs placebo	211 8 weeks	Japanese women, hot flashes
Huang 2007	Transdermal estradiol vs. placebo	382 12 months	Bone turnover and BMD (appears to be post-hoc analysis from ULTRA trial)
Huang 2009	CEE vs placebo	2763 1 year	Secondary analysis from HERS study data, risk of coronary heart disease
Kalleinen 2008	Cyclic estrogen-progestin vs. placebo	25 6 months (before-after)	Sleep
Lee 2007	Estradiol/drospirenone vs. placebo	90 4 months	Vasomotor symptoms
Lin 2011	Drospirenone 2 mg + 17-estradiol Placebo	244 4-28 day cycles	Hot flushes in Chinese women
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
Maki 2009	CEE vs black cohosh vs red clover vs placebo	66 1 year	Cognition
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
Merz 2010	Norethindrone 1 mg + ethinyl estradiol 10 mcg Placebo	35 12 weeks	Chest pain
Michael 2010	CEE vs placebo	1458 6 years	Secondary analysis of WHI data, physical function in women ages 65 to 79 years at enrollment
Mizunuma 2010	Oral estradiol 0.5 mg or 1.0 mg, with or without levonorgestrel 40 mcg vs	152 52 weeks	Bone mineral density

Study Year	Comparison	N Duration	Focus
	Placebo		
Moriyama 2008	Estradiol valerate vs. exercise	44 6 months	Health-related quality of life, 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 2007	Various doses of continuous combined HRT consisting of estradiol valerate/medroxyprogesterone	NR 12 months	Health related quality of life
Prior 2007	Conjugated equine estrogen vs. medroxyprogesterone	41 12 months	Vasomotor symptoms
Resnick 2009	CEE vs placebo	886 3 years	Secondary analysis of WHI data, cognition in women age 65 years and older
Samsioe 2007	Transdermal vs. oral estradiol/norethisterone	677 1 year	Harms (safety), tolerability
Schierbeck 2012	Intact uterus: triphasic estradiol and norethisterone acetate No uterus: 2 mg estradiol vs No treatment controls	1006 Intervention stopped after 11 years but followed for up to 16 years	Long term effect of HRT on cardiovascular outcomes
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
Stevenson 2010	17 beta-estradiol 0.5 mg/dydrogesterone 2.5 mg vs 17 beta-estradiol 1 mg/dydrogesterone 5 mg vs Placebo	313 52 weeks	Vasomotor symptoms
Valen-Sendstad 2010	Estradiol 1 mg + norethisterone 0.5 mg Placebo	65 12 month	Depressive symptoms and cognitive function in women with Alzheimer disease
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.	3721 12 months	Health related quality of life, emotional and physical

Study Year	Comparison	N Duration	Focus
	placebo		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
Ziaei 2010	CEE 0.625 mg + medroxyprogesterone + Ca+D Tibolone 2.5 mg + Ca+ D Ca+D	140 6 months	Climacteric symptoms and sexual function

Along with the 47 trials identified in previous update scans, there are now 58 potentially relevant new trials for this drug class with 8 previously identified head-to-head trial, nine total active-controlled trials, 37 placebo-controlled or no treatment-controlled trials, and four studies of various doses of the same included drug.

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

Active-controlled (N=4)

Gambacciani, M., G. Rosano, et al. (2011). "Clinical and metabolic effects of drospirenone-estradiol in menopausal women: a prospective study." Climacteric 14(1): 18-24.

OBJECTIVES: To describe the effects of low-dose hormonal replacement therapy (HRT) on quality of life, metabolic parameters and blood pressure in postmenopausal women.
METHODS: Postmenopausal women untreated with HRT or sex steroids in the previous 12 months were randomized to treatment with 17-estradiol (1mg/day) plus drospirenone (2mg/day) (E2+DRSP) or to calcium (controls). Quality of life was evaluated by the Women's Health Questionnaire (WHQ) at baseline and after 6 and 12 weeks of treatment. Anthropometric, metabolic and blood pressure measurements were performed before and after 3 months of treatment.
RESULTS: WHQ domain scores for vasomotor and somatic symptoms, anxiety/fears, depressed mood, sexual behavior and sleep problems decreased significantly in the E2+DRSP group relative to both baseline and control values ($p<0.05$). Body mass index was unchanged, while waist circumference decreased significantly ($p<0.001$) after E2+DRSP treatment. Significant decreases were also observed after E2+DRSP treatment for blood insulin values, insulin resistance (estimated by homeostasis model assessment) and systolic blood pressure ($p<0.001$, all). In subjects with systolic blood pressure<130mmHg at baseline, no changes in systolic values were registered, while women with baseline high-normal systolic blood pressure (130-139mmHg) showed significant decreases ($p<0.0069$). E2+DRSP did not modify diastolic blood pressure values. In the calcium-treatment group, there were no significant changes in WHQ scores or in anthropometric, metabolic or blood pressure measurements.
CONCLUSION: In postmenopausal women, E2+DRSP administration improves vasomotor symptoms and general aspects of quality of life and may positively influence cardiovascular risk factors.

Genazzani, A. R., M. Stomati, et al. (2011). "Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality." Climacteric 14(6): 661-668.

BACKGROUND: Sexual desire is affected by endocrine and psychosocial factors. Menopausal hormonal changes are relevant to the causes of sexual dysfunction during reproductive aging.
AIM: To evaluate the effects of different types of hormonal replacement therapy (HRT) on sexual function, frequency of sexual intercourse, and quality of relationship in early postmenopausal women. We recruited 48 healthy postmenopausal women aged 50-60 years (mean age 54.5 +/- 3.3 years). Women with climacteric symptoms were uniformly randomized into three groups receiving either dehydroepiandrosterone (DHEA 10 mg) daily, or daily oral estradiol (1 mg) plus dihydrogesterone (5 mg), or daily oral tibolone (2.5 mg) for 12 months. Women who refused hormonal therapy were treated with oral vitamin D (400 IU). Efficacy was evaluated using the McCoy Female Sexuality Questionnaire before treatment and after 12 months. We evaluated the hormonal profile before treatment and after 3, 6 and 12 months.

RESULTS: The groups receiving DHEA or HRT reported a significant improvement in sexual function compared to baseline ($p < 0.001$ and $p < 0.01$, respectively) using the McCoy total score. The quality of relationship was similar at baseline and after 3, 6 and 12 months of treatment. There were significant increases in the numbers of episodes of sexual intercourse in the previous 4 weeks in women treated with DHEA, HRT and tibolone in comparison with the baseline value ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). No changes in the McCoy score occurred in women receiving vitamin D.
CONCLUSIONS: Daily oral DHEA therapy at the dose of 10 mg, HRT and tibolone all provided a significant improvement in comparison with vitamin D in sexual function and in frequency of sexual intercourse in early postmenopausal women.

Hayashi T, Ina K, Maeda M, Nomura H. (2011). "The effects of selective estrogen receptor modulator treatment following hormone replacement therapy on elderly postmenopausal women with osteoporosis. " Nitric oxide. 24(4):199-203, 2011 May.

OBJECTIVES: A comparison between the atheroprotective and osteoprotective effects of the selective estrogen receptor modulator (SERM) raloxifene and those of hormone replacement therapy (HRT) has not been made in elderly women., METHODS: A randomized prospective controlled trial was performed in a cohort of 32 elderly Japanese women with osteoporosis receiving HRT (estriol plus medroxyprogesterone) for more than 1 year. In 16 randomly selected subjects, HRT was changed to raloxifene therapy (60mg/day, 71.4+/-3.4 years, SERM group). The other 16 patients were continued on HRT (71.8+/-2.9 years, HRT group). As a control group, 14 subjects were enrolled, did not take any medications and were age-matched to experimental patients (72.5+/-3.3 years, control group). Plasma lipids, TNF[alpha], adiponectin, NO metabolites (NOx:NO2(-) and NO3(-)), cyclicGMP and bone-mineral density (BMD) were evaluated at baseline and at 26 and 52 weeks after enrollment., RESULTS: SERM (Raloxifene) increased high-density-lipoprotein cholesterol levels and tended to decrease low-density-lipoprotein cholesterol levels (P=0.058) compared with baseline. Adiponectin, NOx and cGMP levels were significantly increased after 6 months compared with baseline or the HRT group. TNF[alpha] was decreased by raloxifene. In control subjects, no significant changes were observed in any of these markers. Bone-mineral density was higher at baseline in the raloxifene and HRT groups than in the control group, and BMD increased 12 months after baseline in the HRT and control group.
CONCLUSION: SERM improved BMD and endothelial function in elderly postmenopausal women with osteoporosis who had received HRT, and these effects were comparable to or slightly stronger than those of HRT. Changes in adiponectin and TNF[alpha] may underlie the improvements in endothelial function, such as NO signaling.

Ziaei, S., M. Moghasemi, et al. (2010). "Comparative effects of conventional hormone replacement therapy and tibolone on climacteric symptoms and sexual dysfunction in postmenopausal women." Climacteric 13(2): 147-156.

OBJECTIVE: To compare the effects of tibolone with those of conventional hormone replacement therapy on climacteric symptoms and sexual function in postmenopausal women.
MATERIALS AND METHODS: In a randomized, controlled trial, 140 postmenopausal women were allocated into three groups. Of the subjects included, 47 women received 2.5 mg tibolone + one Cal+D tablet (500 mg calcium and 200 IU vitamin D) daily; 46 women received 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily; and 47 women received only one Cal+D tablet as the control group. The Greene Climacteric Scale (GCS) questionnaire was used to detect the efficacy of

treatment on climacteric symptoms. Rosen's Female Sexual Function Index (FSFI) was used for sexual function evaluation. Sex hormone binding globulin (SHBG), free estradiol index (FEI) and free testosterone index (FTI) were measured before and after treatment. The women were followed up for 6 months
RESULTS: After treatment, all subscores in the GCS improved in the tibolone and CEE/MPA groups ($p < 0.01$), except the sexual subscore in the CEE/MPA group, compared with baseline. There were significant differences in the FSFI in the tibolone and CEE/MPA groups in comparison to the control group after treatment. Tibolone, in comparison to CEE/MPA, significantly lowered SHBG levels and increased the FTI and FEI and improved the desire, arousal and orgasm sexual domains of the FSFI ($p < 0.001$).
CONCLUSION: Tibolone may be an alternative to conventional hormone replacement therapy in the treatment of climacteric symptoms and sexual dysfunction in postmenopausal women.

Placebo- controlled or no treatment-controlled (N=7)

Alhola, P., H. Tuomisto, et al. (2010). "Estrogen + progestin therapy and cognition: a randomized placebo-controlled double-blind study." Journal of Obstetrics & Gynaecology Research 36(4): 796-802.

AIMS: The use of hormone therapy (HT) is a relevant and topical issue in the treatment of menopausal symptoms in women. Information regarding the effects of combination treatment with estrogen and progesterone as well as treatment timing on cognitive function is lacking and was evaluated in healthy pre- and postmenopausal women.
METHODS: Sixteen premenopausal (45-51 years) and 16 postmenopausal (58-70 years) women were randomly assigned to receive either estrogen + progestin therapy (HT) or placebo (PL) for six months. The study was double-blind. Cognitive performance was measured at baseline and follow up with tests of verbal and visuomotor functions, verbal and visual memory, and attention.
RESULTS: In premenopausal women, cognitive attention, when compared to baseline, improved with HT but declined slightly with PL in the two-choice reaction time task ($P = .049$), while PL was associated with better performance in tests of shared attention ($P = 0.024$) and auditory attention ($P < 0.05$). In postmenopausal women, HT was associated with improved performance in verbal episodic memory ($P = 0.024$) and a minor decline in auditory attention ($P = 0.025$).
CONCLUSIONS: HT, with estradiol valerate and norethisterone, in healthy women showed only minor effects on attention around the menopausal transition and on memory in postmenopause.

Chlebowski, R. T., G. L. Anderson, et al. (2010). "Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women." JAMA 304(15): 1684-1692.

CONTEXT: In the Women's Health Initiative randomized, placebo-controlled trial of estrogen plus progestin, after a mean intervention time of 5.6 (SD, 1.3) years (range, 3.7-8.6 years) and a mean follow-up of 7.9 (SD, 1.4) years, breast cancer incidence was increased among women who received combined hormone therapy. Breast cancer mortality among participants in the trial has not been previously reported.
OBJECTIVE: To determine the effects of therapy with estrogen plus progestin on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (SD, 2.7) years, through August 14, 2009.

DESIGN, SETTING, AND PARTICIPANTS: A total of 16,608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo pill. After the original trial completion date (March 31, 2005), reconsent was required for continued follow-up for breast cancer incidence and was obtained from 12,788 (83%) of the surviving participants.
MAIN OUTCOME MEASURES: Invasive breast cancer incidence and breast cancer mortality.
RESULTS: In intention-to-treat analyses including all randomized participants and censoring those not consenting to additional follow-up on March 31, 2005, estrogen plus progestin was associated with more invasive breast cancers compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year]; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; P = .004). Breast cancers in the estrogen-plus-progestin group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] vs 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; P = .03). There were more deaths directly attributed to breast cancer (25 deaths [0.03% per year] vs 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00-4.04; P = .049) as well as more deaths from all causes occurring after a breast cancer diagnosis (51 deaths [0.05% per year] vs 31 deaths [0.03% per year]; HR, 1.57; 95% CI, 1.01-2.48; P = .045) among women who received estrogen plus progestin compared with women in the placebo group.
CONCLUSIONS: Estrogen plus progestin was associated with greater breast cancer incidence, and the cancers are more commonly node-positive. Breast cancer mortality also appears to be increased with combined use of estrogen plus progestin.

Fahlen, M., B. Wallberg, et al. (2011). "Health-related quality of life during hormone therapy after breast cancer: a randomized trial." Climacteric 14(1): 164-170.

AIM: To study the effects of menopausal hormone therapy (HT) on health-related quality of life in women after breast cancer.
PATIENTS AND METHODS: In the Stockholm trial, breast cancer survivors were randomized to HT (estradiol and progestogen) or to a control group (no treatment). A subgroup of 75 women was studied (38 with HT, 37 controls). Fifty patients were on concomitant tamoxifen. Patients completed three questionnaires (EORTC QLQ C-30, EORTC QLQ-BR 23 and the Hospital Anxiety and Depression Scale (HADS)) during 1 year of treatment.
RESULTS: A significant group-by-time interaction was found for improvement of insomnia in the HT group ($p<0.001$). Within the HT group, but not in the control group, there was significant improvement for HADS anxiety, HADS depression, emotional, cognitive, and social functions and global quality of life. When HT was added to tamoxifen, the increase in global quality of life was significant ($p<0.01$).
CONCLUSION: The effects of HT on quality of life in breast cancer survivors have not previously been reported. The present data suggest that this controversial treatment may improve quality of life after breast cancer.

Lin, S. Q., L. Z. Sun, et al. (2011). "Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women." Climacteric 14(4): 472-481.

OBJECTIVES: Drospirenone is a novel progestogen that, combined with 17-estradiol, reduces the frequency and severity of menopausal vasomotor symptoms (VMS) in different populations. This double-blind, multicenter study compared the efficacy, safety and

tolerability of 2 mg drospirenone/1 mg estradiol (DRSP/E2) vs. placebo in Chinese postmenopausal women with moderate to severe VMS.
METHODS: Women, aged 45-65 years, were randomized to DRSP/E2 (n=183) or placebo (n=61) once daily for four 28-day cycles. Changes in the frequency and severity of hot flushes were analyzed as primary variables, together with other climacteric and urogenital symptoms, clinical global improvement, adverse events and physical/gynecological parameters.
RESULTS: Relative changes in numbers of hot flushes/week were -80.4% for DRSP/E2 vs. -51.9% for placebo (treatment difference -28.5%, p<0.0001). There were trends toward a greater reduction in severity of hot flushes with DRSP/E2 treatment. Patients treated with DRSP/E2 were more often free from sweating episodes (p<0.0001) and vaginal dryness (p=0.0008). Other climacteric symptoms, including nervousness and pollakisuria, followed a trend of greater response with DRSP/E2. Similar to other combination HRT regimens, DRSP/E2 increased occurrences of bleeding, but these decreased over time. Adverse events in patients treated with DRSP/E2 were mostly mild to moderate and withdrawal rates were low.
CONCLUSIONS: Daily treatment of postmenopausal Chinese women with DRSP/E2 for 16 weeks significantly reduced the incidence of hot flushes and demonstrated advantages vs. placebo for other climacteric symptoms. These results indicate that DRSP/E2 is effective, safe and well tolerated in postmenopausal Chinese women.

Merz, C. N. B., M. B. Olson, et al. (2010). "A randomized controlled trial of low-dose hormone therapy on myocardial ischemia in postmenopausal women with no obstructive coronary artery disease: results from the National Institutes of Health/National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE)." American Heart Journal 159(6): 987.e981-987.

BACKGROUND: Compared with men, women have more evidence of myocardial ischemia with no obstructive coronary artery disease. Although low endogenous estrogen levels are associated with endothelial dysfunction, the role of low-dose hormone therapy has not been fully evaluated. We postulate that a 12-week duration of low-dose hormone replacement therapy is associated with myocardial ischemia and endothelial dysfunction.
METHODS AND RESULTS: Using a multicenter, randomized, placebo-controlled design, subjects were randomized to receive either 1 mg norethindrone/10 microg ethinyl estradiol or placebo for 12 weeks. Chest pain and menopausal symptoms, cardiac magnetic resonance spectroscopy, brachial artery reactivity, exercise stress testing, and psychosocial questionnaires were evaluated at baseline and exit. Recruitment was closed prematurely because of failure to recruit after publication of the Women's Health Initiative hormone trial. Of the 35 women who completed the study, there was less frequent chest pain in the treatment group compared with the placebo group (P = .02) at exit. Women taking 1 mg norethindrone/10 microg ethinyl estradiol also had significantly fewer hot flashes/night sweats (P = .003), less avoidance of intimacy (P = .05), and borderline differences in sexual desire and vaginal dryness (P = .06). There were no differences in magnetic resonance spectroscopy, brachial artery reactivity, compliance, or reported adverse events between the groups.
CONCLUSIONS: These data suggest that low-dose hormone therapy improved chest pain symptoms, menopausal symptoms, and quality of life, but did not improve ischemia or endothelial dysfunction. Given that it was not possible to enroll the prespecified sample size, these results should not be considered definitive.

Schierbeck, L. L., L. Rejnmark, et al. (2012). "Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial." BMJ 345: e6409.

OBJECTIVE: To investigate the long term effect of hormone replacement therapy on cardiovascular outcomes in recently postmenopausal women.
DESIGN: Open label, randomised controlled trial.
SETTING: Denmark, 1990-93.
PARTICIPANTS: 1006 healthy women aged 45-58 who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal serum follicle stimulating hormone values. 502 women were randomly allocated to receive hormone replacement therapy and 504 to receive no treatment (control). Women who had undergone hysterectomy were included if they were aged 45-52 and had recorded values for postmenopausal serum follicle stimulating hormone.
INTERVENTIONS: In the treatment group, women with an intact uterus were treated with triphasic estradiol and norethisterone acetate and women who had undergone hysterectomy received 2 mg estradiol a day. Intervention was stopped after about 11 years owing to adverse reports from other trials, but participants were followed for death, cardiovascular disease, and cancer for up to 16 years. Sensitivity analyses were carried out on women who took more than 80% of the prescribed treatment for five years.
MAIN OUTCOME MEASURE: The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.
RESULTS: At inclusion the women on average were aged 50 and had been postmenopausal for seven months. After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint compared with 33 in the control group (hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015) and 15 died compared with 26 (0.57, 0.30 to 1.08; P=0.084). The reduction in cardiovascular events was not associated with an increase in any cancer (36 in treated group v 39 in control group, 0.92, 0.58 to 1.45; P=0.71) or in breast cancer (10 in treated group v 17 in control group, 0.58, 0.27 to 1.27; P=0.17). The hazard ratio for deep vein thrombosis (2 in treated group v 1 in control group) was 2.01 (0.18 to 22.16) and for stroke (11 in treated group v 14 in control group) was 0.77 (0.35 to 1.70). After 16 years the reduction in the primary composite outcome was still present and not associated with an increase in any cancer.
CONCLUSIONS: After 10 years of randomised treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

Valen-Sendstad, A., K. Engedal, et al. (2010). "Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone." American Journal of Geriatric Psychiatry 18(1): 11-20.

OBJECTIVE: To elucidate the effects of low-dose 17beta-estradiol and norethisterone (hormone therapy [HT]) versus placebo in women with Alzheimer Disease (AD) on cognition, depressivesymptoms, and activities of daily living.
DESIGN: A 12-month randomized, double-blind, placebo-controlled study, stratified by apolipoprotein E (ApoE) genotype (with versus without the epsilon4 allele), duration of education (< or =9 versus >9 years), and age (< or =75 versus >75 years) performed during 2000-2004.
SETTING: Ambulatory memory clinic in a general hospital.

PARTICIPANTS: Sixty-five female outpatients aged 65-89 years who met criteria for probable AD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition and International Classification of Diseases, tenth edition. Ten patients were excluded, resulting in 55 participants who had at least one posttreatment efficacy evaluation.
INTERVENTION: Randomly assigned to receive either 1-mg estradiol and 0.5-mg norethisterone or placebo once daily.
MEASUREMENTS: Cognitive variables were the Dementia Rating Scale, tests from Consortium toEstablish a Registry for AD, Global Deterioration Scale (GDS) and Barthel Index.
RESULTS: When only treatment effects were compared by analysis of variance, there were nonsignificant differences between treatment groups for all efficacy variables. A linear model analysis, including stratifying factors in addition to treatment in the model, revealed a significant main effect on mood. The depressive symptoms were lower in the HT group than in the placebo group. Those treated with HT without the ApoE epsilon4 allele had better mood, Word Learning Memory score, and GDS score. Those in the HT group with a higher level of education obtained a better GDS score. Adverse events did not differ between the groups.
CONCLUSION: HT interacts with ApoE genotype in women with AD. Women without an ApoE epsilon4 allele may get better mood and cognition with HT. HT may reduce depressive mood a nd give less cognitive decline.

Appendix B. Abstracts of potentially relevant trials of estrogens previously identified (N=47)

Head-to-head (N=8)

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.

Hassa, H., H. M. Tanir, et al. (2010). "Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?" Clinical & Experimental Obstetrics & Gynecology **37**(2): 135-137.

OBJECTIVE: To evaluate the short-term effects of two hormone therapy (HT) regimens and placebo on the Greene Climacteric Scale (GCS) of women with surgical menopause following six months of treatment. METHODS: This 6-month, prospective, randomized, parallel-group, masked evaluator study compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (group I), 3.9 mg transdermal 17beta-estradiol patch applied every week (group II) and placebo (group III). Mean GCS before and after six months of treatment in each group was compared. RESULTS: In groups I and II, vasomotor symptoms ($p < 0.005$, $p < 0.05$), somatic symptoms ($p < 0.05$, $p < 0.05$) and total score ($p < 0.005$, $p < 0.01$) significantly reduced from baseline values respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, vasomotor ($p < 0.05$), subscore and total score ($p < 0.05$) decreased significantly while other subscore reductions were not significant. CONCLUSIONS: Estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Additional larger prospective randomized studies need to be conducted in an aim to look at not only short-term but also long-term effects on climacteric symptoms, in comparison to both placebo arms and different dose and mode of HT use.

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.

Mizunuma, H., Y. Taketani, et al. (2010). "Dose effects of oral estradiol on bone mineral density in Japanese women with osteoporosis." Climacteric **13**(1): 72-83.

OBJECTIVES: This 2-year study compared 0.5 and 1.0 mg oral estradiol (E(2)), with or without levonorgestrel (LNG), for the treatment of postmenopausal osteoporosis in Japanese women. METHODS: Japanese women with osteoporosis after natural menopause or bilateral oophorectomy were randomized to receive E(2) 0.5 or 1.0 mg/day with LNG 40 microg as required, or placebo, for 52 weeks. Women treated with E(2) in the first year continued therapy at the same doses in the second year. Efficacy, safety and pharmacokinetics were assessed. RESULTS: There were 73 women randomized to E(2) 0.5 mg, 157 to E(2) 1.0 mg and 79 to placebo. Lumbar bone mineral density at 52 weeks increased significantly more with E(2) 1.0 mg ($p < 0.001$) and 0.5 mg ($p < 0.001$) than with placebo (no change). After 2 years, a 10% increase in bone mineral density with E(2) 1.0 mg was significantly greater than with E(2) 0.5 mg (8%; $p = 0.008$). E(2) was associated with an acceptable safety and tolerability profile, with slightly more adverse events with E(2) 1.0 than 0.5 mg. Serum E(2) concentration increased in a dose-dependent manner. CONCLUSION: This study showed that E(2), at both 1.0 mg and 0.5 mg doses, was effective in increasing bone mineral density with an acceptable safety and tolerability profile in Japanese postmenopausal women with osteoporosis but that the bone mineral density response was higher with the 1.0 mg dose.

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.

Active-controlled (N=5)

Carmignani, L. O., A. O. Pedro, et al. (2010). "The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial." Maturitas **67**(3): 262-269.

OBJECTIVES: To compare the effects of daily ingestion of dietary soy supplementation, l ow-dose hormone therapy (HT) and placebo on psychological, somatic and urogenital symptoms in postmenopausal women. STUDY DESIGN: A double-blind, randomized, controlled trial. Sixty healthy, symptomatic, postmenopausal women of 40-60 years of age were allocated to use dietary soy supplementation (containing 90 mg of isoflavone) or HT (1mg estradiol and 0.5mg norethisterone acetate) or placebo. Main outcome measures: the Menopause Rating Scale (MRS) was used to assess menopausal symptoms at baseline and after 16 weeks of treatment. Intention-to-treat analyses were performed using the chi-square test, Fisher's exact test, the Kruskal-Wallis non-parametric test and analysis of variance (ANOVA). RESULTS: No statistically significant differences were found between the groups with respect to baseline clinical and sociodemographic characteristics. The psychological, somatic and urogenital symptoms analyzed in the MRS improved during

treatment in all the groups, except for urogenital symptoms in the placebo group in which no significant changes were detected. Comparison between groups revealed a statistically significant improvement in somatic symptoms (hot flashes and muscle pain) in the users of HT (-45.6%) and dietary soy supplementation (-49.8%). Urogenital symptoms (vaginal dryness) improved significantly in HT users (-38.6%) and in users of the dietary soy supplementation (-31.2%). There was no statistically significant difference between the groups with respect to overall MRS score or to scores obtained in the psychological symptoms subscale. CONCLUSION: Dietary soy supplementation may constitute an effective alternative therapy for somatic and urogenital symptoms of the 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.

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.

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.

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.

Placebo-controlled and no treatment-controlled (N=30)

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 ($P <$ or $= 0.001$), including those for dyspareunia ($P <$ or $= 0.01$). 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., 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.

Bachmann, G. A., M. Schaefers, et al. (2007). "Lowest effective transdermal 17beta-estradiol dose for relief of hot flushes 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 flushes 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 flushes at the week 4 and 12 endpoints. RESULTS: At the week 12 endpoint, mean weekly frequencies of moderate and severe hot flushes 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 flushes 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.

Bachmann, G. A., M. Schaefers, 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.

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.

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 flushes. 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 flushes per week. Weeks 5-12 of treatment were compared with the 2 weeks preceding the treatment phase. RESULTS: Moderate and severe hot flushes 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 flushes (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 flushes 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 intrapatient 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.

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.

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.

Haines, C., S. L. Yu, et al. (2009). "Micro-dose transdermal estradiol for relief of hot flushes 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 flushes 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 flushes (-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.

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.

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 flushes in Japanese women with climacteric symptoms. METHODS: Women (n = 211) aged 40-64 years who had experienced natural menopause or bilateral oophorectomy, with > or = three moderate/severe hot flushes 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 flushes over 7 days from baseline to final examination. RESULTS: Percentage change in mean daily number of hot flushes 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 flushes in Japanese women.

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 spectometry) 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 >or=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.

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.

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.

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 >or=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.

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.

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 t hat low-dose estrogen neither benefits nor harms cognitive function in older women after 3 years of treatment, but confirmation is needed from larger trials.

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.

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.

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.

Stevenson, J. C., G. Durand, et al. (2010). "Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17beta-oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study." Maturitas **67**(3): 227-232.

OBJECTIVES: Guidelines recommend using the lowest effective dose of oestrogen for the management of vasomotor symptoms in postmenopausal women. The primary aim of this double-blind, multi-centre, randomised study was to assess the efficacy of oral ultra-low dose continuous combined hormone replacement therapy with 17beta-oestradiol and dydrogesterone. STUDY DESIGN: 313 women with >=50 moderate to severe hot flushes during the previous week were randomised to 0.5 mg 17beta-oestradiol/2.5 mg dydrogesterone (E 0.5 mg/D 2.5 mg), 1mg 17beta-oestradiol/5mg dydrogesterone (E 1mg/D 5 mg) or placebo for 13 weeks. The placebo group then switched to E 0.5 mg/D 2.5 mg for a further 39 weeks, whilst the other groups continued on the same treatment. RESULTS: After 13 weeks, the reduction in the number of moderate to severe hot flushes/day in the E 0.5 mg/D 2.5 mg group was greater than in the placebo group (-6.4 vs. -4.9, p<0.001) and comparable to that in the 1/5 mg group (-6.3). E 0.5 mg/D 2.5 mg and E 1mg/D 5 mg significantly improved the total Menopause Rating Scale score. The number of bleeding/spotting days was lower with E 0.5 mg/D 2.5 mg than with E 1 mg/D 5 mg. The overall amenorrhoea rate with E 0.5 mg/D 2.5 mg was 81%; this increased to 91% in months 10-12. CONCLUSIONS: Continuous combined 0.5 mg 17beta-oestradiol and 2.5mg dydrogesterone was effective in alleviating vasomotor symptoms and improving quality of life, and was associated with a high amenorrhoea rate and a good tolerability profile. Copyright Copyright 2010 Elsevier Ireland Ltd. All rights reserved.

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.

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 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.

Varying dose study (N=4)

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.

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 >or=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.

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 I mprovement 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.

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 estriol 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.