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

Final Report Update 3 Evidence Tables

October 2007

Original Report Date: February 2003
Update 1 Report Date: November 2003
Update 2 Report Date: July 2004
A literature scan of this topic is done periodically

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.

Heidi D. Nelson, MD, MPH
Peggy Nygren, MA
Michele Freeman, MPH
Benjamin K. S. Chan, MS

Update #3 conducted by
Susan L. Norris, MD, MPH
Susan Carson, MPH

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description. Prior versions of this report can be accessed at the DERP website titled "Drug Class Review of Estrogens".

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Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population charactersitcis	Inclusion criteria
Oral estrogens				
Archer 1992*	128 in 5 groups		Post and perimenopausal women with 5 or more vasomotor symptoms/day; Mean age 50.6 (40-60); General and gyn practices in USA	
Saure 2000	376 in 2 groups		Perimenopausal women with symptoms; Mean age 49; Denmark	
Odmark 2004	249	289/249/249	55.9 yrs (SE 0.28) Race NR Mean time to menopause 5.5 yrs (SE 0.31) HRT naïve 89/246 (36%)	Physically and mentally healthy women with an intact uterus and climacteric symptoms or ongoing HRT; age > 52yrs; at least 2 yrs since last spontaneous menstrual period

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Oral estrogens					
Archer 1992*				NR	CEE: 0.625, 1.25 mg/day; E2: 1, 2 mg/day
Saure 2000				0/376	E2: 1.5 mg/day for 24 days; E2V: 2 mg/day for 21 days Desogestrel: 0.15 mg/day for 12 days/mo with E2; MPA: 10 mg/day for 10 days/mo with E2V
Odmark 2004	Adenomatous hyperplasia w/ or w/o atypia; undiagnosed vaginal bleeding; hisotry of cancer of any kindl CV or thromboembolic disease; uncontrolled hypertension; diabetes; chronic medication w.barbituates, benzodiazepines, antidepressants, other psychtropic drugs, anti-epileptics or steroid hormones	NR	NR		0.625 mg conjugated estrogen (CE)/5 mg medroxyprogesterone acetate (MPA) qd 2 mg estradiol/1 mg norethisterone acetate (NETA) qd

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Oral estrogens				
Archer 1992*	DB RCT	12 weeks		Mean % change in daily frequency of vasomotor events: CEE 0.625 mg/day= -80.3 CEE 1.25 mg/day= -94.8 E2 1 mg/day= -91.2 E2 2 mg/day= -91.7 All significantly different from placebo, no differences between groups.
Saure 2000	DB RCT cross-over	12 weeks		Hot flashes, night sweats: decreased in both Rx groups; no difference between groups.
Odmark 2004	RCT multicenter (mix of clinic and hospital settings)	1 yr	38/0/246	Improvement in symptom "sweating" during first 6 months in both treatment groups ($p<0.001$); subsequent deterioration comparing 6th and 13th cycle in estradiol group ($p<0.01$); no deterioration in CE group. Breast tenderness worse in estradiol group ($p<0.001$) Otherwise, no significant differences between treatment groups on well-being variables (total physical, swelling, total positive, cheerful, energetic, total negative, tension, irritability, fatigue, depression, insomnia, headache, and negative effects on daily life)

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Pornel 2005	1219	NR/NR/1219	52.6 yrs (SD 4.5) 99.3% white Mean 4.3 yrs since last menstrual period	Age 40-65 yrs; intact uterus, amennorheic at least 6 mos or treated w/HRT for at least 12 mos, serum FSH concentration > lower limit of normal for post menopausal women and serum estradiol concentration < upper limit of normal range for post menopausal women; average 3 hot flashes/day during a period of seven days

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Pornel 2005	Known or suspected estrogen-dependent neoplasia, presence of endometrial hyperplasia, endometrial polyp or endometrial carcinoma at screening, evidence of malignant changes on prestudy mammogram, abnormal cervical smear at screening; known sensitivity to estrogens and/or progestins, presence of cerebrovascular or CV disease, uncontrolled arterial hypertension, diabetes mellitus, use of lipid-lowering drugs, use of medications known to affect vasomotor symptoms	NR	NR		1 mg 17β estradiol (days 1 -14) followed by 1 mg 17β estradiol + 0.125 mg or 0.25 mg trimegestone (days 15-28) 1 mg estradiol valerate (days 1-16) followed by 1 mg estradiol valerate + 1 mg norethisterone (days 17-28)

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Pornel 2005	RCT multicenter (outpatient clinics)	1 yr (+ 1 yr extension)	352/NR/1143 (efficacy)	Hot flushes Mean daily number decreased from cycle 1 in both treatment groups; no significant difference between groups at cycle 13: Adjusted mean (SEM), estradiol vs E2V: -0.06 (0.07); 95% CI -0.19, 0.08 Mean total hot flush severity score, estradiol vs E2V (p-value not reported): Change from baseline: -299 (SD 235) vs -328 (SD 258) Cycle 13: 10 (SD 34) vs 16 (SD 51) Night sweats (reported graphically only) Significant improvement from baseline in both groups; estradiol treatment "at least as good as" E2V (ANCOVA analysis) Kupperman index Significant improvement from baseline in both groups; NSD between groups; mean total score higher at most time points for E2V than for estradiol, indicating slightly better improvement with estradiol. Fewer sleep disorders in estradiol group than E2V at cycles 3, 4, and 5 only (p=0.02). No differences between groups on other psychofunctional disturbances or quality-of-life responses.

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Utian 2005 US	249	NR/NR/249	52.8 yrs (SD 6.7) 73.4% white Previous hysterectomy 50.4% Bilateral oophorectomy 27.0%	Postmenopausal women experiencing seven or more moderate or severe vasomotor symptoms (MSVS) daily for 1 week or 60 or more MSVS in 1 week. Women who had not undergone hysterectomy were eligible if they were 40 years or older and either had amenorrhea for at least 12 months or had amenorrhea for more than 6 months with serum follicle-stimulating hormone (FSH) levels above 40 U/L, serum estradiol levels below 20 pg/mL, and a negative pregnancy test result. Women who had undergone a hysterectomy with bilateral oophorectomy and were 35 years or older were eligible 6 weeks after surgery or if removal of the ovaries could be confirmed by FSH levels above 40 U/L and serum estradiol levels below 20 pg/mL. For all women with an intact uterus, an endometrial biopsy was required to rule out endometrial hyperplasia, carcinoma, or polyp. All participants discontinued estrogen/hormone therapy before the screening period by the following time points: oral, more than 8 weeks; vaginal, more than 1 week; transdermal, more than 4 weeks; intramuscular, more than 6 weeks; implantable/injectable, more than 3 months

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Utian 2005 US	History of cardiovascular or thrombotic disease; treatment with anticoagulants; known or suspected malignancy; uncontrolled hypertension or thyroid disorders; type 1 diabetes mellitus; past or current depression; severe systemic disease; or abnormal baseline laboratory values considered clinically significant.	NR	NR		0.9 mg estradiol acetate 1 mg micronized estradiol 0.625 mg conjugated equine estrogens therapy

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Utian 2005 US	RCT multicenter (33 US sites)	12 wks	7/NR/241	Mean percent reduction in number of weekly MSVS EA 0.9 mg vs estradiol 1 mg vs CEE: Week 4: 66.2% vs 72.2% vs 68.2%; NS Week 12: 77.8% vs 84.1% vs 84.1%; NS Least squares mean reduction in severity of MSVS (SE): EA 0.9 mg vs estradiol 1 mg vs CEE: Week 4: -0.53 (0.11) vs -0.51 (0.11) vs -0.59 (0.10); NS Week 12: -1.05 (0.13) vs -1.341 (0.13) vs -1.17 (0.12); NS Participant-assessed urogenital symptoms: estradiol group had improvement in dyspareunia and worsening of urinary urgency scores at 12 weeks; no differences between treatments on other symptom scores (Total, vaginal dryness, urinary incontinence, and nocturia) Investigator-assessed vaginal atrophy: No significant differences between groups on any measure (Total score, atrophy, pallor, dryness, tissue integrity/friability, petechiae)

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Oral CEE compared with transdermal E2				
Good 1999	321 in 4 groups		Postmenopausal women recruited from general population; 60 or more hot flashes per week; 70% white; Mean age 50-51; USA	
Gordon 1995	604 in 6 groups		Postmenopausal women with symptoms; Mean age approx. 50 (25-74); USA	

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Oral CEE compared with transdermal E2					
Good 1999				147/321	E2: 0.05, 0.1 mg/day; CEE 0.625, 1.25 mg/day
Gordon 1995				382/604	E2: 0.05, 0.1 mg/day (Climera); CEE: 0.625 mg/day oral

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Oral CEE compared with transdermal E2				
Good 1999	DB RCT	12 weeks		Reduction of hot flashes by 90% for both Rx; no Significant differences between Rx at comparable doses; data provided in graphs.
Gordon 1995	DB RCT	11 weeks		Number and severity of hot flashes: all groups decreased, Rx groups had Significant decline compared to placebo (67-72% decrease, $p<0.05$); no Significant difference between Rx groups but some dose-response trends for 2 doses of E2.

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Akhila 2006 India	116	NR/NR/116	NR; groups reported at being 'comparable'	Women who attained natural or surgical menopause presenting with post-menopausal symptoms

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Akhila 2006 India	Women with conventional contraindications for HRT	NR	NR		0.625 mg/day conjugated equine estrogen Estradiol percutaneous gel – hydroalcoholic gel delivered from a pressurized device. Two measures (1.25 g each) applied to shoulder or thigh per day. Each measure releases 0.75 mg of E2 Transdermal patch – ETS patch, alcohol reservoir based patch. Each patch contains estradiol USP 1.8 mg, releases 50 µg estradiol/24 hours. Applied over side of truck or buttocks and changed every 7 days. Estraderm Mx, Matrix releasing system releases 50 µg/day. Changed every 3 or 4 days All three groups received MPA 2.5 mg orally every day in presence of uterus or with history of endometriosis

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Akhila 2006 India	RCT Blinding NR Single center (hospital clinic)	1yr	NR/28/88	**% of patients with complete symptom improvement;** *one month followup* Vasomotor symptoms (N=75) data not reported; no significant differences between groups oral CEE vs E2 gel: p=0.306 E2 gel vs E2 patch: p=0.228 oral CEE vs E2 patch: p=0.107 Psychological disturbances (N=71; memory disturbances, anxiety, depressive episodes, loss of libido, emotional outbursts) 15% oral CEE; 47% E2 gel; 35% E2 patch oral CEE vs E2 gel: p=0.0004 E2 gel vs E2 patch: p=0.05 oral CEE vs E2 patch: p=0.001 Genital symptoms (N=34; dyspareunia, vaginal dryness and itching) 36% oral CEE; 57% E2 gel; 100% E2 patch oral CEE vs E2 gel: p=0.61 E2 gel vs E2 patch: p=0.04 oral CEE vs E2 patch: p=0.003 Urinary symptoms (N=42; frequency, dysuria) 25% oral CEE; 45% E2 gel; 70% E2 patch oral CEE vs E2 gel: p=0.017 E2 gel vs E2 patch: p=0.186 oral CEE vs E2 patch: p=0.002 **% of patients with complete symptom improvement;** *one year followup* Vasomotor symptoms (N=75) 62% oral CEE; 95% E2 gel; 100% E2 patch oral CEE vs E2 gel: p=0.023 E2 gel vs E2 patch: p>0.05 oral CEE vs E2 patch: p=0.0025 Psychological disturbances 30% oral CEE; 65% E2 gel; 68% E2 patch oral CEE vs E2 gel: p=0.009 E2 gel vs E2 patch: p>0.05 oral CEE vs E2 patch: p=0.004 Genital symptoms 64% oral CEE; 100% E2 gel; 100% E2 patch oral CEE vs E2 gel: p=0.029 E2 gel vs E2 patch: p>0.05 oral CEE vs E2 patch: p=0.0025 Urinary symptoms 40% oral CEE; 90% E2 gel; 100% E2 patch oral CEE vs E2 gel: p=0.024 E2 gel vs E2 patch: p>0.05 oral CEE vs E2 patch: p=0.002

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Serrano 2006	226	551/NR/226	52.5 yrs Race NR Mean time since menopause 22.1 months	Postmenopausal women with at least 6 months of amenorrhea and FSH levels greater than 40 U/L who were willing to initiate HRT for menopausal symptom relief
Oral CEE compared with transdermal E2				
Studd 1995	214 in 2 groups		Postmenopausal women with symptoms (at least 21 hot flashes per week); Mean age approx. 52 (40-65)	

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Serrano 2006	Prior HRT use, hysterectomy, previous malignancy, a first-degree relative with breast cancer aged <50 years, endometrial proliferative disorders, alterations of metabolic, liver, renal and cardiac function, hypersensitivity to retinoids, photodermatitis, retinal diseases or glaucoma, venous thromboembolic events, active infections, severe depression, porphyry and otosclerosis	NR	NR		CEE 0.625 mg/day and placebo CEE 0.625 mg/day and fenretinide 100 mg/bid Transdermal E2 50 µg/day released by a weekly patch and placebo Transdermal E2 50 µg/day released by a weekly patch and fenretinide 100 mg/bid
Oral CEE compared with transdermal E2					
Studd 1995				1%	E2: 0.05 mg/day (Menorest); CEE: 0.625 mg/day Dydrogesterone: 10 mg/day days 16-28

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Serrano 2006	RCT blinding NR setting NR	1yr	34/0/184	MENQOL mean score (SD) at 12 months; effect size for reduction from baseline <u>Vasomotor symptoms</u> CEE + placebo: 1.27 (0.9); 1.19 CEE + fenretinide: 1.3 (0.62); 1.19 E2 + placebo: 1.48 (1.12); 1.19 E2 + fenretinide: 1.51 (1.14); 1.19 <u>Physical</u> CEE + placebo: 2.46 (1.13); 1.19 CEE + fenretinide: 2.83 (1.65); 1.19 E2 + placebo: 2.54 (1.35); 1.19 E2 + fenretinide: 2.53 (1.34); 1.19 <u>Psychosocial</u> CEE + placebo: 2.42 (1.44); 1.19 CEE + fenretinide: 2.44 (1.6); 1.19 E2 + placebo: 2.43 (1.43); 1.19 E2 + fenretinide: 2.45 (1.29); 1.19 <u>Sexual</u> CEE + placebo: 2.51 (1.67); 1.19 CEE + fenretinide: 2.31 (1.77); 1.19 E2 + placebo: 2.52 (2.11); 1.19 E2 + fenretinide: 2.23 (1.83); 1.19 Reductions from baseline statistically significant in all domains; but in multiple regression the only significant variable was time; no other effect achieved statistical significance, indicating that the type of hormonal treatment or administration of fenretinide di not affect improvement. p-value for CEE vs E2: 0.287
Oral CEE compared with transdermal E2				
Studd 1995	DB RCT	12 weeks		Mean number of hot flashes per day: Significant decrease from baseline in both Rx groups (E2 7.1 to 0.9 per day, CEE 6.7 to 0.5 per day), no Significant differences between groups.

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
Vaginal E2 compared with oral E2				
Al-Azzawi, 2003 Buckler et al, 2003	159 in 2 groups		Postmenopausal women younger than age 65 with 20 or more hot flushes/night sweats per week. Mean age 51 (31-63); UK	

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
Vaginal E2 compared with oral E2					
Al-Azzawi, 2003 Buckler et al, 2003				71/159	vaginal E2: vaginal ring releasing 50 mcg/day. Oral E2: 1 mg/day Norethisterone 1 mg/day for last 12 days of each 28-day cycle.

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Vaginal E2 compared with oral E2				
Al-Azzawi, 2003 Buckler et al, 2003	DB RCT Multi-center	24 weeks		Percent change from baseline in number per week of hot flushes/night sweats at Week 24: 50 mcg vaginal ring vs 1 mg oral E2 95% vs 94% 50 mcg then 100 mcg vs 1 mg then 2 mg E2: 93% vs 89% No significant differences between groups at 12 or 24 weeks From Buckler 2003: Significant improvement from baseline in total Greene Climacteric Scale scores in both treatment groups at 12 and 24 weeks, no between-group differences.

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	N	No. screened/eligible/ enrolled	Age, ethnicity and other population characteristcis	Inclusion criteria
E2 vaginal ring compared with E2 vaginal tablet				
Weisberg 2005 Australia	185	NR/NR/185	57.9 yrs Race NR Mean duration of estrogen deficiency syndrome 3.7 yrs Mean time since menopause 8.5 yrs	Women who were more than 2 years postmenopausal, with significant symptoms or objective signs of urogenital atrophy. Women had to exhibit symptoms such as vaginal dryness, genital pruritus, dyspareunia, dysuria, urinary urgency, frequency or nocturia, have an endometrium equal to or less than 5 mm thickness on a transvaginal ultrasound scan and a negative progestogen challenge test (PCT)

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Exclusion criteria	Run-in/ wash out	Allowed other medications/ interventions	Hysterectomy (#/n)	Interventions
E2 vaginal ring compared with E2 vaginal tablet					
Weisberg 2005 Australia	Women who were hysterectomized or had a significant uterine prolapse, had received hormonal treatment within the previous 3 months, experienced bleeding after the PCT or had vaginal bleeding of unknown origin, had clinically significant hepatic or kidney disease, acute or intermittent porphyria or a confirmed history of thromboembolic disease	NR	NR		ESTring vaginal ring containing 2 mg micronized 17β-estradiol (releases 8 µg per 24 h in continuous amounts over 90 days, equalling a total dose of 0.7 mg over the 3-month lifespan of the device) Vagifem mucoadhesive tablet containing 25 µg of 17β-estradiol

Evidence Table 1. Head to head trials with hot flash/flush or other symptom outcomes

Study/Year	Study design, setting	Length of trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
E2 vaginal ring compared with E2 vaginal tablet				
Weisberg 2005 Australia	RCT Open Multicenter	1yr	39/NR/varied by outcome (155-185)	Investigator rated pelvic floor strength not changed by either treatment. Self-reported vaginal symptoms at week 48, ESTring vs Vagifem Dryness: 31% vs 26% Pruritus vulvae: 17% vs 20% Dysuria: 2% vs 0% Urinary frequency: 30% vs 32% Urinary urgency: 36% vs 39% Dyspareunia: 33% vs 18% No significant differences between treatments Vaginal signs on inspection at week 48, ESTring vs Vagifem Erythema: 6% vs 7% Irritation: 1% vs 2% Ulceration: 0% vs 0% Bleeding: 4% vs2% No significant differences between treatments Improvement in urogenital quality of life (sexual function, sleep quality, urinary burden of condition, vaginal burden of condition, and total burden of condition) was statistically significant at 48 weeks for both groups, with no difference between treatments

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Oral estradiol								
Almeida 2006		278/NR/115	73.7 yrs Race NR Previous use of HRT 37.6 %	Women aged 70 years or over	Women with intact uterus, history of breast cancer or abnormal breast examination, history of deep vein thrombosis or other disorders of coagulation, coronary heart disease, Mini-Mental State Examination score lower than 24, non-English speaking background, severe impairment of	subjects in the treatment group had run-in: 0.5 mg/d during initial 2 weeks, 1mg/d in weeks 3-4 and 2mg/d weeks 5-16/ washout also for treatment group 1mg in week 17-18 and 0.5mg in weeks 19-20	NR	0/115
Baerug 1998*	119 in 3 groups		Post and perimenopausal women in gyn clinics with "moderate to severe" symptoms; Mean age 51 (45-61); Norway					NR
Bech 1998*	151 in 3 groups		Post and perimenopausal women from community; Age not reported; Denmark					NR
Chung 1996*	100 in 2 groups		Chinese women post TAHBSO 66% had vasomotor symptoms at baseline (23-35% considered moderate to severe); Mean age 43.8; Hong Kong					100/100
Crisafulli 2004 (17-beta estradiol)		NR/NR/90	51.7 yrs Race NR Mean time since menopause 6.7 yrs	Healthy, postmenopausal, ambulatory women who were 47 to 57 years of age, had not undergone surgically induced menopause, had not had a menstrual period in the preceding year, and had a follicle-stimulating hormone level greater than 50 IU/L and a serum 17β-estradiol level of 100 pmol/L or less	Clinical or laboratory abnormalities that suggested cardiovascular, hepatic, or renal disorders; coagulopathy; use of oral or transdermal estrogen, progestin, androgen or other steroids in the preceding year; and smoking more than 10 cigarettes per day	4-week stabilization on diet/NR	NR	
Conard 1995*	57 in 3 groups		Post and perimenopausal women from hospital clinics; all with symptoms, 93% with "moderate to severe" symptoms; Mean age 51.8 (44-61); Paris, France					0/57

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Oral estradiol					
Almeida 2006	0.5 mg estradiol during the initial 2 weeks, 1 mg during weeks 3 and 4, 2 mg from weeks 5 to 16, and again 1 and 0.5 mg during the remaining 4 weeks (2 weeks each, respectively)	RCT DB	20 weeks	29/7/115	Mean change from baseline to end of study, estradiol vs. placebo Beck Depression Inventory score: -1.5 vs. -1.3, NS Beck anxiety inventory: -0.8 vs. 0.4, NS SF-36 Score: -0.7 vs. -2.7, NS CAMCOG: 3.2 vs. 2.6, NS
Baerug 1998*	E2: 1 mg/day NETA: 0.25, 0.5 mg/day (CCT)	DB RCT	12 weeks		Hot flash frequency (mean): E2= 6-9 over 2 weeks (Significant different from placebo, includes all levels of hot flash intensity, no differences between progestin groups); vasomotor severity (Kupperman's Index, Greene's Climacteric Score): E2= Significant improvement compared to placebo on Kupperman Index and Greene scales (vasomotor and psychological subscales). Women in early (3-12 months amenorrhea) as well as late menopause (>12 months ammenorrhea) had benefit.
Bech 1998*	E2: 2 mg/day (CCT), 2 mg/day days 1-12, then 1 mg/day days 23-28 (cyclic) NETA: 1 mg/day (CCT & cyclic)	DB RCT	1 year		Hot flash severity: Kupperman scores Significantly different (E2= 3-3.7, placebo=9; p<0.01), no difference between CCT and cyclic.
Chung 1996*	E2: 2 mg/day	DB RCT cross-over	1 year		Vasomotor severity score, number with hot flashes, number with moderate to severe hot flashes: no Significant differences between Rx and placebo.
Crisafulli 2004 (17-beta estradiol)	1 mg/day 17β-estradiol combined with norethisterone acetate 54 mg/day of the phytoestrogen genistein placebo	DB RCT	NR	7/NR/90	Mean % change in daily flushe socre as compared with placebo 3 months: -53% (p<0.001) 6 months: -56% (p<0.001) 12 months: -54% (p<0.001)
Conard 1995*	E2: 1, 1.5 mg/day days 1-24 Nomegestrol acetate: 2.5, 3.75 days 11-24 (cyclic)	DB RCT	3 months		Daily hot flash frequency, vasomotor severity score, number with hot flashes: Significantly decreased among all groups, Significantly better effect in Rx groups compared to placebo, no difference between Rx groups.

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Derman 1995*	82 in 2 groups		Post and perimenopausal women; at least 20 vasomotor events/week; Mean age 50 (40-60); USA					0/82
Freedman 2002	24 in 2 groups		Healthy postmenopausal women reporting 5 or more hot flashes per day in university setting; Mean age 52; US					NR
Gelfand 2003	119 in 2 groups		Postmenopausal women with a Kupperman Index of at least 15, at least 20 hot flushes per week, serum E1 of 100 pmol/L or less, and serum FSH of 30 IU/L or more. Mean age 52.6					0/119
Jensen J 1983*	100 in 4 groups		Postmenopausal women; 62% had hot flashes at baseline; Mean age 51.5 (46-55); Denmark					0/100
Jirapinyo et al, 2003	120 in 2 groups		Postmenopausal women; Mean age 54.3 (SD 4.3); Thailand					0/120
Notelovitz 2000a	333 in 5 groups		Menopausal women with moderate or severe hot flashes; Mean age 51 (40-60); US					0/333
Notelovitz, 2000b	145 in 3 groups		Menopausal women with 8 or more hot flashes/day; Mean age 49 (31-63); US					101/145

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Derman 1995*	E2: 2 mg/day days 1-12, 1 mg/day days 23-28 NETA 1 mg/day days 13-22 (cyclic)	DB RCT	16 weeks		Hot flash frequency: decrease in both groups (Rx from 7 to 1.3/day; placebo 6 to 4.2/day; Significant diff); also Significant differnces between Rx and placebo for Kupperman, Greene, and Beck scores.
Freedman 2002	E2: 1 mg/day	DB RCT	3 months		Hot flash frequency: Significant decline with E2, increased in placebo (determined by laboratory measures rather than self-report).
Gelfand 2003	E2: 1 mg/day norgestimate 90 mcg/day for 3 days on, 3 days off.	DB RCT	90 days		Change in Kupperman Index at 90 days (lower score means improvement): E2 vs placebo -16.8 vs -7.8 (p<0.001) at 45 days: -14.8 vs -7.2
Jensen J 1983*	E2: 1 mg/day days 1-12 NETA 1 mg/day days 13-22 (cyclic)	RCT	1 year		Hot flash severity and frequency: decrease in all Rx groups compared to placebo, dose-reponse relationship.
Jirapinyo et al, 2003	E2: 2mg/day NETA: 1mg/day	DB RCT Single center	1 year		Mean decrease in Greene's score (range 0-63) after 12 months did not significantly differ between E2 and placebo (p=0.24): -4.67 (95% CI -7.34 to -2.0) vs -6.98 (95% CI -9.7 to -4.2) Analysis included only 84 of 120 randomized patients.
Notelovitz 2000a	E2: 0.25, 0.5, 1, 2 mg/day	DB RCT	12 weeks		Number and severity of hot flashes: all Rx and placebo groups had reduction; Significant difference for 0.5, 1 mg, 2 mg Rx groups compared to placebo, not Significant for 0.25 mg group. Demonstrated dose-response relationship.
Notelovitz, 2000b	E2: 0.5, 1 mg/day	DB RCT	12 weeks		% change from baseline in number of hot flashes: -83.2% 1 mg/day, -65.5 0.5 mg/day, stat Significantly lower than placebo.

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Characersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Schurmann 2004		286/NR/225	53.6 yrs 100% caucasian	Healthy postmenopausal Caucasian women, 45–65 years old, who complained of at least five moderate to severe hot flushes per day on at least 7 of the 14 days preceding the study. Subjects were required to have an intact uterus with a normal endometrium, as determined by either transvaginal ultrasound or biopsy, estradiol levels≤20 pg/ml and serum follicle stimulating hormone (FSH) levels ≥50 U/l	Contraindications for hormone replacement therapy, treatment with anticoagulant medications, use of oral, transdermal, transvaginal hormonal preparations within 6 weeks or long-acting injectable or implanted preparations 6 months preceding the study; a past medical history significant for cardiovascular disease, depression, diabetes mellitus, hypertension, thromboembolic disease, alcohol or drug abuse, or other diseases or conditions that could, in the opinion of the investigator, affect study results; participation in another clinical study within 1 month or use of an investigational drug within 3 months prior to the study	NR	None	
Speroff 2006 (estradiol acetate)		Study 1: NR/NR/293 Study 2: NR/NR/259	Study 1: 53.4 yrs 78.2% caucasian 8.7% black 12.5% hispanic Study 1: 52.2 yrs 80.1% caucasian 13.6% black 4.5% hispanic	Women with or without prior hysterectomy were eligible if they self-reported 7 or more daily or 60 or more weekly episodes of moderate to severe vasomotor symptoms for at least 1 week of the 2-week screening period. Women with an intact uterus aged 40 years or older were included if they had amenorrhea for at least 12 months or for 6 to 12 months with a follicle-stimulating hormone level above 40 U/L and estradiol level below 20 pg/mL. Women were required to have a negative urine pregnancy test result, Pap smear, and mammogram, and endometrial biopsy or transvaginal ultrasound showing no evidence of endometrial hyperplasia, carcinoma, or polyps. Women with bilateral oophorectomy aged 35 years or older were required to be at least 6 weeks postsurgery or, if removal of both ovaries was unconfirmed, have follicle-stimulating hormone and estradiol levels as above. Women were not required to have any symptoms of vulvovaginal atrophy to be included in either study	Women with known or suspected malignancy; history of cardiovascular disease, diabetes, or thrombotic condition; clinically significant abnorma laboratory value at baseline; had taken hormone therapy within the following time periods before screening: oral within 8 weeks, vaginal within 1 week, transdermal within 4 weeks, intramuscular within 6 weeks, progestational implants, estrogen or estrogen/progestational injection within 3 months, or estrogen pellet or progestational injectable within 6 months	NR	NR	
Viklyleva 1997* English abstract	64 in 2 groups		Perimenopausal women; moderate to severe symptoms; Age 39-56; Moscow, Russia					NR

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Schurmann 2004	1 mg estradiol/1 mg drospirenone 1 mg estradiol/2 mg drospirenone 1 mg estradiol/3 mg drospirenone placebo	DB RCT Multicenter	2 weeks	20/0/225	Relative Change in number of hot flushes for ITT population, mean change (%) 1 mg estradiol/1 mg drospirenone vs. 1 mg estradiol/2 mg drospirenone vs. 1 mg estradiol/3 mg drospirenone vs.placebo -85.6 (p<0.001) vs. -88.0 (p<0.001) vs.-84.5 (p<0.001) vs.-47.0 Change in incidence of menopausal syptoms for Valid case population, (% of patients with symptoms) Sweating Episodes change: -67.6 vs. -63.2 vs. -59.5 vs. -28.3 Sleep Problems change: -46 vs. -63.1 vs. -66.7 vs. -23.9 Depression change: -29.7 vs. -18.4 vs. -33.3 vs. -17.4 Nervousness change: -35.2 vs. -28.9 vs. -23.9 vs. -19.5 Vaginal Dryness change: -32.4 vs. -21.1 vs. -23.8 vs. -10.8 Pollakisuria change: -18.9 vs. -10.5 vs. -30.9 vs. -10.9 Nocturia change: -21.6 vs. -29 vs. -28.6 vs. -8.7
Speroff 2006 (estradiol acetate)	Study 1: oral EA 0.9 mg, oral EA 1.8 mg, or placebo Study 2: oral EA 0.45 mg or placebo	DB RCT Multicenter	NR	Study 1 and 2:11/NR/548 Study 1: NR/4/289 Study 2: 38/NR/221	Study 1: mean change in vasomotor symptom severity score (1-3 scale) from baseline to week 12, 1.8mg vs. 0.9 mg vs. placebo -1.5 (p<0.001) vs. -1.1 (p<0.001) vs.-0.3; decrease in mean number of moderate to severe vasomotor symptoms in both treatment groups vs placebo (p <0.001); relative decrease in number of vasomotor symptoms: 77.8% in EA 0.9 mg, 91% in 1.8 mg EA and 45.6% with placebo Vaginal atrophy: reduction in investigator-assessed vaginal atrophy, dryness, friability for both EA groups vs placebo (p<0.05) Study 2: mean change in vasomotor symptom severity score from baseline to week 12, 0.45mg vs. placebo -0.7 (p<0.001) vs.-0.3; decrease in mean number of moderate to severe vasomotor symptoms in both treatment groups vs placebo (p <0.05);
Viklyleva 1997* English abstract	E2: 2 mg/day days 1-22, 1 mg/day days 23-28 NETA: 1 mg/day days 13-22 (cyclic)	DB RCT	24 weeks		Hot flash frequency: improvement on Kupperman index for Rx group vs placebo (p=0.01).

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Wolf 2005		NR/NR/51	64.1 yrs Race NR Mean time since estrogen therapy 13.5 yrs	Previous hysterectomy, non-smokers between 58 and 75 years and a body mass index (kg/m2) between 20 and 34. Antihypertensives, lipid lowering agents, aspirins, and vitamins were permitted. Subjects were screened for depression (Centre for Epidemiological Studies Depression Scale) and dementia (MMSE)	Estrogen treatment within the past year; cancers, tumors, deep vein thrombosis, metabolic, cardiovascular or neurological diseases	NR	NR	
Yang, 2002	56 in 2 groups		Postmenopausal women Mean age 50 (47-52)					0/56
Transdermal								
Bacchi-Modena 1997	109 in 2 groups		Menopausal women with symptoms (7 or more hot flashes/day); Mean age 51.9 (39-61); Italy					NR
Baksu 2005		NR/NR/75	NR, only that NS difference with regard to age or other population characteristics	total abdominal hysterectomy and bilateral oophrectomy for benign conditions	history of cerebrovascular or thromboembolitic disease, chronic renal or liver disease, genital bleeding of undetermined origin, some form of cancer or with dementia; self-admitted history of depression, current or past antidepressant use or a score of more than 13 points on the Hamilton Depression Score.	NR	NR	
De Aloysio, 2000	156 in 3 groups		Menopausal women with at least 5 hot flashes/day; Mean age 53-54; Italy					8/156
de Vrijer 2000	254 in 3 groups		Menopausal women with symptoms (7 or more hot flashes/day); Mean age 52 (40-64); Netherlands					89/254
Gordon 1995	604 in 6 groups		Postmenopausal women with symptoms; Mean age approx. 50 (25-74); US					382/604

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Wolf 2005	2 mg oral estradiol 2 mg oral estradiol/100 mg oral progesterone placebo	DB RCT	NR	9/NR/35	Mean change in cognitive tests, E2 vs. E2/Prog vs. placebo Paragraph recall immediate: 0.75 vs. 1.45 vs. 2.2, p= 0.43 Paragraph recall delayed: 1.29 vs. 0.9 vs. 1.69, p=0 .90 Verbal PA immediate: -1 vs. 2.8 vs. 2.92,p= .25 Verbal PA delayed: 0.08 vs. 0.4 vs. 1, p=0.67 Visual PA immediate: 2.33 vs. 0.5 vs. 2.07, p=0.90 Visual PA delayed: 0.42 vs. 0.6 vs. 0.16, p=0.23 Digit span forwards: -0.09 vs. 0.9 vs. -0.15, p=0.14 Digit span backwards: 0.58 vs. 0.5 vs. 0.31, p=0.88 Block span forwards: 0.84 vs. 0.1 vs. 0.61, p=0.16
Yang, 2002	E2: 2 mg/day norethisterone acetate 1 mg/day	DB RCT	4 months		Change in Greene Climacteric Scale at 4 months (decrease means improvement): E2 vs placebo -3.3 (+/-4.5) vs +3.2 (+/-8.0) p=0.009
Transdermal					
Bacchi-Modena 1997	E2: 0.05 mg/day (Estraderm, MX 50)	DB RCT	12 weeks		Mean number of moderate to severe hot flashes per 24 hours: Significantly reduced compared to placebo (-8 from baseline for Rx, -4 for placebo, p<0.001); Kupperman index: -18 for Rx, -9 for placebo (p<0.001).
Baksu 2005	Tibolone 2.5mg/day continuously transdermal estradiol 3.9mg/week placebo oral qd	DB RCT	NR	10/NR/65	Change in mean scores E2 vs. Placebo Hamilton Depression Rating Scale:-8.4 vs. -0.7 (p<0.05) Hamilton Anxiety Rating Scale (0-56): -12.5 vs. -0.7 (p<0.05) Kupperman's Scale (0-51): -14.7 vs. -1.9 (p<0.05)
De Aloysio, 2000	E2: 0.25, 0.375 mg/day	DB RCT	12 weeks		% decrease in number of hot flashes: 83-84% in E2 groups, 58% placebo (p<0.05).
de Vrijer 2000	E2: 0.05, 0.10 mg/day (Estraderm MX 50, 100)	DB RCT	12 weeks		Mean number of moderate to severe hot flashes per 24 hours: similar for both Rx groups, Significantly reduced compared to placebo (-5 to -5.3 for Rx, -0.3 for placebo, p<0.001); Kupperman index and night sweats also Significantly decreased for both Rx groups compared to placebo (presented in graph).
Gordon 1995	E2: 0.05, 0.1mg/day; CEE: 0.625 mg/day oral	DB RCT	11 weeks		Number and severity of hot flashes: all groups decreased, Rx groups had Significant decline compared to placebo (67-72% decrease, p<0.05); no Significant differece between Rx groups but some dose-response trends for 2 doses of E2.

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Joffe 2006		NR/NR/52	51.0 years 88% white Previous hormone therapy use: 82%	healthy women ages 40 to 60 who were in the early menopause transition, late menopause transition or early post menopausal years; baseline FSH levels above 25 IU/L	psychiatric disorders; major depression or dysthymia or if they had another psychiatric or substance use disorder within 1 year of enrollment; previous bilateral oophrectomy, contraindiications to HT, Mini-mental status Examination score of less than 29, educational achievement below high school, lack of proficienncy in english, neurological disorders, use of psychotropic or hypnotic medications within the past 3 months and use of estrogen therapy within the past year	NR	NR	
Levine 2005		Trial 1; NR/NR/624 Trial 2: NR/NR/226	Trial 1: 54.67 years NR Trial 2: 52.52 years NR	common eligibility criteria: healthy postmenopausal aged 40-70 years with intact uterus, no mensesfor at least 1 year; serum concentrations of FSH >/=40 IU/L and estradiol </= 20 pg/ml; normal pelvic, PAP smear and mammogram examinations; no major contraindications to estrogen therapy; ability and willingness to complete daily diary records; and ability to understand fully all study procedures and provide written informed consent. Trial 2: 8 or more hot flashes/day	current endometrial hyperplasia; unexplained vaginal bleeding; any use of HT with estrogens or progestins taken within 4 weeks preceeding baseline screening visit; any nonhormonal therapy for hot flashes or menopausal symptoms in the 2 weeks before the screening visit; any use of lipid-lowering drugs within 3 months before baseline; alleric dermatitis or eczema; intolerance of estrogen or progestin or patch; known or suspeted malignancies or carcinoma; and documented or active thrombophlebitis or active coagulation disorders	NR		
Notelovitz 2000c	220 in 2 groups		Postmenopausal women with 8 or more hot flashes per day; Mean age approx. 53					0/220
Schiff 2005		NR/NR/24	71 yrs 92% white HRT naïve 5/24 (21%)	Previous hysterectomy, age >60yrs, no use of any form of ERT for at least 12 mos prior to study entry, no use of any medications which might enhance cognition, no standard clinical contraindication to ERT, mini mental state exam score >26 with normal results (<7) on the brief assessment scale depression cards.	NR	NR	NR	

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Joffe 2006	Estradiol 0.05mg/day patch placebo patch	DB RCT	NR	2/none/50	Cognitive Process Estrogen Mean vs. Placebo Mean Verbal Skills CVLT trails 1-5 immediate verbal recall: 0.6 vs. 2.6, NS CVLT perspective errors during verbal recall: -2.8 vs. -0.8 (p= .03) CVLT proactive interference during verbal recall: -1.2 vs. 0 (p= .07) CVLT verbal recall: 0.6 vs. 0.7, NS CVLT retroactive memory: 0.7 vs. -0.1, NS WMS-R verbal memory: 0.9 vs. -0.1, NS WMS-R delayed memory: 5.0 vs. 3.0, NS Visual Skills WMS-R visuospatial memory: 1.9 vs. 1.0, NS Rey-Osterreith short-term visuospatial memory: -0.2 vs. -0.12, NS Rey-Osterreith long-term visuospatial memory: -0.17 vs. -0.1, NS General Skills WMS-R mental control: 0.2 vs. 0.2, NS WMS-R digit span: -0.5 vs. 0.2, NS WMS-R visual span: 1.3 vs. 0.9, NS WMS-R general memory: 3.0 vs. 0.9, NS
Levine 2005	Trial 1: not included Trial 2: combined patch with estradiol 50mcg/day and Norethindron acetate (140, 250 or 400 mcg/day) or placebo	DB RCT	NR	Trial 1; 150/NR/624 Trial 2: 21/NR/226	Trial 2: pre vs post difference vs. placebo control: Hot flashes: 8.96 (SD=3.3) vs. 5.42(SD=3.6), p<0.0001 WHIIRS; 4.79(SD=5.0) vs. 2.97 (SD=3.8), p=0.035
Notelovitz 2000c	E2: 0.05 mg/day (Vivelle) Norethidrone acetate:140, 250, 400 microgm/day days 15-28	DB RCT	12 weeks		Mean number of hot flashes per day, mean intensity of hot flashes and sweating: Significant reductions for all outcomes for all Rx regimens compared to placebo (p<0.001).
Schiff 2005	50 ug/day transdermal estradiol transdermal placebo	Crossover RCT single center	24 wks (12 wks each arm)	NR	Outcome: Mean depression score (BASDEC - Brief Assessment Scale Depression Cards) estradiol 1.05 (SD 1.41) vs placebo 1.55 (SD 1.47); p=0.05 Mean change from baseline score estradiol -0.45 vs placebo 0.05

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Shulman, 2002	293 in 3 groups		Symptomatic women with 7 or more moderate to severe hot flashes/day for 1 week; with and without a uterus; mean age 51-52 (44-68); US					NR
Speroff 1996 Symons 2000 (vaginal bleeding) Ethinyl estradiol +	324 in 7 groups		Postmenopausal women with hysterectomy with hot flashes; Mean age 49; US					324/324
Speroff 2000 2 studies, differing dosages and F/U interval Symons 2000 (vaginal bleeding) Ethinyl estradiol + norethindrone acetate		Study 1, 2 NR/NR/219, 266	Study 1: 51.7 yrs 90.5% caucasian 8.3% black 1.2% other Study 2: 50.9 yrs 88.8% caucasian 7.5% black 3.7% other	Study 1: ≥ 40 years and spontaneous menopause within 5 yrs, defined as amenorrhea for at least 12 months, with serum concentrations of FSH >/=40 IU/L and estradiol </= 40 pg/ml. Discontinued HT at least 3 months before study entry. >/=10 hot flashes/week in 1-month screening period. Study 2: ≥ 40 years and spontaneous or surgical menopause within 5 yrs., defined as amenorrhea for at least 12 months or for 6-12 months with serum concentrations of FSH >/=50 IU/L and estradiol </= 25 pg/ml. Discontinued HT at least 2 months before study entry. >/=56 moderate to severe hot flashes in 2-week screening period.	NR	NR	Study 1 and 2: NR	Unclear
Utian 1999	196 in 4 groups		Postmenopausal women with symptoms; 81% White, 17% Black, 4% other race; Mean age 50; US					124/196
van Holst 2000	186 in 2 groups		Postmenopausal women with symptoms; Mean age 53; Germany					186/186
van Holst 2002	179 in 3 groups		Postmenopausal with symptoms; Mean age 53; Germany					0/179

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Shulman, 2002	E2: 0.045 mg/day Levonorgestrel: 0.03, 0.04 mg/day	DB RCT	12 weeks		Mean decrease from baseline in daily number of hot flashes: 9 and 10 for E2 groups, 5 for placebo (p<0.001).
Speroff 1996 Symons 2000 (vaginal bleeding) Ethinyl estradiol +	E2: 0.02 mg/day (different delivery systems)	DB RCT	12 weeks		Hot flash frequency: 84% decrease in Rx groups significantly lower than in placebo group Vaginal bleeding: increased with dosage and was greater than placebo for 2 highest dosage (p<0.05); maximal week 4, decreased over time
Speroff 2000 2 studies, differing dosages and F/U interval Symons 2000 (vaginal bleeding) Ethinyl estradiol + norethindrone acetate	Study 1: norethindrone acetate/estradiol: 0.2mg/1mcg, 0.5mg/2.5mcg, 1mg/5mcg or 1mg/10mcg or placebo/day Study 2: norethindrone acetate/estradiol: 0.5mg/2.5mcg, 1mg/5mcg or 1mg/10mcg or placebo/day	DB RCT	NR	Study 1, 2, 3 NR/NR/84, 113, 419	Study 1: mean change in hot flushes from baseline to week 16, NA/EE 0.5mg/2.5mcg compared with placebo -30.0 (-73.7%), p<0.05; responder rate: greater than 75% improvement from baseline 63.4% vs. 27.9%, p=0.002 Study 2: mean change in hot flushes from baseline to week 12, NA/EE 0.5mg/2.5mcg compared with placebo -63.8 (-82.2%), p<0.001; mean change from baseline in mean intensity score -1.30 vs. -0.67, p=0.001 Vaginal bleeding: increased with dosage and was greater than placebo (no statistics); maximal week 4, decreased over time
Utian 1999	E2: 0.025, 0.05, 0.1 mg/day (Esclim)	DB RCT	12 weeks		Frequency of moderate to severe vasomotor symptoms: Significantly reduced compared with placebo (p<0.05).
van Holst 2000	E2: 0.05 mg/day (Fem 7)	DB RCT	12 weeks		Changes in Kupperman index: declined in both groups, Significantly lower in Rx group (27.6 to 11.2 for Rx, 27.9 to 16 for placebo, p=0.0006); mean hot flashes: Significantly lower in Rx group (44.3 to 11.8 in Rx, 41.4 to 19.4 in placebo, p=0.0025).
van Holst 2002	E2: 0.05 mg/day (Fem 7 and Fem 7 Combi) Levonorgestrel patch: 10 microgm/day	DB RCT	12 weeks		Changes in Kupperman index: Significantly lower in Rx group (26.3 to 9.5 in Rx group, 27.1 to 15.9 for placebo, p=0.0001); number of hot flashes: Significantly lower for Rx group.

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Yaffe, 2006 Diem 2006 Waetjen, 2005 ULTRA		1509/604/417	67 yrs 92.3% white 16.5 yrs. Since menopause	Age 60-80yrs, intact uterus, at least 5 yrs beyond menopause, normal bone mineral density for age	Previous use of estrogen or progestin w/in 3 months of randomization, unexplained uterine bleeding, enometrial hyperplasia or endometrium 5mm or more in double wall thickness, abnormal mammogram suggestive of breast cancer, history of metabolic bone disease, cancer, coronary disease, cerebrovascular disease, uncontrolled hypertension, uncontrolled thyroid disease, liver disease, fasting triglycerides >300 mg/dL, fasting glucose > 180 mg/dL	NR	oral calcium 400mg and Vitamin D 400IU/ day	
Wiklund, 1993	242 in 2 groups		Symptomatic postmenopausal women age 45-65; Mean age 52-53; Sweden					0/242
Vaginal estradiol								
Speroff, 2003	333 in 3 groups		Postmenopausal women with at least 7 moderate to severe hot flushes per day or an average of at least 56 moderate to severe vasomotor symptoms per week for 2 weeks. Mean age 51.7 (range 29-85)					165/333

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Yaffe, 2006 Diem 2006 Waetjen, 2005 ULTRA	14 ug/day transdermal estradiol transdermal placebo	RCT multicenter (clinics)	2yrs	83/41/417	Mean difference in Modified Mini Mental State Examination, 2 yrs, estradiol vs placebo: (Yaffe 2006) In pts w/baseline score ≤90: -1.21 (-5.05 to 2.64; p=0.53) In pts w/baseline score ≥90: -0.30 (-0.74 to 0.14; p=0.18) Mean difference in SR-36, 2 yrs, estradiol vs placebo Physical test: -0.37 (-1.47 to 0.72; p=0.50) Mental test: -0.95 (-2.16 to 0.26; p=0.12) Estradiol vs placebo, 2 yrs: (Waetjen 2005) Any incontinence: OR 1.35 (075-2.42; p=0.32) Stress incontinence: OR 1.52 (0.79-2.93; p=0.21) Urge incontinence: OR 0.95 (0.50-1.82; p=0.88) % improved, unchanged or worsened incontinence, estradiol vs placebo, 2 yrs: Improved - Any type of incontinence: 27.4% vs 38.2%; Stress incontinence: 17.9% vs 29.2%; Urge incontinence: 13.1% vs 16.9% Unchanged - Any type of incontinence: 56.0% vs 44.9%; Stress incontinence: 72.6% vs 61.8%; Urge incontinence: 73.8% vs 65.2% Worsened - Any type of incontinence: 16.7% vs 16.9%; Stress incontinence: 9.5% vs 9.0%; Urge incontinence: 13.1% vs 18.0% Change in proportion reporting postmenopausal symptoms, estradiol vs. placebo Hot flashes: -8.0 vs. -7.1, NS Vaginal Dryness: -5.2 vs. -3.8, NS Trouble Sleeping: 2.7 vs. -0.9, NS Change in proportion reporting potenial side effects, Estradio Breast tenderness: 0.4 vs. -0.2, NS
Wiklund, 1993	E2: 0.05 mg/day	DB RCT	12 weeks		Mean change from baseline for vasomotor symptoms score and Kupperman index stat Significant reduced compared to placebo (p<0.0001).
Vaginal estradiol					
Speroff, 2003	intravaginal ring delivering the equivalent of E2 50 mcg or 100 mcg per day; placebo vaginal ring 2.5 mg per day oral norethindrone or 10 mg per day oral medroxyprogesterone acetate for 14 days after removal of the vaginal ring.	DB RCT	13 weeks		Percentage reduction from baseline in number of moderate to severe vasomotor symptoms per week at 13 weeks: E2 50 mcg vs E2 100 mcg vs placebo: 79.9% vs 90.6% vs 49.1% (p<0.05 vs placebo for both E2 groups)

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Orald estradiol valerate								
Blumel 1994*	50 in 2 groups		Post and perimenopausal women hospital workers; 68% had baseline vasomotor symptoms; Mean age 52.6 (37-66); Chile					NR
Heinrich 2005		NR/NR/51	64.1 yrs Race NR Age at hysterectomy 43.8 (SD 1.4) yrs Time since treatment with gonadal hormones 13.5 (SD 1.5) yrs	Age 58-75 yrs, nonsmokers, BMI 20-24previous hysterectomy, no estrogen treatment within 12 mos	Cancers, tumors, deep vein thrombosis, metabolic diseases, cardiovascular diseases, neurological or psychiatric disorders	NR	Lipid lowering agents, antihypertensives, aspirin herbal products, vitamins	
Jensen P 1987*	76 in 2 groups		Post and perimenopausal women; 89% had hot flashes at baseline; Mean age 49.8; Denmark					0/76
Marslew 1992*	50 in 2 groups		Post and perimenopausal women; 90% had hot flashes at baseline; Mean age 51 (45-54);					0/50
Oral CEE								
Dayal, 2005		50/40/32	56.6 yrs 78% white	Menopausal age 44-70 yrs, history of no menstrual cycle for at least 1 year or at least 6 mos of amenorrhea with a documented FSH level >40 mIU/ML, no exposure to hormone therapy at least 60 days prior to study, normal Pap smear and mammogram within last year, normal liver transaminase levels, renal function, total cholesterol and triglyceride levels	Any contraindication to ET including known or suspected brast cancer, endometrial hyperplasia/carcinoma, undiagnosed vaginal bleeding, active thromboembolic disorders, history of cerebrovascular disease, coronary artery disease, MI, DM, uncontrolled hypertension, abnormal liverl or renal function, major psychiatric disorder, contraindication to the use of MRI	10 day progestin run-in for pts without hysterectomy	NR	

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Orald estradiol val					
Blumel 1994*	E2V: 2 mg/day MPA 2.5 mg/day (CCT)	DB RCT	6 months		Vasomotor severity score (0-3), number with hot flashes, number with moderate to severe hot flashes: improvement in both Rx and placebo groups over time, Significantly better response with Rx group.
Heinrich 2005	2 mg estradiol valerate 2 mg estradial valerate + 100 mg progesterone placebo	RCT single center	24wks	9/0/35 (7 post-randomization exclusions)	Outcome: Results of screening questionnaires, scores at 24 wks estradiol vs estradiol/progesterone vs placebo Depression: 6.42 (SD 1.17) vs 9.80 (SD 1.44) vs 6.85 (SD 1.75) Mood: 31.17 (SD 1.20) vs 32.80 (SD 1.40) vs 34.23 (SD 1.73) Wakefulness: 27.50 (SD 1.86) vs 24.90 (SD 2.73) vs 30.77 (SD 1.65) Calmness: 29.42 (SD 1.69) vs 28.90 (SD 1.56) vs 29.62 (SD 1.58) Menopause index (total) 15.08 (SD 2.25) vs 17.10 (SD 2.63) vs 19.85 (SD 4.01) Somatic complaints: 5.25 (SD 0.58) vs 4.50 (SD 0.86) vs 7.08 (SD 1.85) Psychosomatic complaints: 1.25 (SD 0.45) vs 2.30 (SD 0.72) vs 2.23 (SD 0.67) Psychological complaints: 8.58 (SD 1.73) vs 10.30 (SD
Jensen P 1987*	E2V: 2 mg/day days 1-21 Cyproterone acetate 1 mg/day days 12-21 (cyclic)	DB RCT	2 years		Number with hot flashes: Significant reduction for Rx group (93% to 22%), no Significant change for placebo (87% to 77%).
Marslew 1992*	E2V: 2 mg/day Cyproterone acetate 1 mg/day (CCT)	DB RCT	2 years		Number with hot flashes: Significant reduction for both Rx groups (28 to 8), no Significant change in placebo group (20 to 17); Significant reduction in Kupperman score for Rx groups (-70), no Significant change for placebo (-16).
Oral CEE					
Dayal, 2005	DHEA 50 mg qd conjugated equine estrogen (CEE) 0.625 mg qu DHEA 50 mg + CEE 0.625 mg qd placebo	RCT single center	12 weeks	0/0/32	Outcome: % change from baseline CEE vs DHEA + CEE vs placebo: Overall QOL: -1.00% vs 7.00% vs -6.00% General health: -3.00% vs 0.00% vs 11.00% Vitality: 4.97% vs 4.59% vs 5.00% Health, compared to 1 yr ago: -6.00% vs 4.00% vs 7.00% Depression: 12.0% vs -3.00% vs 3.00% Somatic: 15.00% vs 3.00% vs 14.00% Cognitive: -2.00% vs -17.00% vs -8.00% Vasomotor: 25.00% vs -29.00% vs 43.00% Anxiety: 15.00% vs -1.00% vs 2.00% Sexuality: -14.00% vs 31.0% vs 18.00% Sleep: -2.00% vs -12.00% vs -5.00% Attractive: -5.00% vs -13.00% vs 18.00%

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Greenspan, 2005		573/485/373	71.3 (SD 5.2) yrs Race NR 35% hysterectomy	Community-dwelling age≥65 yrs	Any illness that could affect bone mineral metabolism (e.g. hyperthyroidism, hyperparathyroidism, renal failuer, hepatic failure, active malignancy), use of medications known to alter bone mineral metabolism, treatment with anti-osteoporosis medications within 1 yr of screening, known contraindication to hormone replacement	3 mo open label run-in w/hormone replacement, placebo, calcium and vitamin D	NR	
Newton, 2006 US, HALT		3433/509/351	52.2 (SD 2.4) yrs 93% white 52% menopausal transition vs 48% postmenopausal Mean vasomotor symptoms per day 6.5 (SD 3.7)	45-55yrs, late menopausal transition (≥1 skipped menses within preceding 12 mos) or postmenopausal (no bleeding w/in 12 mos, or FSH >20 IU/mL if patient had undergone hysterectomy without bilateral oophorectomy), 2 or more vasomotor symptoms/day over 2 ks (≥6 moderate to severe symptoms)	Contraindications to hormonal therapy, use of hormone therapy or oral contraceptives within 3 mons before the trial, use of herbal medicines for menopausal symptoms w/in 1 month before the trial, soy allergy, bilateral oophorectomy, history of breast cancer, non-adherence during the run-in period (<80% of capsules taken)	2 wk placebo run-in	NR	
Reddy 2006		589/106/60		Menopausal age 35-60 yrs, experience at least 50 moderate-severe hot flushes/week for > 2 mos, bilateral salpingo-oophorectomy for > 12 mos or amenorrhea > 6 mos or FSH level > 30 miu/mL	History of DVT, MI, stroke, functional decine, malignancies, undiagnosed vaginal bleeding, chronic liver, gallbladder, renal, cardian or endocrine disease, failure to record data in the hot flush diare for > 3 days during the 2 wk baseline period, unable or unwilling to make required visits at the specified times over the course of therapy	Hormonal therapy or other medications for hot flashes - 1 mo washout 2 wk diary run-in	NR	
Baumgardner 1978*	160 in 4 groups		Post and perimenopausal women in US gyn practices with "moderate to severe" hot flashes; Age not reported					58/156
Campbell 1976*	68 in 2 groups		Post and perimenopausal women in menopause clinic; most had vasomotor symptoms; age NR; London, UK					NR
Carranza-Lira 2001 Brief report	75 in 5 groups		Healthy postmenopausal women with hot flashes; Age not reported; Mexico					15/15 in CEE group

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Greenspan, 2005	0.625 mg qd conjugated equine estrogen (CEE) 0.625 mg CEE + 2.5 mg medroxyprogesterone qd placebo	RCT single center	3 yrs	36/NR/373	Outcome: Self-reported functional assessment tests at 3 yrs, CEE vs placebo Instrumental Activities of Daily Living test: -0.2 (SD 0.8) vs -0.2 (SD 1.1); Mean difference: 0.1 (-0.1 to 0.3); p=0.49 Physical Activity Scale of the Elderly -25 (SD 54) vs -22 (SD 59); Mean difference -3 (-15 to 8); p=0.30 Outcome: Folstein Mini-Mental State Exam at 3 yrs, CEE vs placebo 0.1 (SD 1.1) vs 0.2 (SD 1.3); Mean difference -0.1 (-0.3 to 0.2); p=0.53
Newton, 2006 US, HALT	0.625 mg qd conjugated equine estrogen (+ 2.5 mg medroxyprogesterone acetate for hysterectomy patients only) 160 mg qd black cohosh multibotanical multibotanical + soy diet	RCT single center	1yr	45/NR/323 at final timepoint	3 mo data: CEE vs placebo Outcome: Adjusted mean number of vasomotor symptoms per day (data interpolated from graph): 1.0 vs 4.9 Outcome: Adjusted mean Wiklund Vasomotor Symptom Subscale scores (data interpolated from graph): 1.3 vs 4.1 Outcome: Difference in adjusted mean change in vasomotor symptom frequency: -4.55 (-6.51 to -2.59; p<0.001) Outcome: Difference in adjusted mean change in vasomotor symptom intensity: 0.07 (-0.17 to 0.31; p=0.57) Outcome: Difference in adjusted mean change in Wiklund Vasomotor Symptom Subscale score: -2.60 (-3.74 to -1.46;
Reddy 2006	0.625 mg conjugated estrogen (Premarin) qd Gabapentin 400 mg starting dose, titrated to 2,400 mg qd placebo	RCT single center	12 weeks	7/5/1960	All results interpolated from graphs; 12 wk data % of baseline hot flush composite score (frequency and severity): CEE 23% vs 46% mean very severe hot flushes: CEE 2.0 vs placebo 1.0 mean severe hot flushes: CEE 5.0 vs placebo 24.0 mean moderate hot flushes: CEE 30.0 vs placebo 42.0 mean mild hot flushes: CEE 31 vs placebo 54
Baumgardner 1978*	CEE: 1.25 mg/day for 21/28 days	DB RCT	24 weeks		Number of subjects with moderate to severe hot flashes: Significant decrease for Rx group (results provided in graphs); women with TAHBSO also had Significant relief compared to placebo.
Campbell 1976*	CEE: 1.25 mg/day for 21/28 days	DB RCT cross-over	12 months		Hot flash rating: improved mean scores with CEE compared to placebo.
Carranza-Lira 2001 Brief report	CEE: 0.625 mg/day	DB RCT	3 months		Number, severity, and duration of hot flashes; if insomnia and sweating accompanied hot flashes: all Significantly decreased in CEE group compared to placebo.

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	N	No. Screened/Eligible/ Enrolled	Age, Ethnicity and Other Population Charactersitcis	Inclusion Criteria	Exclusion Criteria	Run-in/Wash out	Allowed other medications/interventions	Hysterectomy (#/n)
Coope 1975*	66 in 2 groups		Post and perimenopausal women from semi-rural general practice; some with depression; Mean age 52 (40-61); UK					NR
Greendale 1998*	875 in 5 groups		Postmenopausal women from several populations (PEPI trial); 52.5% had vasomotor symptoms at baseline; Mean age 56.1 (45-64); USA					279/875
Utian 2001	2,673 in 8 groups		Healthy postmenopausal women; Mean age 53; US					0/2,673
Oral synthetic conjugated estrogen								
Utian et al. 2004	281 in 4 groups		Healthy menopausal women experiencing 7 or more moderate to severe hot flashes/day, or 50/week; Mean age 51 (26-65);					NR
Oral estropipate								
Coope 1981*	66 in 2 groups		Post and perimenopausal women from semi-rural general practice with depression; Mean age 48 (40-60); UK					19/55

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Placebo-controlled trials of estrogens with hot flash/flush or other symptom outcomes

Study/Year	Interventions	Study Design, Setting	Length of Trial	Number withdrawn/ lost to fu/analyzed	Main outcomes/results
Coope 1975*	CEE: 1.25 mg/day for 21/28 days	DB RCT cross-over	6 months		Number with hot flashes: 10 women with complete relief of hot flashes in CEE group, 4 in placebo (p=0.78); results become Significant when only women with hot flashes at baseline were evaluated (p=0.04).
Greendale 1998*	CEE: 0.625 mg/day alone and with MPA (CCT and cyclic) MPA: 10 mg/day days 1-12 (cyclic), 2.5 mg/day (CCT); micronized progesterone 100 mg/day days 1-12 (cyclic)	DB RCT	3 years		Number with any vasomotor symptoms: Significantly reduced among all Rx groups compared with placebo, no diff between Rx groups.
Utian 2001	CEE: 0.625, 0.45, 0.3 mg/day; combined and unopposed regimens MPA 1.5, 2.5 mg/day (CCT)	DB RCT	1 year		Mean daily number and severity of hot flashes: Significant reduced for all Rx groups compared to placebo; dose-response relationship.
Oral synthetic con					
Utian et al. 2004	Synthetic conjugated estrogens B: 0.3, 0.625, 1.25 mg/day None during study; MPA 10 mg/day, 14 days at end of study	DB RCT Multi-center	12 weeks		Mean % change at Week 12 in daily frequency of moderate-to-severe hot flushes: CE 0.3 mg/day= -72% CE 0.625 mg/day= -85% CE 1.25 mg/day= -87% Placebo= -47% Percent reductions differed from placebo (P<0.05) at 4, 8, and 12 weeks for all dosage strengths. Dose-response relationship not reported.
Oral estropipate					
Coope 1981*	Estropipate: 1.5 mg/day for 21/28 days	DB RCT cross-over	14 months		Hot flash frequency/week: both Rx and placebo groups improved, Rx improved Significantly more than placebo (p<0.05).

* Included in Cochrane review (MacLennan, 2000)

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Inclusion criteria	Population	Intervention	Sample size Follow-up period (years)	Primary endpoint: efficacy or safety
Cardiovascular outcomes					
CEE + MPA					
Rossouw 2002 (prior review)	Women 50-70 years; intact uterus; could have taken HT previously (3-m wash-out) Exclusion criteria: Menses ≤ 6m previously (≤ 12m if 50-54y); life expectancy <3y; history of breast cancer, melanoma, other cancers in last 10y; low hematocrit; alcoholism; dementia	Age: Mean 63.6 (SD 7.1) Race: non-Hispanic white: 75% Education: 24% college education History of MI, angina, stroke, PE: each <3.0%	CEE 0.625 + MPA 2.5 mg qd	Total N: 16,608 CEE: 8506 Placebo: 8102 Average F/U: 5.2 (stopped early due to concerns regarding increased breast cancer and some increase in CHD, stroke, and PE)	CHD events: HR 1.29 (95% CI, 1.02-1.63) CHD deaths: HR 1.18 (95% CI, 0.70 - 1.97) Global index (earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, death due to other causes): HR 1.15 (95% CI,1.03 - 1.28) Safety: Invasive breast cancer: HR 1.26 (95% CI, 1.00 - 1.59) Total deaths: HR 0.98 (95% CI, 0.82 - 1.18)
CEE					
Anderson 2004	Women 50-70 years; hysterectomy >3m prior; could have taken HRT previously (3-m wash-out) Exclusion: As above	Age: 63.6 (SD 7.3) Race: Non-Hispanic white: 75.3% Prior MI: 4.1%	CEE 0.625 mg qd	Total: 10,739 CEE: 5,310 Placebo: 5,429 Average F/U: 6.8 (range 5.7 to 10.7y)	Incidence per 10,000 person-years CHD events: CEE 49, placebo 54 (p>0.05); HR 0.91 (95% CI, 0.75-1.12) Total CVD events: CEE 225, placebo 201; HR 1.12 (95% CI, 1.01 - 1.24) Global index of health risks and benefits: HR 1.01 (95% CI, 0.91-1.12) Safety: Invasive breast cancer: CEE 26, placebo 33 (p=0.06); HR 0.77 (95% CI, 0.59 - 1.10) Total mortality: HR 1.04 (95% CI, 0.88 - 1.22)

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Other endpoints	Population subgroups	Attrition Adherence	Conclusions
Cardiovascular outcomes				
CEE + MPA				
Rossouw 2002 (prior review)	Strokes: HR 1.41 (95% CI, 1.07 - 1.85) Venous thromboembolic disease: HR 2.11 (95% CI, 1.58 - 2.82) Colorectal cancer: HR 0.63 (95% CI, 0.43 - 0.92) Total fractures: HR 0.76 (95% CI, 0.69 - 0.89) Hip fractures: HR 0.66 (95% CI, 0.45-0.98)	CHD at baseline (N=400): HR for subsequent CHD in CEE vs placebo: 1.28 (95% CI, 0.64-2.56) Prior HT use for 5-10y: HR for breast cancer in CEE vs placebo: 4.61 (95% CI, 1.01 - 21.02)	Data available on 96.5% At end of study 42% of CEE and 38% of placebo had stopped taking study medication	CEE + MPA after mean follow-up of 5.2 y: Increased: CHD events, invasive breast cancer, stroke, PE Decreased: colorectal cancer, hip and vertebral fractures Total mortality and endometrial cancer did not differ significantly between groups
CEE				
Anderson 2004	Incidence per 10,000 person-years Hip fractures: CEE 11, placebo 17 (p=0.01), HR 0.61 (95% CI, 0.41 - 0.91) Total osteoporotic fractures: CEE 139, placebo 195 (p<0.001), HR 0.70 (95% CI, 0.63 - 0..79) Stroke: CEE 44, placebo 32 (p=0.007); HR 1.39 (95% CI, 1.10 - 1.77) VTE (DVT and PE): CEE 28, placebo 21 (p>0.05); HR 1.33 (95% CI, 0.99-1.79) Colorectal cancer: HR 1.08 (95% CI, 0.75 - 1.55)	Prior MI (n=441): HR MI: 1.04 (95% CI, 0.63-1.71) Those without prior MI: HR 0.91 (95% CI, 0.73 - 1.14)	At study termination: 53% had already stopped taking study medication; NSD between groups	CEE in women with a hysterectomy increases the risk of stroke (12 cases per 10,000 P-Y) , reduces the risk of hip (6 cases per 10,000 P-Y) and other fractures, and does not significantly affect CHD event rates or overall mortality. There was a nonsignificant reduction in breast cancer (7 cases per 10,000 P-Y)

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Inclusion criteria	Population	Intervention	Sample size Follow-up period (years)	Primary endpoint: efficacy or safety
Symptoms					
Barnabei 2005	Women 50-70 years; intact uterus; could have taken HRT previously (3-m wash-out)	Age: mean 63 (range 50-79) Race: Non-hispanic white: 84%; non-Hispanic black: 6.8% Education: 35% college educated Post-menopausal: mean 13.4y	CEE 0.625 + MPA 2.5 mg qd	Total: 16,608 F/U 5.6	Relief/improvement of symptoms at 1y: Symptomatic at baseline: Hot flashes, night sweats, breast tenderness, vaginal/genital dryness, joint pain/stiffness: improved (p<0.05) Vaginal/genital discharge, irritation/itching, headaches, mood swings, extremity swelling: NSD Asymptomatic at baseline: Hot flashes, night sweats, vaginal dryness, joint pain/stiffness, general aches or pains: improved (p<0.05) Safety: Vaginal bleeding: most frequently reported treatment effect in CEE+MPA (42.5% and 51.0% at 6w and 6m); placebo < 5% throughout study
Bone					
CEE+MPA					
Cauley 2003 (prior review)	Women 50-70 years; intact uterus; could have taken HT previously (3-m wash-out) Exclusion: As above If femoral neck BMD >3 SD below the age-specific mean	Mean age: 63 Race: Non-Hispanic white: 84%	CEE 0.625 + MPA 2.5 mg qd	Total N: 16,608 Patients with BMD measurements: 1024 F/U 5.6 (average)	F/U average 5.6y Total fractures: CEE+MPA 8.6%, placebo 11.1%; HR.76 (95% CI, 0.69-0.83) Hip fracture: HR 0.67 (95% CI, 0.47-0.96)
CEE					
Jackson 2006 Update of Anderson 2004	Women 50-70 years; hysterectomy >3m prior; could have taken HRT previously (3-m wash-out)	Age: Mean 63.6 Race: non-Hispanic white: 75% Education: 24% college education	CEE 0.625 mg qd	Total N: 10,739 I: 5310 C: 5429 F/U: mean 7.1y	Hip fracture: HR 0.65 (95% CI, 0.45-0.94) Total fracture: HR 0.71 (95% CI, 0.64-0.80) BMD lumbar spine (n=938): CEE increase 7.1%, placebo increase 1.9% (p<0.0001)

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Other endpoints	Population subgroups	Attrition Adherence	Conclusions
Symptoms				
Barnabei 2005	Weight 1y: higher proportion lost weight with CEE+MPA than placebo (no statistics) Breast tenderness, vaginal irritation and discharge, headaches: increased (p<0.05) Mood swings, extremity swelling: NSD	8.6% subsample at year 3: Moderate-to-severe symptoms at baseline: NSD hot flashes, various genital and musculoskeletal symptoms Asymptomatic at baseline: decreased joint pain or stiffness (p=0.04); NSD other symptoms	NR	CEE+MPA decreased vasomotor symptoms, especially in younger women. Vaginal or genital dryness and joint aches and pains were also decreased. Vaginal bleeding in the CEE+MPA group was common, especially in the first 6 months. In a subsample examined at 3y, women who were asymptomatic at baseline were less likely to report vaginal or genital dryness; there were no significant differences between groups in other symptoms either for women asyptomatic or symptomatic at basline.
Bone				
CEE+MPA				
Cauley 2003 (prior review)	BMD at 3y: Total hip: increased 3.7% in CEE+MPA vs 0.14% increase in placebo (p<0.001)		Data available on 96.5% of participants At end of study 42% of CEE+MPA and 38% of placebo had stopped taking study medication	CEE+MPA increases BMD and reduces the risk of fractures in health postmenopausal women, regardless of fracture risk
CEE				
Jackson 2006 Update of Anderson 2004		Interaction between fracture risk and global index NS (p=0.42) Greater reduction in hip fracture in women >20y after menopause	Nonadherence to study medications over 7.1y of trial: I 57.5%, C 57.7%	CEE in hysterectomized women after menopause significantly reduces incident fractures at the hip, spine and wrist, as well as total fractures. BMD increased significantly persisting for 6y of F/U. Positive effects were consistent largely irrespective of individual risk factors for osteoporosis or fracture. global index was not related to fracture risk, suggesting that even in women at highest risk for fracture, the global index was balanced with no evidence of overall benefit or risk.

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Inclusion criteria	Population	Intervention	Sample size Follow-up period (years)	Primary endpoint: efficacy or safety
Health-related quality of life					
CEE + MPA					
Hays 2003 (prior review)	Women 50-70 years; intact uterus; could have taken HT previously (3-m wash-out)	Age: mean 63.2 (range 50-79) Race: non-hispanic white: 84; non-Hispanic black: 6.8 Education: 35% college educated	CEE 0.625 + MPA 2.5 mg qd	CEE+MPA: 8,506 Placebo: 8,102 F/U: 1y	HRQL (SF-36, 8 subscales) 1 y: CEE+MPA > placebo for physical function, bodily pain, sleep disturbance (all p<0.001) 3 y: NSD between CEE+MPA and placebo (9% subsample)
CEE					
Brunner 2005	Women 50-70 years; hysterectomy >3m prior; could have taken HT previously (3-m wash-out)	Age: Mean 63.6 Race: non-Hispanic white: 75% Education: 24% college education	CEE 0.625 mg qd	I: 5310 C: 5429 F/U: 1 and 3 y	1y: Sleep disturbance: positive effect CEE vs placebo (absolute effect 2%) (p<0.001) SF-36: negative effect of CEE on social functioning (p=0.003); NSD other measures 3y: NSD any HRQL measure (8.6% subsample)
Cognition and dementia					
CEE + MPA					
Rapp 2003 **WHIMS**	Subset of WHI CEE+MPA study: women ≥ 65y; intact uterus; could have taken HRT previously (3-m wash-out) English-speaking Exclusion: As above Probable dementia	Age: mean NR; 46% 65-59y Race: Non-Hispanic white: 90% Completed college: 34%	CEE 0.625 + MPA 2.5 mg qd	Total N: 4,532 F/U mean 4.2 (range, 0.9 - 6.4)	Safety: Rates of change in 3MSE (global cognitive function): Both groups increased over the first 4y, then decreased; Y3 and Y4 scores for placebo > CEE (p<0.05); NSD Y5 and Y6

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Other endpoints	Population subgroups	Attrition Adherence	Conclusions
Health-related quality of life				
CEE + MPA				
Hays 2003 (prior review)	Subgroup analyses: no significant interactions between baseline age, race, BMI, symptoms and outcomes Age 50-59: same findings as main study Moderate-to-severe vasomotor symptoms at baseline: same findings as main study	Post hoc analyses: Age 50-54 and moderate-to-severe symptoms at baseline: improved sleep; NSD other outcomes	Loss to follow-up: 0.1% Stopped study medications: CEE+MPA 9.7%, placebo 6.6% Adherence (taking ≥ 80% of study medications): CEE+MPA 74%, placebo 81%	In postmenopausal women CEE+MPA did not have a clinically significant effect on HRQL
CEE				
Brunner 2005	Global QOL rating: NSD in distributions of scores between CEE and placebo	Moderate-to-severe symptoms at baseline: % not reporting symptoms at 1-y F/U: I 72%, C 56% (p<0.001) Post hoc analyses: Moderate-to-severe symptoms at baseline and age 50-54y: SF-36 subscales: NSD	1y Loss to F/U: 0% Drug discontinuation: CEE: 8.4%, placebo: 8.0% Adherence (taking 80% of study medications): CEE: 78%, placebo: 82% 3y Adherence: I and C: 59%	Estrogen therapy alone in women with a hysterectomy did not improve HRQL to a clinically significant degree compared to placebo at up to 3-y follow-up
Cognition and dementia				
CEE + MPA				
Rapp 2003 **WHIMS**	Strokes: NSD between groups (p=0.62) Probable dementia: CEE 40, placebo 21 (p=0.01)	Rates of change in 3MSE for subgroups (age, race, BMI, diabetes, education): NSD between groups Decrease in score of >2SD: CEE 6.7%, placebo 4.8% (p=0.008)	Attrition: 3.2% (no F/U data available) Adherance: higher in placebo than CEE (p<0.01)	Mean rate of change in global cognition scores was slightly less favorable in the CEE group than in placebo over average F/U of 4.2y, a result that is not clinically significant. CEE offers no benefit for global cognitive function or no negative effect. There may be a subgroup of women who suffer a detrimental effect.

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Inclusion criteria	Population	Intervention	Sample size Follow-up period (years)	Primary endpoint: efficacy or safety
Schumaker 2003 **WHIMS**	Subset of WHI CEE+MPA study: women ≥ 65y; intact uterus; could have taken HRT previously (3-m wash-out) English-speaking Exclusion: As above Probable dementia	As above for Rapp 2003	CEE 0.625 + MPA 2.5 mg qd	Total N: 4,532 F/U mean: 4.05y (SD 1.19)	Safety: incidence probable dementia: CEE + MPA vs placebo: HR 2.05 (95% CI, 1.21-3.48) (p=0.01)
Resnick 2006, 2004 **WHISCA**	As for Rapp 2003 Subset of WHIMS participants	Age: 73.9 (SD 3.8) Race: Non-Hispanic white: 92% Completed college: 35%	CEE 0.625 + MPA 2.5 mg qd	Total N: 1,416 Mean F/U: 1.35 Study started 3y after WHI randomization	Safety: Verbal memory: CEE negative impact vs placebo (p<0.01) Figural memory: CEE positive impact vs placebo (p=0.012) Other cognitive domains, affect, depressive symptoms: NSD
CEE alone					
Espeland 2004 **WHIMS**	Subset of WHI CEE study: women ≥ 65y; hysterectomy; could have taken HRT previously (3-m wash-out) English-speaking Exclusion: As above Probable dementia	Age: mean NR; 45% 65-69 Race: non-Hispanic white: 83% Completed college: 24%	CEE 0.625 mg qd	CEE: 1,387 Placebo: 1,421 Mean F/U: 5.4y	Safety: Rates of change in 3MSE (global cognitive function): Both groups increased over the first 4y, then decreased; NSD between groups for each year Overall mean 3MSE score: placebo slightly higher than CEE (p=0.04)
Schumaker 2004 **WHIMS**	As above for Espeland 2004	As above for Espeland 2004	CEE 0.625 + MPA 2.5 mg qd or CEE 0.625 mg qd	CEE alone: 2,947 Pooled data (CEE alone and CEE+MPA): 7,479 F/U CEE alone: 5.21y (SD 1.73) F/U Pooled data: 4.05y (SD 1.19)	Safety: Incidence of probable dementia: CEE alone: HR 1.49 (95% CI, 0.83 - 2.66) Pooled data: HR 2.05 (95% CI, 1.21 - 3.48) NSD between CEE alone CEE+MPA (p=0.11)

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Other endpoints	Population subgroups	Attrition Adherence	Conclusions
Schumaker 2003 **WHIMS**	Mild cognitive impairment: CEE + MPA vs placebo: HR 1.07 (95% CI, 0.74-1.55) Probable dementia or mild cognitive impairment: CEE vs placebo: HR 1.37 (95% CI, 0.99 - 1.89)	Exclude those with high risk dementia at baseline (3MSE scores below screening cut point): HR CEE+MPA vs placebo: 2.64 (95% CI, 1.26-5.53) Risk dementia aged 70-74y vs 65-69y: HR 3.54 (95% CI, 1.57-8.00) Risk dementia in those with high risk dementia at baseline: HR 24.84 (95% CI, 13.19 - 47.75)	NR	
Resnick 2006, 2004 **WHISCA**			Attrition 2nd annual assessment F/U: I 93.3%, C 92.7% 3rd annual assessment F/U: I 42.2%, C 44.1% Adherence 2-y F/U: I 47.4%, C 61.2%	CEE + MPA effect on cognitive function varies across cognitive domains in women over 65y.
CEE alone				
Espeland 2004 **WHIMS**	Largest declines in scores occurred more frequently in CEE than placebo: relative risk of decline of 10 units in 3MSE with CEE vs placebo: 1.47 (95% CI, 1.04 - 2.07)	Baseline 3MSE score lowest had greatest decline in cognitive function (p<0.01)	Cumulative drop-out rates year 7: CEE 59.4%, placebo 54.2%	During F/U of mean 5.4y, global cognitive function decreased with CEE compared to placebo (p=0.04); the adverse effect was more pronounced among women with lower cognitive function at baseline.
Schumaker 2004 **WHIMS**	Mild cognitive impairment: CEE alone: HR 1.34 (95% CI, 0.95 - 1.89) Pooled data: HR 1.25 (95% CI, 0.97 - 1.60)		Adherence rates dropped over time; at Y7: CEE 36.8%, placebo 45.1%	CEE does not reduce dementia or mild cognitive impairment incidence; Pooling data for CEE alone and CEE+MPA increased risk for both endpoints. HT is not recommended to prevent dementia or cognitive decline in women ≥ 65y.

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 3. Outcomes in Women's Health Initiative Hormone Therapy Studies

Study	Inclusion criteria	Population	Intervention	Sample size Follow-up period (years)	Primary endpoint: efficacy or safety

Abbreviations: BMI= body mass index (kg/m2), BMD=bone mineral density, CVD=cardiovascular disease, CEE=conjugated equine estrogens, C=control, CI=confidence interval, CHD=coronary heart disease, DVT=deep vein thrombosis, F/U=follow-up, HR=hazard ratio, HRQL=health-related quality of life, HT=hormone therapy, I=intervention, MPA= medroxyprogesterone acetate, MSE=mini-mental state examinations, m=month, MI=myocardial infarction, N=sample size, NSD=no significant difference, NR=not reported, p=patients, PE=pulmonary embolism, qd=daily, QOL= quality of life, SD=standard deviation, VTE=Venous thromboembolism, WHI=the women's health initiative, WHIMS=the women's health initiative memory study, WHISCA= the women's health initiative study of cognitive aging, y=year

Abbreviations: CEE= Conjugated Equine Estrogens;MPA=Medroxyprogesterone acetate;BMI=Body Mass Index (kg/m2); y=year;

Evidence Table 4. Quality assessment Women's Health Initiative hormone therapy studies

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Hays et al 2003 (prior review)	Method not reported	Method not reported	Yes	Yes	Not reported	Yes	Yes	Y, N, Y, N
Brunner 2005	Method not reported	Method not reported	Yes, except more prior biliateral oophorectomy in C than I (p=0.01)	Yes	Not reported	Yes	Yes	Y, N, Y, N
Anderson 2004	Method not reported	Method not reported	Yes	Yes	Yes	Yes	Yes	Y, Y, Y, Y (non study use of HRT reported)
Barnabei 2005	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported	N/Y/Y/Y
Rossouw 2002 (prior review)	Method not reported	Yes	Yes	Yes	Yes	Yes	Yes	Y, Y, Y, N
Cauley 2003 (prior review)	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported	Y, N, Y, N
Jackson 2006 (continuation of Anderson 2004)	Method not reported	Method not reported	Yes	Yes	Yes	Not reported	Yes	Y, N, Y, N
Resnick 2006, 2004 (continuation of WHISCA)	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Yes	Y, N, Y, N
Rapp 2003	Method not reported	Method not reported	Yes, except higher rate of prior stroke and statin use in I than C (p=0.03)	Yes	Yes	Yes	Not reported	Y, N, Y, N
Espeland 2004	Method not reported	Method not reported	Yes	Yes	Yes	Not reported	Not reported	Y,N,Y,Y (% taking other HT reported)
Schumaker 2004	Method not reported	Method not reported	CEE alone and pooled data: Yes, except more hypertension in CEE	Yes	Yes	Yes	Not reported	Y, N, Y, N
Schumaker 2003	Method not reported	Method not reported	Yes, except greater % history of stroke in C; greater statin use in I	Yes	Yes	Yes	Yes	Y,N,Y,Y (% taking other HT reported)

Evidence Table 4. Quality assessment Women's Health Initiative hormone therapy studies

Author, Year Country	Total attrition high (>15%)	Loss to follow-up: differential / high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Hays et al 2003 (prior review)	No: 0.3% deceased or lost to F/U	No; loss to F/U 0.1% for year 1; only 9% reported HRQL at year 3	Yes	No	Fair-good
Brunner 2005	No	Year 1: 0% loss to F/U	Yes	No	Good
Anderson 2004	No; total attrition 5.2%	No; loss 2.2%	Yes	No	Good
Barnabei 2005	NR	NR	Unclear	Unclear; likely used ITT as in main study results	Fair
Rossouw 2002 (prior review)	No	No; 3.5% loss to F/U or stopped providing outcomes information for >18m	Yes	No	Good
Cauley 2003 (prior review)	No	No	Yes	No	Good
Jackson 2006 (continuation of Anderson 2004)	No	No; vital status known for 94.8% at F/U	Yes	No	Good
Resnick 2006, 2004 (continuation of WHISCA)	No	No (5.5% loss to F/U)	Yes	No	Good
Rapp 2003	No	No (2.3% loss to F/U)	Yes	No	Good
Espeland 2004	No	No: 16% lost to F/U, but still analyzed in ITT	Yes (96%)	Yes: excluded 4% who had no F/U data	Good
Schumaker 2004	No	No	Yes	No	Good
Schumaker 2003	No (I 10.4%, C 8.8%)	No	Yes	No	Good

Evidence Table 5. Head-to-head trials with bone density outcomes

Study/Year	N	No. Screened/Eligible/Enrolled	Age, Ethnicity & Other Population Characteristics	Hysterectomy (#/n)	Interventions	Study Design, Setting	Length of Trial (years)	Main outcomes/results
Oral CEE compared with transdermal E2								
Castelo-Branco 1992*	99		Postmenopausal; 4 groups Age NR Barcelona, Spain	NR	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR MPA: 2.5 mg/day (all treatment groups)	Open	1	BMD: Lumbar spine (percent change). Baseline comparisons: All treatment groups had increases in BMD. CEE CCT group (+4.4%, p<0.05); E2 transdermal (+7.1%, p<0.01); CEE cyclic (+1.3%, NS); Placebo (-1.5%, p<0.05). Between group comparisons: CEE CCT vs. placebo (p<0.05) ; E2 transdermal vs placebo (p<0.01).
Oral CEE compared oral E2								
Castelo-Branco 1993*	118		Postmenopausal with hysterectomy; 4 groups Age NR Barcelona, Spain	118/118	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR MPA: 2.5 mg/day (all treatment groups)	Unclear	1	BMD: Lumbar Spine (percent change). Baseline comparisons: All treatment groups had increases in BMD. CEE cyclic (+1.8%, NS); CEE CCT group (+2.8%, p<0.05); E2 transdermal (+2.8%, p<0.05); Placebo (-1.5%, p<0.05). Between group comparisons: CEE CCT vs. placebo (p<0.05) ; E2 transdermal vs placebo (p<0.05).

Evidence Table 5. Head-to-head trials with bone density outcomes

Study/Year	N	No. Screened/Eligible/Enrolled	Age, Ethnicity & Other Population Characteristics	Hysterectomy (#/n)	Interventions	Study Design, Setting	Length of Trial (years)	Main outcomes/results
Davas et al, 2003	173 in 4 groups		Postmenopausal women with menopausal symptoms and BMD T score <-1 SD, recruited at menopause outpatient clinic. Mean age 50.7 (46-60) years. Istanbul, Turkey.	NR	CEE: 0.625 mg/day; E2: 0.05 mg twice weekly; CEE+AL: 0.625 mg/day + alendronate 10mg/day; E2+AL: 0.05 mg twice weekly + alendronate: 10mg/day; Calcium: 1000 mg/day (all treatment groups) MPA: 5 mg/day (all treatment groups)	Unclear if blinded; Single center	1	BMD: Lumbar spine (mean increase) Baseline comparisons: All treatment groups had increases in BMD. Increases in BMD did not differ significantly between CEE and E2 groups, alone or with alendronate. Mean change in BMD at 12 months as follows: CEE: +0.034 for osteopenic, +0.078 for osteoporotic women E2: +0.035 for osteopenic, +0.072 for osteoporotic women CEE+AL: +0.056 for osteopenic, +0.107 for osteporotic women E2+AL: +0.052 for osteopenic, +0.104 for osteoporotic women Hormone therapy plus AL increased BMD significantly more than HT alone, and significantly more so among osteoporotic women compared with osteopenic women.
Oral E2V compared with transdermal E2								
Marslew 1991*	73		Healthy women average 0.5-3 years after menopause Mean age 51 (45-54 years) Glostrup, Denmark	NR	E2: 1.5 mg/day (12 days); E2V: 2 mg/day (11 days); calcium NR DG: 150 micrograms/day cyclic; MPA: 10	Blind	2	BMD: Lumbar spine, forearm (mean gain or loss). Differences between groups: No significant differences between Rx groups at any site. Placebo vs. Rx groups 7% in the forearm and 8.5% in the spine (p<0.001). Placebo group had a mean loss of 5-7% in the forearm and 4% in the spine (p<0.001).

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year Placebo Comparisons	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Oral E2										
Abrahamsen 1997*	95		Women 6 months to 2 years after menopause; 2 groups Mean age, 52.5 Denmark (2 yrs of followup to The Danish Osteoporosis Prevention Study)					0/95	E2: 2 mg/day (22 days), 1 mg/day (6 days); calcium NR MPA: 1 mg/day (10 days)	Open
Arrenbrecht 2004 European (13 centers, 5 countries)		Number screened/eligible not reported, 146 enrolled	Mean age 55 (44-65), BMI (kg/m2)-26 Central European Non-hysterectomized	Healthy, non-hysterectomised, postmenopausal for > 12 months, between the ages for 45 and 65 years with BMI 16 - 32 kg/m2, no vasomotor symptoms, serum E2 level ≤20 pg/ml (≤73 pmol/l), BMD lumbar had to be above the mean - 2 S.D. of the peak bone density for women (t-score >-2), endometrial double-layer thickness ≤5 mm, cervical smear w/out moderate or severe dysplasia or CA,	Hormone depot injections w/in 1 year; calcitonin or 1.25 (OH)2 vitamin D3 or active vitamin D3 analogs w/in 6 months; any prior bisphosphonate	Oral HRT stopped at least 30 days (60 days w/use of conjugated equine estrogens), transdermal HRT 14 days prior to treatment start.	NR		Continuous oral Estradiol 1mg/day plus intermittent norgestimate 90µg per day (3 of 6 days) for 1 year	Blind Multicenter (13 centers) r, R in a 4:3 ratio of active/placebo
Cheng 2002	80		Healthy 50-57 yrs; < 5 yrs after menopause 4 groups Finland					NR	E2: 2 mg/day; calcium NR NETA: 1 mg/day CCT	Blind
Christiansen 1990*	40		Postmenopausal Mean age 65 Denmark					NR	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day NETA: 1 mg/day CCT	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year Placebo Compa	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Oral E2				
Abrahamsen 1997*	2		BMD: Lumbar/spine, forearm, femur Baseline comparisons: All treatment groups showed increases in BMD and placebo showed a decrease. At 2 years: lumbar and forearm BMD were significantly increased for the treatment group compared to placebo. Mean + SD: placebo, lumbar: 0.98+ 0.150; treatment: 1.060 + 0.16 (p = 0.01); placebo, forearm: 0.610 + 0.050; treatment: 0.650 + 0.040 (p=0.01); femur BMD NS.	
Arrenbrecht 2004 European (13 centers, 5 countries)	1	29 withdrawn and didn't have on-treatment BMD assessments/117 analyzed at 12 months	Between groups: (ITT populations): placebo; n=55; E2/iNGM; n=62) BMD (g/cm2): Mean (S.D.) P vs. E2/iNGM L1-L4: 0.945 (0.098) (n=55) vs. 0.961 (0.102) (n=62) Trochanter: 0.734 (0.096) (n=55) vs. 0.751 (0.114) (n=62) Intertrochanter: 1.063 (0.126) (n=37) vs. 1.084 (0.146) (n=38) Ward's triangle: 0.632 (0.153) (n=39) vs. 0.659 (0.659) (n=42) Femoral neck: 0.812 (0.124) (n=55) vs. 0.826	117 subjects completed >6 months of treatment as stated in abstract results section, 105 completed 12 months treatment (54 placebo and 51 active) as stated in section 3.2; Section 3.2 also states that the ITT population for the first year consisted of 55 subjects on placebo and 62 subjects on E2/iNGM. 2 inclusion violations noted-(one women was enrolled 11 months post-menopause and one women shortly before her 45th birthday) The study was also followed by a
Cheng 2002	1		BMD: Femur, tibia Increase in BMD for treatment group; decrease or maintenance for placebo group. Proximal femur BMD was significantly greater in the Rx group compared to the placebo at 12 months (326 vs. 293 mg/cm, p<0.05). Similar trend was seen with the tibia shaft. No differences in mid femur or proximal femur.	
Christiansen 1990*	1yr		BMD: Spine and forearm BMD was increased in all groups compared to placebo, forearm and spine (8%), proximal forearm (3%), (p<0.05). Placebo remained the same or decreased, NS.	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Ettinger 1992*	51		Women more than 6 months after menopause Mean age 51 (40-58 years) Kaiser Permanente San Francisco					NR	E2: 0.5, 1.0, or 2.0 mg/day + Ca 1500 mg/day; placebo: Ca 1500 mg/day	Blind
Franke 2006 Dutch		32/31/31	Average age: 50 Not reported average BMI: 27 kg/m2 normal cycle duration: average 28 days but a prolonged menstrual bleeding (average 10 days)	perimenopausal women with dysfunctional uterine bleeding (DUB)	osteoporosis (BMD T-score < -2.5), malignant disease, any contraindication for the study drugs or treatment with GA in the 6 months prior to participation	NR	goserelin acetate (GA) 10.8 mg depot SQ once q 12 weeks		placebo vs. combined 1mg 17B-estradiol and 0.5mg norethisterone acetate therapy oral daily (CENT) x 6 months	DB, R, PC , Multicenter (2 centers) for 6 months (n=31)
Gambacciani 1995*	60		Postmenopausal with hysterectomy Mean age 49 Pisa, Italy					60/60	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	Open
Greenwald 2005 USA		NR/NR/327	Mean age 53 years (range 45 to 62) not reported	healthy postmenopausal, 45 years of age, nonhysterectomized, and 1 5 years beyond their last menstrual period. Eligibility lab screening criteria included serum E2<20 pg/mL and lumbar spine BMD that were no more than 2 SD below the mean of young adult women.	known or suspected bone disease, includign osteoporosis or the evidence of nontraumatic osteoporotic fracture within the past 2 years; skeletal or other conditions/diseases that limited the assessment of BMD or interfered with the study procedure or the interpretation of the results; immobilization for any reason for 2 months or more during the past 6 months before screening; treatmetn with fluroide, calcitonin, or bisphosphonates at any tiem for more than 14 dyas; estrogen use within the past 6 months; long-term use of corticosteriods; known, suspected, or past history of hormone-dependent tumors, presence or suspicion of endometrial hyperplasia or cancer, or endometrial thickness greater	NR	1000 mg calcium and 400 IU of vitamin D/day		E2 0.25 mg; E2 0.5; E2 1mg; E2 1mg/NETA 0.25mg, E2 1mg/NETA 0.5mg, or E2 2mg/NETA 1mg; placebo for 26 months	DB,R,PC Multicenter (17 centers)

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Ettinger 1992*	1.5 yrs		BMD: Lumbar spine Within group differences showed increase in E2 groups, NS for placebo. All 3 estrogen groups had a statistically significant increase compared to placebo (p<0.001). An increase of 0.3% in 0.5 mg group; 1.8% in 1.0 mg group; 2.5% in 2 mg group.	
Franke 2006 Dutch	6 months	2/NR/NR--(4 hospitalizations took place-2 in each group but it was not mentioned whether data was analyzed for these pts	BMD: Lumbar spine Within group: From BL to tx cycle 6 (6 months): Lumbar BMD decreased in both groups: Between group: From BL to 6 months: The percentage decrease was more in the P group than CENT group (p<0.0001).	
Gambacciani 1995*	1yr		BMD: Lumbar spine, forearm, total body No significant modification in radial bone density in E2 groups- trend toward increase. Decrease for placebo. No difference between E2 dose groups.	
Greenwald 2005 USA	24 months	138/0/189	BMD: LS, femoral neck (FN), Femoral trochanter (FT) Within groups: from baseline to 2 years by LOCF analysis dependent on the dose of unopposed E2. **LUMBAR SPINE:** placebo: decreased 2.3% , E2 (0.25)-maintained the bone mass-increased 0.4%-NS-(differences in mean percentage change in BMD between placebo (p=0.0019) E2 0.5mg-increased 2.3%, p<0.0001 E2 1mg-increased 2.7%, (p<0.0001) E2 1mg/NETA 0.25mg-increased 3.5% (p<0.0001) E2 1mg/NETA 0.5mg-increased 3.8% (p<0.0001) E2 2mg/NETA 1mg-increased 5% (p<0.0001) FEMORAL NECK: LCOF analysis placebo: lost 2.3% over 2 years E2 0.25mg increase 0.3%-NS compared to baseline E2 0.5mg-increased 0.3%-NS compared to baseline E2 1mg increased 1.6% (p<0.05)	study was not powered for comparison among active treatment groups to determine the effect of NETA, there was a trend toward a greater response with the E2 1mg and NETA combination compared with E2 1mg alone

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Jirapinyo et al, 2003	120 in 2 groups		Postmenopausal women; mean age 54.3 (SD 4.3); Thailand					0/120	E2: 2mg/day NETA: 1mg/day	DB RCT Single center
Lees 2001	595		Healthy, at least 6 months postmenopause Mean age 55 (44-65 years) Canada and UK					0/595	E2: 1 or 2 mg/day; Canadian group encouraged to take 500 mg/day Ca Dydrogesterone: 5, 10 or 20 mg/day cyclic	Blind
Lui 2005 USA(KY and Ohio)		550/162/132	mean age 52.5 Not reported	less than 5 years from menopause; FSH levels > 40 IU/L; bone density T-score less than -2 on baseline BMD; a normal mammogram; and a normal Pap smear within the past 6 months.	severe basomotor symptoms; HTN; bone disease; vertebral fracture; any medical contraindications to taking estrogen; a serious psychiatric disorder; hyperTG > 300 mg/dL; previous treatment with a bisphosphonate or fluoride; and use of any steroid medications within the past 3 months.	NR	1000 mg calcium and 400 IU of vitamin D/day		6 treatment groups: micronized progesterone (P4) 300mg/day; MPA 10mg/day; NET 1mg/day; E2 1mg/day; E2 - 1mg/day + MPA 10mg/day; or placebo	DB, PC, R (double-dummy, double-blinded medication packaging strategy was used) Multicenter (Univ of Kentucky and Univ of Cincinnati
Mosekilde 2000	1,006		Postmenopausal women recruited by mailed questionnaire Mean age 48 (45-58 years) Denmark					NR	E2: 1-2 mg/day; calcium NR NETA: cyclic 1 mg/day 10 days (intact uterus); CCT 1 mg/day (without uterus)	Open

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Jirapinyo et al, 2003	1		BMD: lumbar spine and femoral neck Lumbar BMD increased 6% in E2 compared with 2% in placebo (p<0.05). Femoral neck BMD increased 2% in E2 compared with 0% in placebo (p<0.01).	
Lees 2001	2		BMD: Lumbar spine, proximal femur, femoral neck, Ward's triangle Within group: E2 1 mg or 2 mg had increased BMD of LS +5.2-6.7% (p<0.001) from baseline. Femoral neck was similar. Placebo (-1.9% BMD). Between group: E2 2 mg group showed a significantly greater increase in lumbar BMD than the E2 1 mg group at 24 months (p<0.001). All groups vs placebo at all sites were significant (p<0.001).	
Lui 2005 USA(KY and Ohio)	2 yrs	23/NR/109	BMD: spine and hip Between groups: SPINE over 2 year interval: E2 + MPA increased BMD from 2% to 4% (p<.05) MPA, P4 or placebo had a trend towards a -2 to -4% decrease in BMD With NET-did not change significantly from baseline--not SS different from placebo. Femoral neck site: over 2-year study) placebo-no change E2 or E2 + MPA showed a trend towards increased BMD--did not achieve significance. All 3 progestin tx were similar to placebo. Within groups: adjusted % changed from baseline for ITT with last observation carried forward: Spine (L2-L4) MPA + E2; tx 6 months (p< 05; at tx months	authors state: results suggest that MPA or P4 treatment alone will have very little additional impact on bone metabolism, while NET may have modest effects relative to estrogen.
Mosekilde 2000	5		Fractures: Vertebral, forearm, hip BMD: Lumbar spine, femoral neck, forearm Within group: Hip BMD declined after 5 yrs in control group and remained stable (p<0.01) in treatment groups (p=0.20). Overall fracture risk was NS (RR=0.82, 95% CI 0.53-1.29). Forearm fracture risk was reduced (RR=0.45, 95% CI 0.22-0.90).	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Munk-Jensen 1988*	151		Women average 15 months after menopause Denmark					NR	E2: 2 mg/day CCT vs. cyclic; calcium NR NETA: 1 mg/day	Blind
Prestwood et al, 2003	167		Women over age 65 (mean age 74.2) recruited via newspaper and community settings. 63% white, 20% Hispanic, 15% black, 1% other. US					59/167	E2: 0.25 mg/day E2 and placebo groups also received Calcium 1300 mg/day + Vitamin D 1000 IU/day Progesterone (type not specified): 100 mg/day for 2	DB RCT Single center
Resch 1990*	31		Postmenopausal osteoporotic women with spine fractures Age NR Austria					NR	E2: 2 mg/day cyclic + Ca 500 mg/day; placebo: Ca 500 mg/day NETA: 1 mg/day CCT	Blind
Riis 1988*	49		Healthy, postmenopausal 0.5 to 3 yrs Mean age 50 (45-54 years) Denmark					NR	E2: 2 mg/day CCT; calcium NR NETA: 1 mg/day CCT	Blind
Warming 2004 Denmark		NR/NR/240	Mean age 58.4± 3.9 years	at least 1 year post a natural menopause and 45-65 years of age	evere systemic disease, bone disease including osteoporosis, history of malignancy or clinically abnormal blood or urine tests at baseline	NR	None of the women received medications with significant effect on bone metabolism or the endometrium		1mg E2 + 1mg drospirenone, 1mg E2 + 2mg drospirenone, 1mg E2 + 3mg drospirenone, or placebo	DB,R,PC Single Center
Transdermal E2										

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Munk-Jensen 1988*	1		BMD: Lumbar spine, forearm Within group: All groups significantly different than baseline. Between group: Treatment group had an increase (6%) in lumbar spine and in distal forearm (3.5%) (p<0.01) compared to placebo. No difference in bone gain between the treatment groups.	
Prestwood et al, 2003	3		BMD: hip, spine, wrist, and total body E2 significantly increased bone density compared with placebo. Compared with placebo, mean BMD in E2 was +2.2% femoral neck, +3.2% total hip, +3.6% trochanter, +2.8% lumbar spine, +0.9% wrist, and 1.3% total body.	
Resch 1990*	1		BMD: Forearm Within group: At 12 months, BMD showed an increase (8%) in treatment group (p<0.02), no significant change in the control group. Between group: NR	
Riis 1988*	2		BMD: Lumbar spine, forearm Within group: Rx: Significant increases of 1-2% in proximal forearm at 12 months; spine BMD increased by 5% (P<0.01) at 24 months. Placebo: Significant decreases of 4-7% over 2 yrs. Between group: Difference between BMD for placebo and treatment were highly significant at all sites.	
Warming 2004 Denmark	2 yrs	46/NR/180	BMD: lumbar spine, hip and total body: in-between groups: SPINE: After 2 years: Difference in BMD between HRT and placebo was 7% (p<0.001) HIP: after 2 years , the difference between HRT-treated groups and placebo was 4% (p<0.001) Total body: after 2 years, the difference between HRT-treated groups and placebo was 3% (p<0.001)	combined phase II/III dose-finding trial of drospirenone
Transdermal E2				

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Adami 1989*	34		Women 2-4 years after menopause, 2 groups Age NR Verona, Italy					NR	E2: 0.5 mg day + Ca 1200 mg/day + vitamin D 600-800 units/day; placebo: Ca 1200 mg/day + vitamin D 600-800 units/day MPA: 10 mg/day (12 days)	Open
Alexandersen 1999*	68		2 groups postmenopausal women Mean age 65 half osteoporotic, half osteopenic Denmark					NR	E2: 0.05 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day Oral NETA: 1 mg/day	Blind
Arrenrecht 2002	160		Postmenopausal with hysterectomy Mean age 53 Netherlands					160/160	E2: 0.05, 0.1 mg/day; calcium NR	
Bhattoa 2004 Hungary		43/32/32	mean age: 55 years Not reported	Definite SLE; menopause of more than 3 years or FSH> 40 IU/l and E2 < 75 pmol/l; BMD T-score <-10 (at L1-L4 lumbar spine or left femur neck); age ≤ 70 years; absence of disorders of bone metabolism and calcium homeostasis	risk for TE (activated protein C resistance; factor V Leiden mutation; protein C, protein S, antithrombin III deficiencies; presence of lupus anticoagulant, anti-cardiolipin and anti-B2-glycoprotein antibodies; low plasminogen levels; prothrombin polymorphism); severe liver	NR	both groups received daily oral 5 mg medroxyprogesterone acetate, 500mg calcium carbonate and 400 IU vitamin D3.		estradiol 50µ transdermal 17B-estradiol/day vs. placebo--The active transdermal patch contained 4 mg estradiol that attains 50ug/day	R, DB, PC NR--suspect single center
Cagnacci 1991*	40		1 - 3 years after menopause Mean age 53.5 Italy					NR	E2: 0.050 mg/day cyclic; calcium NR After 6 months, MPA 5 mg/day cyclic	Unclear

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Adami 1989*	1.5		BMD: Forearm 4.3% increase in treatment group (p<0.01) 3.5% decrease in control group (p<0.01).	
Alexandersen 1999*	2		BMD: Lumbar spine, forearm, hip, femoral neck Fracture: Vertebral, nonvertebral (overall RR: 2.78 [0.12 - 65.09])* Within group: Rx group had a 4.0% increase in spinal BMD; 0% increase in placebo group (no sign level given).	
Arrenrecht 2002	2		BMD: Lumbar spine, wrist, hip Between group: BMD lumbar spine in E2-0.1 group differed by 7.7% (5.8-9.5%) (p<0.0001) compared to placebo.	
Bhattoa 2004 Hungary	1 yr	E:6/1/7 (on-tx analysis) P 2/1/14 (on-tx analysis)	Between group: Estradiol vs. placebo: On treatment : L1-L4 BMD : BL to month 6 (p < 0.005). NS at month 12. Femur neck BMD: NS at months 6 and 12; Total hip BMD: NS at months 6 and 12 Intention-to-treat: L1-L4 BMD: From BL at visit M6 (p<0.01) and M12 (p=0.01). Femur neck BMD: NS Total hip BMD: NS	
Cagnacci 1991*	2		BMD: Forearm Within group: Significant increase in BMD, maximum value at 6 months (+4.3% p<0.02) Between group: Significantly higher than placebo (p<0.05) at 24 months	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Cooper 1999			Women 1-6 years after menopause 4 groups Denmark					NR	E2:.025,.050, 0.075 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day MPA: 20 mg/day cyclic	Blind
Ettinger 2004 USA		1509/605/417	Mean 67 ±5 years 92% white 2% lower lumbar spine BMD in the treatment group compared with the placebo group (p.05)	60-80 years, intact uterus and were at least 5 years beyond menopause. Participants could have osteoporosis (t score <- 2.5), but all were required to have bone mineral density normal for age (z score ≥ -2.0 at the lumbar spine)	unexplained uterine bleeding; endometrial hyperplasis or endometrium of 5 mm or more in double thickness; abnormal mammogram suggestive of breast cancer; hx of metabolic bone disease; cancer (except nonmelanoma skin cancer); coronary disease, stroke, or TIA; venous thromboembolism; uncontrolled HTN; uncontrolled thyroid disease; liver disease;	1 week run-in phase-placebo patch to assess compliance with and tolerance to transdermal system	400mg calcium twice daily and 400 IU vitamin D once daily		unopposed 0.014 mg estradiol per day. (replaced once/week) placebo	R, PC, DB Multicenter (9 centers)
Filipponi 1995*	124		Early postmenopausal Italy					T: 7/42 C: 3/40	E2: 0.05 mg/day + Ca 1200-1500 mg/day; placebo: Ca 1200-1500 mg/day MPA: 20 mg/day cyclic	Open
Gonnelli 1997*	90		Osteoporotic women 2 or more years after menopause Mean age 56 (46-66 years) Siena, Italy					NR	E2: 0.05 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day MPA: 10 mg/day cyclic	Open
Hesley 1998*	91		Surgically menopausal Mean age 48 Rochester, MN					NR	E2: 0.025, 0.05, and 0.1 mg/day; calcium NR	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Cooper 1999	2		BMD: lumbar spine, femoral neck and total hip BMD lumbar spine increased significantly in all 3 E2 groups (4.7%, 7.3%, 8.7% respectively)	
Ettinger 2004 USA	2 yrs	E: 17/NR/208* (*191 completed study-173 were on study drugs X 2 years) 24/NR/209** (** 185 completed study-161 were on study drugs X 2 years)	BMD: Lumbar Spine(L2-L4) and total hip LUMBAR: Increased 2.6% at 2 years with E compared to 0.6% in placebo Between group difference at 2 years: 2.1% (95% CI 1.3-2.8, p=.001) Of note, the between-group differences were similar in women with BMI of -2.5 or less and those above this level, 2.3% (95% CI 0.4-4.1) and 2.0% (95% CI 1.2-2.8), respectively. TOTAL HIP: at 2 years, the difference between E and placebo was 1.2% (95% CI 0.6-1.8, p <.001).	BMD differences observed at 24 months were about 20-25% greater than with the strict ITT criterion (2.5% vs. 2.1% for spine; 1.5% vs. 1.2% for total hip)
Filipponi 1995*	2		BMD: Lumbar spine Between group: Percent change in BMD at 24 months for the treatment (-0.14) and control (-7.3) groups were significant (p<0.0005).	
Gonnelli 1997*	2		BMD: Lumbar spine Within group: E2 BMD showed increase (p<0.001) compared to baseline.	
Hesley 1998*	2		BMD: Lumbar spine, forearm Within group: Spine BMD increased 3% in 6 months for 0.1 mg group; 1.2% in 0.05 group. Between group: All treatment groups were different from placebo at 2 years (p<0.001).	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Lufkin 1992*	75		Postmenopausal women with pre-existing vertebral fractures 2 groups; Mean age 65.5 Mayo Clinic and La Crosse, WI					17/36 treatment; 14/30 placebo	E2: 0.1 mg/day (1-21 days) + Ca 800 mg/day; placebo: Ca 800 mg/day MPA: 10 mg/day, 10 days cyclic	Blind
McKeever 2000	261		Healthy women average 32 months after menopause Mean age 52 Multicenter, US					161/261	E2: 0.025, 0.0375, 0.05, 0.1 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day MPA: 2.5 mg/day	Open
Notelovitz, 2002	355 in 4 groups		Nonosteoporotic, postmenopausal women younger than age 70, who had a hysterectomy at least 12 months earlier.					355/355	E2: 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day	RCT DB
Perez-Jaraiz 1996*	104		Women 1-4 years after menopause 4 groups Mean age 49 Spain					24/104	E2: 0.05 mg/day; calcium NR MPA: 10 mg/day for 10 days	Open

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Lufkin 1992*	1		BMD: Lumbar spine, hip, radius Fractures: vertebral Between group: Lumbar spine 5.3 compared to 0.2 (p=0.007); hip 7.6 compared to 2.1 (p=0.03), radius 1.0 compared to -2.6 (p<0.001), compared to placebo. Vertebral fracture: RR= 0.39; 95% CI 0.16-0.9; lower risk in CEE group; Wells Review reports weighted RR= 0.66; 95% CI 0.41-1.07.	
McKeever 2000	2		BMD: Lumbar spine and femoral neck Percentage change from baseline in BMD of lumbar spine (0.1 and 0.05 mg, p<0.001; 0.375 mg, p=0.024; 0.25 mg, p=0.002). Femoral neck (all p≤0.044).	
Notelovitz, 2002	2		Increase in lumbar BMD at 2 years: placebo: -0.59% E2 0.025 mg vs 0.05 mg vs 0.075 mg: 1.65% (p=0.0065 relative to placebo) vs 4.08% (p=0.0001) vs 4.82% (p=0.0001)	
Perez-Jaraiz 1996*	1		BMD: Total body E2 group showed significant differences when compared to controls on total body BMD (-2.14% vs 0.14% in the E2 group, p<0.05).	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Rubinacci, 2003	124 in 2 groups		Postmenopausal women with intact uterus younger than age 70, at least 4 years past menopause. Mean age 56.8 (sd 4.8)					0/124	E2: 0.025 mg/day norethisterone acetate 0.125 mg/day	RCT DB
Warming 2005 Denmark		NR/214/212	Mean Age: 54± 3.0 , Not reported Height: 164.9± 6.2 cm; weight 67.0 ±9.7 kg.	osteopenic (BMD between -1 and -2.5 SD of the premenopausal mean value in the lumbar spine (L2-L4) and/or the femoral neck. 1-10 year postmenopausal women aged 45-65.	bone disease such as osteoporosis, malignancy, TE disorders, ischemic heart disease, other severe systemic disease, or clinically abnormal blood or urine tests at baseline. Skin intolerance to the placebo patch worn during the screening period.	placebo patch worn during screening --length not reported	500mg calcium		45 micrograms estradiol combined with 30 (n=69) or 40 microgram levonorgestrel daily (n=72) or placebo (n=71)	R, DB, double-dummy, PC Multicenter (2 centers)
Oral E2V										
Doren 1995*	280		Early postmenopausal 3 groups Mean age 54 Germany					64/210	E2V: 2 mg/day + Ca 1000 mg/day; E2: 2 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day NETA: 5 mg/day cyclic; 1 mg/day CCT	Open
Heikkinen 1997*	78		Women 0.5-3 years after menopause 3 groups mean age 53 (49-55 years) Northern Finland					78/78 ovaries removed	E2V: 2 mg/day; calcium NR MPA: 2 mg/day cyclic E2V: 2 mg/day; calcium NR	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Rubinacci, 2003	2		Mean percentage change from baseline in BMD at 24 months: (E2 vs placebo) femoral neck: 1.6% vs -0.9% (p=0.0006) trochanter: 3.2% vs -0.4% (p<0.0001) Ward's triangle: 5.0% vs -0.7% (p=0.0008) intertrochanteric region: 2.0% vs -0.5% (p<0.0001) total hip: 2.2% vs -0.7% (p<0.0001)	
Warming 2005 Denmark	2 yrs	102/0/110	Between groups: BMD of lumbar spine L2-L4: Difference between HRT and placebo group was 8% (p<0.001). Left hip: Difference between HRT and placebo was 6% (p<0.001) Total body BMD: difference between HRT and placebo 3% (p<0.001) In-between groups: No difference was found at any time point when evaluating the % change in lumbar spine BMD vs. placebo between the strata divided according to years after menopause. All p<0.001.)	phase III clinical study.
Oral E2V				
Doren 1995*	2		BMD: Lumbar spine and hip E2 CCT increased BMD (p=0.001); E2V and control, NS. E2 CCT group had increased BMD at 2 yrs compared to control (+17%) (p=0.01). E2V group; NS. No fractures were reported during study.	
Heikkinen 1997*	2		BMD: Femoral neck, lumbar spine, femur Compared with placebo, both estrogen groups had increased BMD: spine (p<0.001); femoral neck (p<0.001) and femur (0.05).	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Isaia 1989*	57		Postmenopausal 2 groups: 1 ovariectomized; 1 within 6 months of natural menopause Mean age 44 Turin, Italy					NR	E2V: 2 mg/day cyclic; calcium NR MPA: 10 mg/day for 40 days	Open
Komulainen 1997*	464		Postmenopausal 16-24 months after menopause Mean age 53 (44-79 years) Finland (subgroup of the OSTPRE Study)					NR	Group 1: E2V 2 mg/day cyclic; Group 2: vit D 300 IU day + Ca 500 mg/day; Group 3: T1 + T2; placebo: Ca 500 mg/day T1 & T3: CPA 1 mg/day cyclic	Open
Marslew 1992*	62		Healthy women average 5-3 years after menopause 3 groups Mean age 55 (38-64 years) Denmark					NR	E2V: 2 mg/day CCT or cyclic; calcium NR Cyproterone acetate (1 mg/day) or levonorgestrel (75	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Isaia 1989*	1		BMD: Lumbar spine BMD was significantly higher in ovariectomized treated groups compared to untreated (p<0.05 after 6 months; p<0.005 after 9 and 12 months). BMD also significant in natural menopause group after 6 months (p<0.005).	
Komulainen 1997*	2.5		BMD: Lumbar and femoral neck Fractures: non-vertebral Within group: At 2.5 yrs, compared to baseline, lumbar spine BMD increased 1.8% in the E2V group (p<0.001) and 1.4% in the E2V + Vit D group, and decreased 3.7% in placebo group (p<0.001). Placebo and vit D only group showed a significant decrease in femoral neck BMD from baseline (p<0.001). Between group: Both treatment groups were significantly different than the placebo group. Fracture: Estimated risk for nonvertebral fractures in the E2V group, RR=0.29, 95% CI 0.10 - 0.90; in the E2V + vit D group, RR=0.44 95% CI 0.17-1.15. Wells review combined results RR=0.40, 95% CI 0.16 - 0.99.	
Marslew 1992*	2		BMD: Lumbar spine, forearm, calcaneus BMD in the spine increased by 3-4% in E2 groups, decreased 2% in placebo. In the forearm, E2 groups had no change in BMD when the placebo group decreased 6%	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Oral CEE										
Agnusdei 1990*	24		Postmenopausal with osteoporosis or osteopenia 2 groups Mean age 57.5 Italy					NR	CEE: 0.625 mg/day (days 1-20) + Ca 800-1200 mg/day; placebo: Ca 800-1200 mg/day MPA: cyclic 5 mg/day	Open
Agnusdei 1995*	83		Women 6 months - 2 years after menopause Mean age 50 Siena, Italy					NR	CEE: 0.3 mg/day CCT and cyclic;Ca 1000/day; placebo: Ca 1000 mg/day MPA 10 mg/day, 15 days every 3	Blind
Anderson 2004 USA Women's Health Initiative Estrogen-Alone Trial		373,092 screened/ 11,941 provided consent and reported hysterectomy/10,739 randomized	Mean age (SD) 63.6 (7.3) 75% white 15% black 6.1% Hispanic 0.7% American Indian 1.5% Asian/Pacific islander 1.4% unknown BMI, mean (SD)	"mostly" healthy 50-79 years old women at initial screening, had undergone hysterectomy (considered post-menopausal for enrollment purposes), and were likely to reside in the area for 3 years.	any medical condition likely to be associated with a predicted survival of < 3 years, safety (eg, prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer), adherence and retetnion concerns (eg, alcoholism, dementia, and transportation problems), or the clinical judgment of the participant's health care practitioner to	3 month washout was required for those using postmenopausal hormones at initial screening.			CEE 0.625 mg/d or placebo	R, DB, PC multicenter (40 centers)
Aloia 1994*	118		3 groups of women 6 months 6 years after menopause, three groups Long Island, NY					0/118	CEE: 0.625 mg + CA: 1700 mg/day + vitamin D 400 IU /day Ca 1700 mg/day + vitamin D 400 IU /day Placebo: vitamin D: 400 IU /day MPA: cvclic	Open

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Oral CEE				
Agnusdei 1990*	1		BMD: Lumbar spine, femoral neck Within group: Placebo had a decrease in BMD at 12 months (p<0.01). Between group: HT group showed increased lumbar spine BMD at 12 months (p<0.01) compared to placebo. Femoral neck BMD remained the same for treatment, decreased for placebo (p<0.05).	
Agnusdei 1995*	1		BMD: Distal forearm Within group: Placebo had a decrease in BMD (1.7%); estrogen only group maintained bone; group with CEE plus MPA had an increase in BMD at 1 year (+5.6% p<0.01). Between group: All groups were different than placebo (P<0.05).	
Anderson 2004 USA Women's Health Initiative Estrogen-Alone Trial	average 6.8 years	321/242 lost to follow-up/ 9596 (580 deceased) Additional information: 563 (5.2%) withdrew, were considered lost to follow-up, or had stopped providing outcomes information for	Within Group: CEE reduced the rates of fractures by 30%-39%. Between groups: Mean Follow-up time in months (SD), 81.6 (19.3) for CEE group and 81.9 (19.7) for placebo group. (CEE n=5310) vs. placebo, n=5429); No of patients (annualized %); HR (stratifed by age, prior disease, and randomization status in the dietary modification trial); nominal 95% CI, Adjusted 95% CI) Hip fracture: CEE 38 (0.11) vs. placebo 64 (0.17) HR 0.77, 95% CI 0.59-1.01; adjusted 95% CI 0.57-1.06) Kaplan-Meier	A small imbalance in the number of women in each group was a consequence of an early protocol change eliminating a CEE-alone intervention in women with a uterus. The adjusted CI were calculated using group sequential methods, and for secondary outcomes a Bonferroni correction based on the data and safety monitoring plan. There was no significant interactions between CEE and race/ethnicity or body mass index on risk of hip fracture, or total osteoporotic fracture. (data not shown).
Aloia 1994*	3		BMD: Lumbar spine, femur, radius Between group: Compared with placebo, femoral neck BMD was greater for the CEE and calcium group (-0.8%/y; p=0.03).	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Cauley, 2003	16,608 in 2 groups		Postmenopausal women with an intact uterus ages 50-79. Mean age 63 (sd 7.10) 40 US centers					0/16,608	CEE: 0.625 mg/day medroxyprogesterone acetate 2.5 mg/day	RCT DB
Civitelli 1988*	21		Postmenopausal osteoporotic Mean age 55 Siena, Italy					NR	CEE: 1.25 mg/day + Ca 800-1000 mg/day; placebo: Ca 800-1000 mg/day	Blind
Civitelli, 2002	135 in 2 groups		Women postmenopausal for at least 1 year with no moderate or advanced periodontal disease. Mean age ERT group 60.0 (sd 5.5) placebo group 58.1 (sd 6.8); p=0.07					49/135	CEE: 0.625 mg/day medroxy-progesterone acetate 2.5 mg/day	RCT DB

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Cauley, 2003	5.6 (average)		Fracture: 8.6% in HRT group vs 11.1% in placebo group had a fracture during 5.6 years followup (hazard ratio 0.76; 95% CI 0.69-0.83). Hip fracture hazard ratio 0.67 (95% CI 0.47-0.96) BMD at year 3: Total Hip: increased 3.7% in HRT group vs 0.14% increase in placebo group (p<0.001)	
Civitelli 1988*	1		BMD: Lumbar spine, femoral shaft Within group: Femoral shaft BMC increase +2.6%; Lumbar spine BMD increases in treatment group (+8.3%, p<0.05). Between group: Treatment group different than placebo.	
Civitelli, 2002	3		BMD: Femoral neck HRT vs placebo 2.39% difference in increase from baseline (p=0.02) Total femur HRT vs placebo 3.37% difference in increase from baseline (p<0.001) Trochanter HRT vs placebo 3.42% difference in increase from baseline (p<0.001) Lumbar spine HRT vs placebo 0.84% difference in increase from baseline (p=0.39)	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Gallagher 1991*	81		Postmenopausal Mean age 52 Omaha, Nebraska and Salt Lake City, Utah					NR	CEE: 0.625 mg/day; progestin only; CEE 0.3 mg/day + progestin; All subjects: Ca 1000 mg/day NETA: 2, 10	Blind
Gambacciani 1997*	80		Postmenopausal Age 40-49 Pisa, Italy					NR	CEE: 0.3 mg/day All subjects: Ca 500 mg/day	Unclear
Gambacciani et al, 2003	120 (90 CEE, 30 control)		White postmenopausal women Mean age 54 (includes only patients completing the study) Pisa, Italy					NR	CEE: 0.3 mg/day + Calcium 1g/day Control: Calcium 1g/day MPA 2.5 mg/day or dydrogesterone 5mg/day, or nomegesterol 2.5 mg/day	Open; Single center

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Gallagher 1991*	2		BMD: Lumbar spine, forearm Within group: All groups showed a significant change. Between group: All Rx groups differed from placebo. CEE groups had 0.3 mg increase in spine and decrease in radial BMD (p<0.05). CEE + progestin had no change (p<0.01).	
Gambacciani 1997*	2		BMD: Lumbar spine Within group: All Rx groups showed a significant decrease in BMD after 12, 18, and 24 months (p<0.001). Between group: When compared with control or CEE alone, CEE had a greater LS BMD increase (p<0.05).	
Gambacciani et al, 2003	3		BMD: femoral neck, Ward's triangle, and trochanter Control: significant decreases in BMD at 36 months: femoral neck -5.3%, Ward's triangle -5.8%, trochanter -4.1%. Rx groups combined: no significant changes in BMD from baseline to 36 months: femoral neck +1.7%, Ward's triangle +2.8%, trochanter +2.5%. Between groups: BMD at 36 months was significantly greater at all femur sites among treatment groups compared with control.	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Genant 1982*	37		Women with hysterectomies Mean age 42 (24-49 years) San Fran., CA					37/37	CEE: 0.15, 0.30, 0.45, 0.625 mg/day; calcium NR	Blind
Greenspan 2003 USA		573/485/373	Mean age: 71.5 Not reported Mean (SD) bone mass of the entire cohort was in the osteopenic classification by WHO criteria; 34% had	65 years or older	history of illnesses that could affect bone mineral metabolism (eg. Current hyperthyroidism or hyperparathyroidism, renal failure, hepatic failure, and active malignancy), taking medications known to alter bone mineral metabolism (eg, glucocorticoids, anticonvulsants, excess thyroid	3-month, open-label, run-in phase with hormone replacement and alendronate placebo, calcium (if necessary) and a MVI	600mg/tablet of elemental calcium to those whose daily calcium intake of less than 1000mg from dietary and supplementary sources based on results from a		CEE 0.625mg with or without medroxyprogesterone 2.5mg/day (women with intact uterus received both agents) and alendronate	R, DB, PC single center
Greenspan 1998*	425		Postmenopausal Age greater than 45 years; spine BMD 2 SD below normal Multicenter US					425/425	CEE: 0.625 mg/day; calcium NR	Blind
Hosking 1998*	1609 total; (CEE group 110, placebo 502)		Menopausal for at least 6 months Mean age 53 (45-59 years) 4 study centers in USA and UK					0 in treatment group; NR in placebo group	US group: CEE 0.625 mg/day; UK: E2 1 to 2 mg/day calcium NR US: MPA 5 mg/day CCT	Open
Hulley 1998*	2763		Postmenopausal with coronary disease Mean age 67 (44-79 years) USA					0/2763	CEE: 0.625 mg/day; calcium NR MPA: 2.5 mg/day CCT	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Genant 1982*	2		BMD: Lumbar spine Within group: CEE 0.15, 0.3 and 0.45 mg/day NS from baseline. CEE 0.625 mg/day maintained axial and peripheral bone mass but were not significant.	
Greenspan 2003 USA	3 yrs	36/8/373* * 337 actually completed the study	BMD: hip (total hip, femoral neck, trochanter, intertrochanter, and Ward triangle), lumbar spine (posteroanterior and lateral), and radius (ultra-distal, mid-third, and one-third distal radius) BETWEEN GROUP: TOTAL HIP: (after 3 years): mean (SD) increase of 4.2% (3.8) with alendronate (ALN), increase of 3.0% (4.9) with HRT, incr. 5.9% (3.8) with HRT + ALN.	A participant was considered a responder if, after 3 years, the change in BMD at the spine or hip was greater (more positive) than -1.0%. At all times points after randomization, BMD was greater in each treatment group than in the placebo group. When ALN vs. HRT (head-to-head analysis without adjustment for multiple comparison), BMD of the total hip, trochanter,
Greenspan 1998*	2		BMD: Lumbar spine, femoral neck, total hip Vertebral fracture Within and between group: BMD increased ($p<0.001$) vs baseline & placebo (+6.0%, +3.4%, +2.6%). Vertebral fracture: RR = 0.70, 95% CI 0.06 - 7.55 (Wells Review 2002)*	
Hosking 1998*	4		BMD: Lumbar spine, forearm, hip Non-vertebral fractures Within group: Hip and spine BMD differed significantly from placebo in US Rx groups. Nonvertebral fracture: RR=0.98, 95% CI 0.29, 3.34; NS*.	
Hulley 1998*	4		Fractures: Hip, other, and any Hip: 1.10 (0.49-2.50) Other: 0.93 (0.73-1.20) Any: 0.95 (0.75-1.24) No differences between groups.	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Hulley 2002 (HERS II)	2763		Postmenopausal with coronary disease Mean age 67 (44-79 years) 20 US Clinical centers					0/2763	CEE: 0.625 day; calcium NR MPA: 2.5 mg/day CCT	Blind
Jackson 2006 United States Women's Health Initiative Estrogen-Alone Trial (subgroup analysis)		NR/NR/1073** 938 subjects were evaluated for this subgroup analysis)	average age: 63.6± 7.3 years 75.1% white; 15% black;6.1% Hispanic; 0.7% American Indian/Native American; 1.5% Asian/Pacific Islander; 1.4% unknown Of the subgroup of 938 with BMD	postmenopausal women 50-79 years with prior hysterectomy	Past use of tamoxifen or current hormone therapy	Women on hormone therapy at recruitment could undergo a 3-month washout period and then enroll.	bisphophonates and calcitonin was permitted; 950 subjects (9.2% total: 10.2% placebo and 8.2% CEE subjects) reported bisphonphonate use at some point during the trial.		CEE 0.625 mg daily (n=5310) or placebo (n=5429)	R, DB, PC Multicenter (40 clinical centers)
Leung 1999	105		Women 2 years after menopause; 3 groups Mean age 48 Age 45+ Hong Kong, China					NR	CEE: 0.625, 0.3 mg/day; calcium NR MPA: 5 mg/day (if uterus present) cyclic	Unclear
Lindsay 1984*	150		Women 18-20 months after menopause Mean age 49 New York, NY					62% overall	CEE: 0.15, 0.3, 0.625, 1.25 mg/day; calcium NR	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Hulley 2002 (HERS II)	4 (3 of follow-up)		Fractures: Hip, other, any Any fracture (RR=1.04, 95% CI .87-1.25) not statistically significant	
Jackson 2006 United States Women's Health Initiative Estrogen-Alone Trial (subgroup analysis)	average 7.1±1.6 years	NR/NR/NR	TOTAL FRACTURE: 1301 fractures occurred during 7.1 years of follow-up: Kaplan Meier estimates of cumulative HR for Total fractures: HR 0.71, 95% CI 0.64-0.80. (See Figure 1 for # events and n at risk per year). CEE was associated with reduced risk of total fracture in older subjects (interaction p=0.03). age at screening: [50-59: CEE (n=5310): 153 (1.26%) vs. placebo (n=5429): 173 (1.39%) HR 0.90 95% CI 0.72-1.12] 60-69 years: [220 (1.32%) vs. 348 (2.01%) HR 0.63, 95% CI 0.53-0.75] ≥20 years: [222 (1.44% vs. 353 (2.19%) HR 0.70 95% CI 0.57-0.85] and in subjects with no current or past	Study was terminated early resulted in a follow-up time ~1 year shorter than planned. Reports of hip, clinical vertebral, wrist/lower arm, and other osteoporotic fractures (excluding chest/sternum, ribs, skull/.face, fingers toes, and cervical vertebrate) were ascertained by semiannual questionnaire. All reported fractures were confirmed by review of the radiology reports by trained local adjudicators. Hip fractures underwent a second central adjudication. Over 7.1 years, 57.3% of CEE and 57.7% of placebo) of study subjects became nonadherent to
Leung 1999	1		BMD: Lumbar spine and femoral neck Within group: Lumbar spine and femoral neck BMD maintained at 1 yr in 0.625 mg/day group; for control and CEE 0.3 group, a decrease was seen. Between group: CEE 0.625 mg/day showed LS BMD was different vs. placebo (p<0.01); not for femoral neck. CEE 0.3 mg/day NS for spine or femoral neck.	
Lindsay 1984*	2		BMD: Metacarpal CEE at 0.625 and 1.25 mg/day showed protection of BMD, less loss than placebo and lower doses	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Lindsay 1990*	50		Women approximately 13 years past menopause with osteoporosis 2 groups New York, NY					11/50	CEE: 0.625 mg/day + 1500 mg Ca/day; placebo: 1500 mg Ca/day MPA: 5 or 10 mg/day cyclic (if	Open
Lindsay 2002	822		Women within 4 years of menopause 8 groups Mean age 51.6 (40-65 years) HOPE trial participants					822/822	CEE: 0.625, 0.45, 1.5, 0.3 mg/day + Ca 600 mg/day; placebo: Ca 600 mg/day MPA: 2.5, 1.5 mg/day CCT	
Meschia 1993*	95		Women 1.5-10 years after menopause 4 groups Mean age 51 Milan, Italy					NR	CEE: 1.25 mg/day; calcium NR MPA: 10 mg/day cyclic	Open
Mizunuma 1997*	52		Postmenopausal 4 groups Mean age 55 Japan					4/52	CEE: 0.3 and 0.625 mg/day; calcium NR MPA: 2.5 mg/day CCT	Open

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Lindsay 1990*	2		BMD: Lumbar spine, femoral neck Lumbar bone mass increased significantly (p<0.01) and was significantly greater in estrogen group (p<0.05)	
Lindsay 2002	2		BMD: Spine, total hip Within group: All treatment groups had significant gains from baseline (p<0.001) for spine and hip BMD. Between group: All Rx groups different than placebo. CEE 0.625 had an increase in spine BMD compared to the CEE 0 .3 group (CEE 0.45 was borderline significant).	
Meschia 1993*	2		BMD: Lumbar spine Within group: CEE group showed an increase in BMD of 0.823 to 0.867 (p<0.01); placebo group had a decrease in BMD of 0.83 to 0.771 (p<0.001). Between group: Rx group differed from placebo (significance level NR).	
Mizunuma 1997*	2		BMD: Lumbar spine, femoral neck Lumbar spine BMD significantly higher in all CEE groups CEE alone: 8.52% (4.61-12.4%); CEE 0.625 + MPA: 7.4% (0.60-14.2%); CEE 0.31 + MPA: 3.2% (0.61-5.84%) (p<0.05)	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
PEPI 1996*	875		Healthy postmenopausal 5 groups Mean age 56 (45-65 years) 7 US clinical sites					159/875	T1: CEE 0.625 mg/day only; T2 - T 3: CEE 0.625 mg/day + progestin; calcium NR T2: MPA 10 mg/day cyclic, 12 days T3: MPA 2.5 mg/day daily T4: MP	Blind
Recker 1977*	60		Healthy postmenopausal 3 groups Mean age 51 Omaha, Nebraska					NR	CEE: 0.625 mg/day; Ca 2600 mg/day MPA: 5 mg/day cyclic	Open
Recker 1999	128		Women over 65 years with low BMD (no previous fractures) recruited by university center; 2 groups; mean age, 73 treatment; 74 controls Omaha, Nebraska					NR	CEE: 0.3 mg day + Ca 1000 mg/day + vitamin D 75 nmol/L/day; placebo: Ca 1000 mg/day + vitamin D 75 nmol/L/day MPA: 2.5 mg/day CCT	Blind
Reid 2004 Europe, North America, Australasia, and South Africa		NR/1522/619	Age: 53 White: 95.6%	40-60 years of age, postmenopausal (naturally or surgically), had undergone a hysterectomy no more than 15 years before beginning the study, had serum estradiol levels of 20 pg/mL and FSH of 40 mIU/mL or higher, and had a lumbar spine BMD measurement between 2.5 SDs below and 2.0 SDs above the mean value for normal premenopausal women.	history of carcinoma of the breast or estrogen-dependent tumors; had cancer within the last 5 years (except excised skin cancers); had taken estrogen (other than vaginal estrogens), progestin, androgen, calcitonin, or systemic corticosteroids within the previous 6 months; had ever taken bisphosphonate or fluoride (except for dental prophylaxis); were taking antiseizure	NR	400-600 mg of elemental calcium daily		raloxifene 60mg/d, raloxifene 150mg/d, CEE 0.625 mg/day, placebo	R, DB, PC Multicenter (38 centers)

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
PEPI 1996*	3		BMD: Lumbar spine, hip Fractures: spine, wrist, hip Within group: CEE groups had an average increase of 1.7% hip BMD compared to average decrease of 1.7% in placebo (p<0.05) Between group: At 3 months, CEE plus MPA CCT regimen showed greater increase in spinal BMD (5%) then those assigned to other regimens (3.8%, p<0.05). No difference in number of fractures between groups.*	
Recker 1977*	2		BMD: Forearm Between group: CEE group showed significant difference in metacarpal thickness from baseline and significant difference compared to placebo (0.00154 mean rate of loss CEE) (0.0124 mean rate of loss placebo)	
Recker 1999	3.5		BMD: Spine, hip, forearm At three years, spinal BMD increased significantly in the estrogen group compared to baseline and to placebo (ranged from 3.5% - 5.2%; p<0.001). Significant increases were also found in forearm bone density (p<0.01). No significant losses in spine BMD in placebo group with calcium + vit D.	
Reid 2004 Europe, North America, Australasia, and South Africa	36 months	234/29/205	BMD: lumbar spine: during 3 years placebo: mean loss amounting to 2% (p<.05) 2 raloxifene groups: bone density maintained at or near baseline values. The effects in the raloxifene groups were different from those observed in the CEE and placebo groups (p<.001) CEE: gain of 4.6% (p<.001) Total Hip: during 3 years placebo: lose of 1.3% (p<.05) raloxifene groups: maintenance of density . The effects in the raloxifene groups were different from those observed in the CEE and placebo groups	authors state that the apparent differences in BMD changes with raloxifene therapy between the various studies are likely attributable to differences in the rates of bone loss in the placebo groups.

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Rosen 1997*	236		Postmenopausal women Mean age 51 Diet of 800-120 mg Ca day Clinical research sites throughout the US					NR	CEE: 0.625 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day MPA: 2.5 mg/day CCT, 5 mg/day cyclic	Blind
Villareal 2001	67		Frail women aged 75 years of older Mean age 82 St. Louis, MO					22/45 treatment; 6/22 control	CEE: 0.625 mg/day + Ca 1200 mg/day MPA: 5 mg/day cyclic	Blind
Rossouw 2002 WHI	16,608		Postmenopausal for at least 6 months Mean age 63.3 (50 years or older) 40 clinical centers in the US					248/8506 treatment; 183/8102 control	CEE: 0.625 mg/day; calcium NR MPA: 2.5 mg/day	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Rosen 1997*	1		BMD: Lumbar spine, femoral neck At 12 months, BMD increased in CEE group at both spine (+2.5%; p<0.0001) and femoral neck (+1.0%; p<0.05). In the calcium group, BMD decreased at the spine and hip (-1.1%; p< 0.01). Between group differences not reported.	
Villareal 2001	9 months		BMD: Lumbar spine, proximal femur, and hip BMD was greater in all sites for the treatment group compared to placebo. The adherent Rx group showed greater increases in lumbar spine BMD than placebo (mean change, 4.3% vs 0.4%; between group difference,) and total hip (mean change, 1.7% vs -0.1%; between group difference).	
Rossouw 2002 WHI	5.2		Fracture: Hip, vertebral.. Hip fracture was decreased in the treatment group when compared with placebo 0.66 (0.33 - 1.33); 106 cases. Vertebral and other osteoporotic fractures were significantly lower in the treatment group (RR=0.66, 95% CI 0.32-1.34; RR=0.7, 95% CI 0.63-0.94), respectively. Total fractures: RR=0.76, 95% CI 0.63 -0.92.	

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Wimalawansa 1998*	72		Postmenopausal with osteoporosis attending bone clinics Mean age 64.9 (58-72 years) UK					0/72	CEE: 0.625 mg/day + Ca 1000 mg/day + vit D 400 units/day; placebo: Ca 1000 mg/day + vit D 400 units/day norgestrel: 150 micrograms/day cyclic	Open
Oral conjugated synthetic estrogen										
Gozansky 2005		Wt loss arm: 138/82/82; wt. stable arm: 61/31/31	age: 57 (?average, mean); Ethnicity: NR using the WHO criteria, 22 women with the weight loss group were osteopenic, and 6 were osteoporotic; 12 women in the wegith stable group were osteopenic, and 5 were osteoporotic.No signifiicant differences among the drug	sedentary, healthy, postmenopausal women defined as the absence of menses for at least 1 yr or, in women who had undergone hysterectomy, a serum FSH level greater than 30 IU/liter., aged 50-70, nonsmokers and overweight or moderately obese, euthyroid or receiving adequate replacement therapy	contraindications to estrogen or raloxifene treatment, including history of breast cancer or other estrogen-dependent neoplasm, liver disease, undiagnosed vaginal bleeding, and history or venous thromboembolism., CAD, clinically significant abnormal resting ECG, angina and/or ECG evidence of myocardial ischemia during the maximal exercise stress test, resting blood pressure above 150/90, clinically significant arrhythmias, CHF, aortic stenosis, or unstable health status, orthopedic or other problems that would interfere with exercise testing or training. Women who had been receiving	NR	women with an intact uterus received trimonthly medroxyprogesterone acetate 5mg/day for 13 consecutive days. Placebo medroxyprogesterone acetate were given to those women with intact uterus in the placebo and raloxifene groups.		placebo , raloxifene 60mg/d, or conjugated estrogen (0.625mg/d)	R, C, DB (drug intervention)
Lindsay 2005 Utian 2004 United States Women's HOPE substudy		1347 screened/ 822 eligible/ 822 enrolled for the substudy [NR/NR2,673 women were enrolled in the HOPE study]	Mean age 51.6 (40-65) 92% white, 8% other Non-hysterectomized. Mean age of 49.3 at menopause. (2 year substudy participants) BL characteristic of total study population in the Women's HOPE study: Mean age	Healthy, between ages of 40 and 65, early postmenopausal for 12 months (≤4 years), intact uteri, FSH levels ≥30 IU/L, E2 levels ≤184 pmol/L (50 pg/ml), w/in 20% normal body weight. For the substudy, participants also had to be within 4 years of their last menses.	Hypersensitivity to estrogens or progestins; use of concomitant drugs affecting vasomotor symptoms w/in 2 weeks of screening; known or suspected estrogen-dependent neoplasia; endocrine disorders, except for controlled thyroid disease; endometrial hyperplasia or an abnormal Pap smear; IUD use w/in last 3 months; chronic renal or hepatic disease; neuro-ocular disorders; history of malignancy other than basal cell carcinoma of the skin; thromboembolic	Estrogen-, progestin-, or androgen-containing medication stopped at least 12 weeks prior to prestudy screening	600 mg/day elemental calcium		All doses mg/day Conjugated estrogens (CE) 0.625, CE 0.625/medroxyprogesterone acetate (MPA) 2.5, CE 0.45, CE 0.45/MPA 2.5, CE 0.45/MPA 1.5, CE 0.3, CE 0.3/MPA 1.5 or placebo for 2 years	DB, PC, R Multicenter (57 sites- for 1 year) with 2 year substudy conducted at 19 of these sties)

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Wimalawansa 1998*	4		BMD: Lumbar spine, hip Fractures: Vertebral, nonvertebral Rx group showed greater BMD when compared to the control group for both lumbar spine and total hip at 4 yrs (7%, p<0.001 and 4.8%, p<0.01, respectively). Ca + vit D group lost BMD from baseline for the lumbar spine and total hip at 4 yrs (2.5% and 4.4%, p<0.01, respectively). Those on no treatment showed a significant loss of bone compared to CEE and Ca groups (p<0.05). No difference in fracture rates was found. Vertebral RR=0.49, 95% CI 0.09 - 1.80; non-vertebral RR=1.00, 95% CI 0.07 - 14.79*.	
Oral conjugatec				
Gozansky 2005	6 months	Wt loss arm: 0/14/68 Please Note: text states 14 were lost to f/u evaluations but there reasons were personal (n=10); medical-worsening of MS (n=1); unknown (n=2) Wt stable arm: NR/3/26--NOTE: Text states 3 were lost to f/u although the reason were 2 did not tolerate drug treatment, one becasue of new infomration regarding risk of	BMD: lumbar spine, total hip, femoral neck, trochanter, femoral shaft: Largest increases in BMD occurred in the HT group, and the effects of raloxifene were intermediate to those of HT and placebo treatment. All sites except femoral neck: HT better than placebo (p<0.05) Total hip and the trochanter and shaft regions of the proximal femur: HT was more effective than raloxifene (p<0.05). Lumbar spine: Raloxifene more effective than placebo (p<0.05). When drug treatment was adjusted, the magnitude of change in body weight was not a significant determinant of changes in BMD. HT, ralox> placebo, p<0.001 (Fig. 1). Composite BMD: HT>ralox, placebo, p< 0.001. Total Hip BMD: HT>ralox, placebo, p<0.001. Femoral neck BMD: NS. Trochanter BMD: HT>ralox, placebo, p<0.001 Femoral shaft BMD HT> ralox, placebo, p+0.001. Weight Loss Group: (moderate weight loss):	randomization to drug interventions were performed separately for the weight loss and weight-stable arms. It was done in a double-blind fashion although side-effects often reveal treatment status to the participant. Women were recruited separately for the weight loss and weight-stable arms of the study. Only 60% of subjects completed 6-month dietary assessments, and detailed information on the mineral content of calcium supplements was not obtained, limiting the reliability of the data for toal daily calcium intake. Authors state that the power to detect a significant interaction effect at any of the sites of BMD measurment was less than 40%. Furthermore, it is possible that the baseline differences between the weight-stable and wight loss groups in body composition and BMD may further limite
Lindsay 2005 Utian 2004 United States Women's HOPE substudy	2yrs	127 withdrawn (48 study violation, 25 not treated, 54 only baseline BMD)/ 695 analyzed--[this is for the substudy at 2 year]	BMD: spine, Total hip: Within group: SPINE BMD at 24 months.Placebo group, 30.4% of women did not lose >2% at both 12 and 24 months. 27% of placebo-treated women who did not lose >2% of spine BMD in 12 months reversed this trend at 24 months, and only 3.6% of women who lost >2% at 12 months did not lose >2% of spine BMD after 24 months. HIP BMD response: 24 months: HT gained ranged from 1.63% to 2.85%. Placebo lost 0.72%. <15% on each active tx experienced >2% losses compared to 36.5% taking placebo. Between groups: SPINE: Did not lose >2% at 24 months: CE 0.45 or CE 0.625 with or without a progestin, bet	Additional exclusion criteria: history or active presence of cerebro- or cardiovascular disease; gallbladder disease; liver function test results >1.5 times the upper limit of normal; smoking (>15 cig/day); fasting levels of glucose >6.94 mmol/L (125 mg/dL), total cholesterol >7.77 mmol/L (300 mg/dL), or triglycerides >3.39 mmol/L (300 mg/dL); sitting blood pressure>160 mm Hg systolic or >90 mm Hg diastolic, or use of more than two antihypertensive agents. For both spine and hip BMD, the response rates were generally higher for the CE/MPA combination than for the corresponding dose of CE alone...however, the difference

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	N	No. Screened/ Eligible/ Enrolled	Age, Ethnicity & Other Population Characteristics	Inclusion Criteria	Exclusion Criteria	Run-in/Wash-out	Allowed other Medications/Interventions	Hysterectomy (#/n)	Interventions	Study Design, Setting
Oral esterified estrogen										
Genant 1997*	406		Women 6 months - 4 years after menopause Mean age 52 29 centers US					128/406	Esterified estrogens: 0.3, 0.625, 1.25 mg day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	Blind

*Included in Wells Review, 2002.

Evidence Table 6. Placebo-controlled trials of estrogens with bone density and/or fracture outcomes

Study/Year	Length of Trial	No. withdrawn/lost to FU/analyzed	Main outcomes/results	Comments
Oral esterified estrogen				
Genant 1997*	2		BMD: Lumbar spine, hip Within and between group: All doses of estrogen showed greater BMD at all sites compared with baseline and placebo ($p<0.05$). LS was greater with 1.25 mg Rx group, than the 0.3 or 0.625 mg Rx groups.	

*Included in Wells Review, 2002.

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
	Oral estrogens						
Archer, 1992	CEE: 0.625, 1.25 mg/day; E2: 1, 2 mg/day	None	21/128	9	NR	Few at baseline, no trends during study.	Increased with higher doses; 78% with 2 mg/day E2 and 70% with 1.25 mg/day CEE had no discomfort.
Saure, 2000	E2: 1.5 mg/day for 24 days E2V: 2 mg/day for 21 days	Desogestrel: 0.15 mg/day for 12 days/mo with E2; MPA: 10 mg/day for 10 days/mo with E2V	59/376	35	3 in E2V; 4 in E2	None	2 in each group
Odmark, 2004	CE: 0.625 mg E2: 2 mg	CE group: 5 mg medroxyprogesterone acetate E2 group: 1 mg	CE: 11/123 E2: 27/123 More patients in E2 group	CE: 10/123 E2: 25/123	(Includes well-being and/or bleeding) CE: 7/123 E2: 22/123	None	None
Pornel, 2005	E2: 1 mg E2V: 1 mg	E2 group: 0.125 mg or 0.25 mg trimegestone on days 15-28 E2V group: 1 mg norethisterone on days 17-28	352/1218	Not reported; adverse reaction was the primary reason for discontinuation	NR	NR	NR
Utian, 2005	E2 acetate: 0.9 mg Micronized E2: 1 mg CEE: 0.625 mg	None	7/249	7/249 (2 EA, 2 E2, 3 CEE)	NR	NR	NR
	Oral CEE compared with transdermal E2						
Good, 1999	E2: 0.05 or 0.1 mg/day; CEE 0.625 or 1.25 mg/day	None	NR	NR	Breakthrough bleeding: 3.8% with E2, 10.1% CEE; withdrawals NR	NR	Dose related: 12% E2, 11% CEE high dose; 3% E2, 4% CEE low dose; withdrawals NR

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Archer, 1992	Most reported at baseline; decreased in all groups during study.	NR	NR	NR	Reports for 2/25 placebo, 1/102 Rx.	NR	NR	Incidence of possible drug-related adverse experiences ranged from 20% placebo, E2 1 mg, CEE 0.625 mg to 35% E2 2 mg and CEE 1.25 mg; no stat sig differences between groups.
Saure, 2000	3 in each group	None	2 in E2; 3 in E2V	None	1 in E2	None	None	Also abdominal pain (1 in E2), depression (2 in each group), edema (1 in each group), feeling unwell (1 in each group), psychiatric changes (1 in E2), fluid retension (1 in E2V).
Odmark, 2004	None	None	None	None	None	None	None	11 serious AEs reported; 4 reported as possibly related to study medication.
Pornel, 2005	NR	NR	NR	NR	NR	NR	NR	No overall differences between groups seen for any of the reasons for discontinuation. 66 AES reported for 62 women (5.1%); 14 considered at least possibly related to the study drug in 13 women.
Utian, 2005	NR	NR	NR	NR	NR	NR	NR	Most commonly reported AEs were headache (5.6%), breast tenderness (4.8%), and metrorrhagia (3.6%). One case of severe metrorrhagia in E2 group.
Good, 1999	Most common adverse reaction; withdrawals NR	NR	NR	NR	6 E2, 4 CEE	NR	NR	No differences between groups except for breakthrough bleeding with higher doses.

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Gordon, 1995	E2: 0.05, 0.1 mg/day (Climera); CEE: 0.625 mg/day oral	None	71/603	54	12 in E2 0.05mg, 22 in E2 0.1 mg, 5 in CEE; withdrawals NR	NR	17 in E2 0.05mg, 55 in E2 0.1 mg, 18 in CEE; withdrawals NR
Akhila, 2006	CEE: 0.625 mg E2 percutaneous gel E2 transdermal patch	MPA 2.5 mg	oral CEE: 12/35 E2 gel: 4/25 E2 patch: 12/28	NR	Incidence of breakthrough bleeding: 60% oral CEE, 71% E2 gel, 66% E2 patch Withdrawals NR	NR	Incidence: 14% oral CEE, 20% E2 gel, 18% E2 patch Withdrawals NR
Serrano, 2006	CEE: 0.625mg plus placebo CEE: 0.625mg plus fenretinide 100 mg BID E2: transdermal patch 50 mcg plus placebo E2: transdermal patch 50 mcg plus fenretinide 100 mg BID	None	34/226	11/226	NR	NR	NR
Studd, 1995	E2: 0.05 mg/day (Menorest); CEE: 0.625 mg/day	Dydrogesterone: 10 mg/day days 16-28	NR	NR	NR	NR	NR

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Headache	Weight change	Dizziness	VTE	Rash & pruritis	Chole-cystitis	Liver effects	Other
Gordon, 1995	Most common adverse reaction; withdrawals NR	NR	NR	NR	41 due to site reactions	NR	NR	No differences between Rx groups except for uterine bleeding; much lower rates in placebo group.
Akhila, 2006	NR	NR	NR	NR	NR	NR	NR	
Serrano, 2006	NR	NR	NR	NR	NR	NR	NR	
Studd, 1995	NR	NR	NR	NR	91% with no pruritis.	NR	NR	Most common symptoms: E2 headache (8), abdominal pain (4), nausea (5), breast pain (6); CEE headache (8), abdominal pain (4), nausea (6), weight gain (3) depression (3); withdrawals not reported.

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
	Vaginal E2 compared with oral E2						
Al-Azzawi, 2003 Buckler, 2003	vaginal E2: vaginal ring releasing 50 mcg/day. Oral E2: 1 mg/day	Norethisterone 1 mg/day for last 12 days of each 28-day cycle.	39/159	at 24 weeks: 19 (10 vaginal ring, 9 oral) 6 additional patients withdrew during 48-week open-label vaginal ring phase.	1 endometrial hyperplasia in oral E2 group (withdrew after switching to vaginal ring).	17 vaginal ring, 11 oral (NS); withdrawals not reported	28 vaginal ring, 14 oral (NS); withdrawals not reported
	E2 vaginal ring compared with E2 vaginal tablet						
Weisberg, 2005	E2 vaginal ring: 2 mg E2 tablet: 25 mcg	None	32/126 (25.4%) vaginal ring, 7/59 (11.9%) vaginal tablet p=0.035	11.9% vaginal ring, 3.4% vaginal tablet	Incidence of withdrawal bleeding following the trial: 4 vaginal tablet, 0 vaginal ring. Withdrawals not reported.	NR	NR

Evidence Table 7. Adverse events reported in head-to-head trials with hot flash or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Al-Azzawi, 2003 Buckler, 2003	49 vaginal ring, 35 oral (NS); withdrawals not reported	NR	13 vaginal ring, 10 oral (NS); withdrawals not reported	NR	NR	NR	NR	No significant differences between groups in frequency of most common adverse events.
Weisberg, 2005	NR	NR	NR	NR	NR	NR	NR	Higher dropout rate in vaginal ring group occurred predominantly during first 3 months of treatment, the main reason being local AEs such as abdominal discomfort, lower back pain, and slippage of the ring.

Evidence Table 8. Adverse effects reported in head-to-head trials with bone density outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects: Atypical bleeding & endometrial hypertrophy	Withdrawals due to specific adverse effects: Nausea & vomiting	Withdrawals due to specific adverse effects: Breast tenderness
Oral CEE compared with transdermal E2						
Castelo-Branco, 1992	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	15	Bleeding: CEE cont 2; Endometrial hyperplasia: transdermal E2 4, CEE cyclic, 3	NR	NR
Castelo-Branco, 1993	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	12	NR	NR	1
Davas et al, 2003	CEE: 0.625 mg/day; E2: 0.05 mg twice weekly; CEE+AL: 0.625 mg/day + alendronate 10mg/day; E2+AL: 0.05 mg twice weekly + alendronate: 10mg/day; Calcium: 1000 mg/day (all treatment groups)	MPA: 5 mg/day (all treatment groups)	13	NR	NR	NR
Oral E2V compared with transdermal E2						
Marslew, 1991	E2: 1.5 mg/day (12 days); E2V: 2 mg/day (11 days); calcium NR	DG: 150 micrograms/day cyclic; MPA: 10 mg/day cyclic	16 12 in treatment 4 in placebo 78% completed	4	NR	NR

Evidence Table 8. Adverse effects reported in head-to-head trials with bone density outcomes

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Oral CEEcompared with transdermal E2									
Castelo-Branco, 1992	NR	NR	NR	NR	NR	Transdermal E2: 4	NR	NR	Poor relief of hot flashes: CEE cyclic 2 withdrawals; transdermal E2 1 withdrawal
Castelo-Branco, 1993	NR	NR	NR	NR	NR	4	NR	NR	3 withdrew due to hot flashes 3 incorrect use of medicine
Davas et al, 2003	NR	NR	NR	NR	NR	NR	NR	NR	13 were dropped from the study because of noncompliance.
Marslew, 1991	3	1	NR	NR	NR	NR	NR	NR	Withdrawal: 6 personal reasons, lack of time, moved

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Placebo Comparisons ***Oral estradiol***							
Almeida, 2006	0.5 mg/day estradiol during the initial 2 weeks, 1 mg/day weeks 3 and 4, 2 mg/day weeks 5 to 16, and again 1 and 0.5 mg/day during the remaining 4 weeks (2 weeks each, respectively)		29/115	16 in E2 group and 5 in placebo	NR	NR	NR
Baerug, 1998*	E2: 1 mg/day	NETA: 0.25, 0.5 mg/day (CCT)	11/119	5	Higher rates of bleeding for E2 compared to placebo; no difference in incidence of severe bleeding.	One wthdl from placebo group.	One wthdl from E2 group.
Bech, 1998*	E2: 2 mg/day (CCT), 2 mg/day days 1-12, then 1 mg/day days 23-28 (cyclic)	NETA: 1 mg/day (CCT & cyclic)	46/151	20	Four withdrawals from E2, none from placebo.	2 withdrawals from cyclic group, 2 placebo group, none CCT.	Significantly more frequent in E2 groups.
Chung, 1996*	E2: 2 mg/day	None	17/100	NR	NR	NR	NR
Conard, 1995*	E2: 1, 1.5 mg/day days 1-24	Nomegestrol acetate: 2.5, 3.75 days 11-24 (cyclic)	7/57	4	One wthdl from E2 group.	NR	Increased in E2 group (31.6% vs 5.3%, p=0.04); 2 withdrawals in E2 group.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Placebo Comparisons ***Oral E2***								
Almeida 2006	NR	NR	NR	NR	NR	NR	NR	
Baerug, 1998*	One wthdl from placebo group.	NR	NR	NR	NR	NR	NR	Additional withdrawals for edema and emotional lability.
Bech, 1998*	NR	One wthdl in cyclic group.	NR	NR	NR	None	None	Few reports of edema in all groups.
Chung, 1996*	No differences between groups.	NR	No differences between groups.	NR	NR	NR	NR	NR
Conard, 1995*	NR	None	NR	NR	NR	NR	NR	Also abdominal pain and metorrhagia.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Crisafulli, 2004 (17-beta estradiol)	E2: 1mg/day Phytoestrogen genistein: 54mg/day	norethisterone acetate 0.5 mg/day	7/90	NR	NR	NR	NR
Derman, 1995*	E2: 2 mg/day days 1-12, 1 mg/day days 23-28	NETA 1 mg/day days 13-22 (cyclic)	35/82	6	Some withdrawals in E2 group (number not given).	NR	NR
Freedman, 2002	E2: 1 mg/day	None	NR	NR	NR	NR	NR
Gelfand, 2003	E2: 1 mg/day	norgestimate 90 mcg/day for 3 days on, 3 days off.	5/119	6 (including open-label phase)	3	5 in E2, 0 in placebo; withdrawals not reported	8 in E2, 3 in placebo; withdrawals not reported
Jensen, 1983*	E2: 1, 2, 4 mg/day days 1-12, 1, 2, 4 mg/day days 13-22, 1 mg/day days 23-28; estriol: 1, 2 mg/day days 1-22, 0.5 mg/day days 23-28.	NETA 1 mg/day days 13-22 (cyclic)	13/100	4	Increased regular and irregular bleeding in E2 groups compared to placebo; some withdrawals (number not given).	withdrawals (number not given)	withdrawals (number not given).
Jirapinyo, 2003	E2: 2mg/day	NETA 1mg/day	17/120	11 (8 in E2, 3 in placebo)	1 in E2	1 in placebo	2 in E2; 1 in placebo

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Headache	Weight change	Dizziness	VTE	Rash & pruritis	Chole-cystitis	Liver effects	Other
Crisafulli 2004 (17-beta estradiol)	NR	NR	NR	NR	NR	NR	NR	
Derman, 1995*	NR	withdrawals from Rx group (number not given)	NR	NR	NR	NR	NR	Also palpitations in Rx group, lack of effect in placebo group.
Freedman, 2002	NR	NR	NR	NR	NR	NR	NR	Also withdrawals due to lack of effect in placebo group.
Gelfand 2003	5 in E2, 9 in placebo; withdrawals not reported	3 in E2, 3 in placebo; withdrawals not reported	NR	NR	NR	NR	NR	
Jensen J, 1983*	NR	No differences between groups.	NR	NR	NR	NR	NR	Also nervousness, depression, rectal cancer, bronchitis; groups not specified.
Jirapinyo, 2003	1 in E2	NR	NR	NR	1 in E2	NR	NR	One death occurred in an E2 patient whose condition had been diagnosed as tension headache and migraine; autopsy reported pneumonia as cause of death; relation to trial medication not assessed. Also benign breast neoplasm (1 in E2); another E2 patient developed right hemiplegia grade III with mild facial palsy.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Johnson, 2005 Adverse effects only; no efficacy data							
Notelovitz, 2000a	E2: 0.25, 0.5, 1, 2 mg/day	None	53/333	26 (5 placebo, 21 E2, more in higher dose groups)	18 (11 from 2 mg group).	NR	Reported in all groups, highest with higher doses.
Notelovitz, 2000b	E2: 0.5, 1 mg/day	None	NR	NR	Reported in E2 groups, more with higher dose; 1 with cancer from E2 1 mg group.	NR	NR
Schurmann, 2004	E2: 1mg/day	drospirenone 1, 2, 3 mg/day with E2 daily	20/225	NR	NR	NR	NR
Speroff, 2006 (estradiol acetate)	Study 1: E2: 0.9mg, 1.8mg/day Study 2: E2: 0.045mg/day	None	Study 1 and 2:NR/548	Study 1 and 2:11/548	NR	NR	NR

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Johnson, 2005 Adverse effects only; no efficacy data								
Notelovitz, 2000a	NR	NR	NR	NR	NR	NR	NR	NR
Notelovitz, 2000b	Reported in all groups by 10-15%.	NR	NR	NR	NR	NR	NR	Also reports of abdominal pain in all groups.
Schurmann 2004	NR	NR	NR	NR	NR	NR	NR	One serious AE in E2/2mg drospirenone: permanent bleeding resulting in hysterrectomy, revealed adenomyosis, uteri interna and several leiomyomata
Speroff 2006 (estradiol acetate)	NR	NR	NR	NR	NR	NR	NR	

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Symons 2000 Speroff 2000 (ethinyl estradiol and norethindrone acetate)	Study 1: estradiol: 1mcg, 2.5mcg, 5mcg or 10mcg or placebo/day Study 2: estradiol: 2.5mcg, 5mcg or 10mcg or placebo/day	Study 1: norethindrone acetate: 0.2mg, 0.5mg, 1mg or 1mg or placebo/day Study 2: norethindrone acetate: 0.5mg, 1mg or 1mg or placebo/day	Study 1: 31/219 Study 2: 36/266	Study 1: 17/31 Study 2: 15/36	Number of subjects among noncompleters: Study 1: 3/31 Study2: 1/36	NR	Number of subjects among noncompleters: Study 1: 1/31 Study2: 0/36
Viklyleva, 1997;* English abstract	E2: 2 mg/day days 1-22, 1 mg/day days 23-28	NETA: 1 mg/day days 13-22 (cyclic)	4/64	NR	Regular bleeding with E2, no excessive bleeding.	NR	NR
Wolf, 2005	E2: 2 mg/day	100 mg oral progesterone	9/51	NR	NR	NR	NR
Yang, 2002	E2: 2 mg/day	norethisterone acetate 1 mg/day	16/56	NR	10 E2, 0 placebo; withdrawals not reported	NR	6 E2, 0 placebo
Transdermal estradiol							
Bacchi-Modena, 1997	E2: 0.05 mg/day	None	NR	NR	Reported 15% E2, 13% placebo.	NR	Reported in 28% E2, 27% placebo.
Baksu, 2005	Tibolone 2.5mg/day, E2: 3.9mg/week placebo oral	None	NR/75	NR	NR	NR	NR
De Aloysio, 2000	E2: 0.025, 0.0375 mg/day	None	NR	2 (E2 0.025); 1 (E2 0.0375)	1 withdrawl(E2 0.375); reports in all groups.	NR	10% placebo; 40-43% E2 groups; 1 withdrawlin E2 0.025.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Symons 2000 Speroff 2000 (ethinyl estradiol and norethindrone acetate)	Number of subjects among noncompleters: Study 1: 3/31 Study2: 2/36	Bloating Number of subjects among noncompleters: Study 1: 0/31 Study2: 1/36	NR	Superficial thrombophlebitis Number of subjects among noncompleters: Study 1: 0/31 Study2: 1/36	NR	NR	NR	Study 2: Palpitations in 1/36 withdrawls due to AEs Study 1: Withdrawals due to AE: not specified in which treatment group Study 2: Withdrawals due to AE: evenly distributed between treatment groups
Viklyleva, 1997;* English abstract	Reduced in Rx group.	NR	No differences between groups.	NR	NR	NR	NR	NR
Wolf 2005	NR	NR	NR	NR	NR	NR	NR	
Yang, 2002	NR	2 E2, 1 placebo	NR	NR	None	NR	NR	
Transdermal E2								
Bacchi-Modena, 1997	Reported in all groups.	None	NR	NR	Reported in 30% E2, 20% placebo.	NR	NR	Also reports of abdominal pain; no changes in blood pressure.
Baksu 2005	NR	NR	NR	NR	NR	NR	NR	
De Aloysio, 2000	Reported in all groups.	None	NR	NR	1 withdrawlE2.	NR	None	Overall systemic events: 10% E2 groups, 8% placebo.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
de Vrijer, 2000	E2: 0.05, 0.10 mg/day	None	NR	18/245	5 withdrawals in E2 0.10; 5 cases of hypertrophy in E2 groups; 1 case cancer.	NR	1 wthdl E2 0.10; reported in 11% placebo, 26% E2 0.05, 61% E2 0.10.
Diem, 2006 Johnson 2005 ULTRA trial	E2: 0.014mg/day	None; had uterii	NR/417	NR	Focal atypical endometrial hyperplasia developed in 1/188 in treatment group, 0/177 in placebo Adenosarcoma of the uterus developed in 1/188 in treatment group, 0/177 in placebo Vaginal bleeding in Y1 5-6% with NSD between groups; Y2 slightly higher rates with NSD between groups	NR	NR
Gordon, 1995	E2: 0.05, 0.1 mg/day; CEE: 0.625 mg/day oral	None	71/603	54	12 in E2 0.05mg, 22 in E2 0.1 mg, 5 in CEE; withdrawals NR	NR	17 in E2 0.05mg, 55 in E2 0.1 mg, 18 in CEE; withdrawals NR
Joffe 2006		none	2/1/1,950	NR	NR	NR	NR
Levine 2005	Trial 1: E2: 50mcg/day vs. positive control Trial 2: E2: 50mcg/day vs. placebo control	Norethindron acetate (140, 250 or 400 mcg/day)	Trial 1: 150/624 Trial 2: 21/226	Trial 1: 108 Trial 2: 5	NR	NR	NR
Notelovitz, 2000c	E2: 0.05 mg/day	Norethidrone acetate: 140, 250, 400 mg/day, 15-28	NR	6 in E2 groups	Reported in E2 groups.	NR	Reported in E2.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
de Vrijer, 2000	1 wthdl E2 0.10.	NR	Reported in E2 group.	NR	3 withdrawals E2, 2 placebo	NR	NR	Other withdrawals: edema (1 E2), sleep disturbances (1 E2), anxiety/mood (2 placebo), leg hematoma (1 placebo).
Diem, 2006 Johnson 2005 ULTRA trial	NR	NR	NR	NR	NR	NR	NR	2-year follow-up
Gordon, 1995	Most common adverse reaction; withdrawals NR	NR	NR	NR	41 due to site reactions	NR	NR	No differences between Rx groups except for uterine bleeding; much lower rates in placebo group.
Joffe 2006	NR	NR	NR	NR	NR	NR	NR	
Levine 2005	NR	NR	NR	NR	NR	NR	NR	
Notelovitz, 2000c	NR	NR	NR	NR	Reported in 4-7% E2, 1-10% placebo.	NR	NR	Overall events: 79% placebo, 83-90% E2.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Shulman, 2002	E2: 0.045 mg/day	Levonorgestrel: 0.03, 0.04 mg/day	NR	11 E2, 6 placebo	4 withdrawals E2	NR	Reported in 12 E2, 2 placebo.
Speroff, 1996	E2: 0.02 mg/day	None	63	18/63	NR	NR	Reported in 6-14% E2, 3% placebo.
Utian, 1999	E2: 0.025, 0.05, 0.1 mg/day	None	NR	3	3 withdrawals in E2 groups; hyperplasia in 19 E2 groups (1 with atypia); 32-57% spotting in E2, 10% placebo.	NR	Most common symptom in E2 groups (23-45% E2, 45 placebo).
van Holst, 2000	E2: 0.05 mg/day	None	NR	18 (9 E2, 7 placebo)	NR	NR	4 withdrawals in E2 group.
van Holst, 2002	E2: 0.050 mg/day	Levonorgestrel patch: 10 microgm/day	NR	NR	NR	None	NR
Wiklund, 1993	E2: 0.05 mg/day	None	NR	NR	8% placebo, 15% E2 (NS difference).	NR	NR
Oral estradiol valerate							
Blumel, 1994*	E2V: 2 mg/day	MPA 2.5 mg/day (CCT)	2/50	2	No difference at 3 months, significantly more in E2V group (12/25) than placebo group (3/23) at 6 months.	NR	At 3 months, 7/25 in E2V group reported symptom, 3/23 of placebo; at 6 months, 1/25 E2V, 0/23 placebo.
Jensen P, 1987*	E2V: 2 mg/day days 1-21	Cyproterone acetate 1 mg/day days 12-21 (cyclic)	19/76	NR	NR	NR	NR
Marslew, 1992*	E2V: 2 mg/day	Cyproterone acetate 1 mg/day (CCT)	11/50	NR	Three in E2V withdrew due to regular bleeding.	NR	Increased in E2V group.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Shulman, 2002	Reported in 10 E2.	Reported in 8 E2, 1 placebo.	NR	NR	3 withdrawals E2, 3 placebo.	NR	NR	Also abdominal and back pain, edema, mood in all groups, flatulence in E2.
Speroff, 1996	Most frequently reported: 20% placebo, 16% E2.	NR	NR	NR	9 withdrawals (5 placebo, 4 E2).	NR	NR	NR
Utian, 1999	NR	NR	NR	NR	5-11% in all groups.	NR	NR	Overall: 11% placebo, 31% E2 0.025, 55% E2 0.05, 58% E2 0.10.
van Holst, 2000	NR	None	NR	NR	4 withdrawals E2, 3 placebo.	NR	None	No blood pressure changes.
van Holst, 2002	Reported in both groups.	None	NR	NR	Erythema & edema in both groups.	NR	NR	No blood pressure changes; general gastrointestinal symptoms in both groups.
Wiklund, 1993	NR	NR	NR	NR	NR	NR	NR	NR
Oral E2V								
Blumel, 1994*	Improvement for Rx group compared to placebo (p=0.05).	NR	No differences between groups.	NR	NR	NR	NR	NR
Jensen P, 1987*	NR	One wthdl due to weight gain.	NR	NR	NR	NR	NR	withdrawals due to varicose veins.
Marslew, 1992*	NR	NR	NR	NR	NR	NR	NR	More reports in Rx group but not specified.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Oral conjugated equine estrogen							
Baumgardner, 1978*	CEE: 1.25 mg/day for 21/28 days	None	23/160	23	No differences between groups.	One wthdl from CEE group.	Few reports, no differences between groups.
Campbell, 1976*	CEE: 1.25 mg/day for 21/28 days	None	7/68	NR	Increased in CEE group.	7% during CEE phase, 3% during placebo.	13% during CEE phase, 10% during placebo.
Carranza-Lira, 2001; Brief report	CEE: 0.625 mg/day	None	NR	NR	NR	NR	NR
Coope, 1975*	CEE: 1.25 mg/day for 21/28 days	None	5/35	NR	Wthdl bleeding in majority of perimenopausal women, no breakthrough bleeding.	Two reported in placebo group.	Two reported in placebo, 1 in CEE group.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Oral CEE								
Baumgardner, 1978*	Few reports, no differences between groups.	No significant weight gain.	Few reports, no differences between groups.	None	None	NR	NR	Additional withdrawals due to edema and visual symptoms (no difference between groups), lack of effect in placebo group.
Campbell, 1976*	Nonsignificant improvement during Rx phase.	No differences between groups.	NR	None	NR	NR	NR	Most common adverse events were leg cramps, breast tenderness, limb pains, fluid retention, eye irritation, nasea, vaginal discharge; all slightly higher during Rx phase but not significantly different.
Carranza-Lira, 2001; Brief report	NR	NR	NR	NR	NR	NR	NR	NR
Coope, 1975*	One reported in Rx group.	Reports of 4 with more than 3 kg weight gain, 2 in placebo, 2 in Rx group.	NR	NR	NR	NR	NR	Other reports of urinary infections, increased blood pressure, nasal stuffiness (groups not specified).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Greendale, 1998*	CEE: 0.625 mg/day alone and with MPA (CCT and cyclic)	MPA: 10 mg/day days 1-12 (cyclic), 2.5 mg/day (CCT); micronized progesterone 100 mg/day days 1-12 (cyclic)	210/875	127	NR	NR	More common with E + P compared to E alone or placebo.
Goldstein 2005 AE only reported; no efficacy data	CEE 0.625 mg qd	None (post hysterectomy)	60% in total; CEE 38%, placebo 43%	17.6% (n=619)	NR	NR	NR
Greenspan, 2005	CEE: 0.625 md qd; combined and unopposed regimens	Medroxyprogesterone: 2.5 md qd	18/187	NR	Menstrual spotting: CEE 60/187 (32%); placebo 16/186 (9%) p<0.0001 Endometrial biopsy: CEE 23/187 (12%); placebo 3/186 (2%) p=0.0008	NR	CEE 102/187 (55%); placebo 38/186 (20%) p<0.0001
Langer 2006 OPAL study Study reports AEs only; no efficacy data	CEE 0.625 mg qd	medrosyprogesterone acetate 2.5 mg qd	CEE/MPA: 28% Placebo: 30%	withdrawals due to bleeding: CEE/MPA 9%, placebo <1%; most in the first 3 months	Bleeding or spotting: CEE/MPA 48%, placebo 3% (p<0.001) Endometrial hyperplasia: 0% both groups Endometrial cancer: 0% CEE/MPA, 0.3% placebo (p>0.05)	NR	NR

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Greendale, 1998*	If HA at baseline, E only group had less, if no HA at baseline, E only group more likely to get.	E + P group more likley to lose weight.	NR	Two cases of DVT in E only group, one case of superficial phlebitis in E + P group.	NR	NR	NR	Reports of joint pain, depression, lack of effect.
Goldstein 2005 AE only reported; no efficacy data	NR	NR	NR	NR	NR	NR	NR	Urinary incontinence: 3-6% at baseline New or worsening incontinence at 3y: CEE 7.0% vs placebo 1.3% (p<0.02)
Greenspan, 2005	NR	CEE 16/187 (9%); placebo 14/186 (8%) p=0.85	NR	CEE 2/187 (1%); placebo 1/186 (1%); p=1.0	NR	NR	NR	Serious AEs CEE (n=187) vs placebo (n=186): Endometrial cancer: 1 (1%) vs 0 (0%); p=1.0 Breast cancer: 2 (1%) vs 2 (1%); p=1.0 Colon cancer: 3 (2%) vs 1 (1%); p=0.62 Hospitalizations: 72 (39%) vs 60 (32%); p=0.23 MI: 1 (1%) vs 3 (2%); p=0.37 Clinical fractures: 9 (5%) vs 16 (9%); p=0.15
Langer 2006 OPAL study Study reports AEs only; no efficacy data	NR	NR	NR	NR	NR	NR	NR	

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Newton, 2006 HALT	CEE: 0.625 mg qd	Medroxyprogesterone acetate: 2.5 mg (for hysterectomy patients only)	CEE 8/32 (25%); placebo 11/84 (13%)	NR	Menstrual disorders: CEE 19/32 (59%); placebo 17/84 (20%) p<0.001	NR	CEE 5/32 (16%); placebo 3/84 (4%); p=0.04
Reddy, 2006	Conjugated equine estrogen (Premarin) 0.625 mg qd	None	CEE 3/20 (15%); placebo 1/20 (5%)	NR	NR	Gastrointentinal AEs (not specified): CEE 8/20 (40%); placebo 5/20 (25%)	NR
Utian, 2001	CEE: 0.625, 0.45, 0.3 mg/day; combined and unopposed regimens	MPA 1.5, 2.5 mg/day (CCT)	521 (19%)	221 (8% overall, highest in 0.625 group)	Most common in CEE 0.625 groups (6-14%); 2% in low dose CEE, none in placebo.	NR	Most commonly reported effect (15% overall), more in combined than in unopposed groups (13-25% vs 7-12%).
Oral synthetic conjugated estrogen							
Utian et al., 2004	Synthetic conjugated estrogens B: 0.3, 0.625, 1.25 mg/day	None during study; MPA 10 mg/day, 14 days at end of study	53/281	18: 8.3% of placebo, 5.7% of combined treatment groups	Average severity of bleeding was less among Rx groups than placebo. Number not reported.	8% of placebo; 9.6% of combined Rx groups (withdrawals not reported)	Increased with higher dose (12% in 0.625 mg, 14% in 1.25 mg, none in 0.3mg); 4% placebo (withdrawals not reported)
Oral estropipate							

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Newton, 2006 HALT	CEE 6/32 (19%); placebo 1684 (19%) p=NR	NR	NR	NR	NR	NR	NR	
Reddy, 2006	Headache, dizziness or disorientation: synthetic CEE 5/20 (25%); placebo 4/20 (20%)	Weight gain and/or edema: CEE 2/20 (10%); placebo 1/20 (5%)	See Headache column	NR	NR	NR	NR	Hormonal problems (not specified0: CEE 2/20, placebo 3/20
Utian, 2001	NR	NR	NR	NR	NR	NR	NR	Also reported leg cramps in CEE groups.
Utian et al., 2004	21% of placebo; 18.7% of combined Rx groups	NR	4% of placebo; 4% combined Rx groups (withdrawals not reported)	None	NR	1 in 0.3mg (withdrawals not reported)	NR	Dose-related trend in % of patients reporting adverse events: 0.3 mg: 72% 0.625 mg: 76% 1.25 mg: 81% placebo: 71%
Oral								

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Coope, 1981*	Estropipate: 1.5 mg/day for 21/28 days	None	11/66	NR	Wthdl bleeding in majority of women, 1/36 with breakthrough bleeding.	NR	One in Rx group.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Coope, 1981*	NR	NR	NR	One with small vein thrombosis.	NR	NR	NR	Also reports of fluid retension and LV failure in Rx group; 2 with severe depression in Rx group. Two deaths (recurrent gastic cancer, epileptic seizure).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

					Withdrawals due to specific adverse effects		
Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Vaginal estradiol							
Speroff, 2003	vaginal E2 delivering the equivalent of 50 mcg or 100 mcg per day; placebo vaginal ring	2.5 mg per day oral norethindrone or 10 mg per day oral medroxyprogesterone acetate for 14 days after removal of the vaginal ring.	54/333 (16.2%) Discontinuation rates lower in E2 50 mcg (p=0.007) and E2 100 mcg (p=0.001) groups than placebo.	NR- discontinuation rates due to adverse events were significantly lower in the E2 groups than placebo.	6.6% intermenstrual bleeding (withdrawals not reported)	NR	6.3% (withdrawals not reported)

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 9. Adverse effects reported in placebo-controlled trials with hot flash/flush or other symptom outcomes

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Vaginal E2								
Speroff, 2003	8.7% (withdrawals not reported)	NR	NR	NR	NR	NR	NR	vaginal candidiasis 6.6% (withdrawals not reported)

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Oral E2			
Abrahamsen, 1997	E2: 2 mg/day (22 days), 1 mg/day (6 days); calcium NR	MPA: 1 mg/day (10 days)	NR
Arrenbrecht, 2004	E2 1mg/day placebo	intermittent 90 µg norgestimate (NGM) (3 days on, 3 days off)	29 22 E2/iNGM 7 placebo. Overall drop out related to side effects was 21%.
Cheng, 2002	E2: 2 mg/day; calcium NR	NETA: 1 mg/day CCT	E2 15 placebo 15
Ettinger, 1992	E2: 0.5, 1.0, or 2.0 mg/day micronized + Ca 1500 mg/day; placebo: Ca 1500 mg/day	None	41 (65%) completed follow-up

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Oral E2								
Abrahamsen, 1997	NR	NR	NR	NR	NR	NR	NR	NR
Arrenbrecht, 2004	Uterine bleeding: placebo: 0 E2/iNGM: 17 (20.2%); p <0.0001. Drop out rate due to side effects related in the HRT during first year for uterine bleeding was 18%.	NR	Breast pain: Placebo: 2, (3.2%) E2/iNGM: 13 (15.5%); p<0.0001. Drop out rate in the HRT group for breast pain	Placebo: 11 (17.7%) E2/iNGM: 13 (15.5%); p<0.0001	Placebo: 10 (15.1%) E2/iNGM:6 (7.14%); p=0.008	NR	NR	NR
Cheng, 2002	NR	NR	NR	NR	NR	NR	NR	NR
Ettinger, 1992	5 due to bleeding	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Oral E2				
Abrahamsen, 1997	NR	NR	NR	NR
Arrenbrecht, 2004	NR	NR	NR	abdominal pain including dysmenorhoeal pain: P 10 (16.1%), E2iNGM 24 (28.6%); p=0.002. Back pain: P 15 (24.2%), E2iNGM 8 (9.52%), p<0.001.
Cheng, 2002	NR	NR	NR	Lack of time or interest; Health concerns; Poor compliance for pill regimen (n=6); Side effects
Ettinger, 1992	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Franke, 2006	1mg/day estradiol groups also received SQ depot gosereling acetate 10.8mg q 12 week	0.5mg/day norethisterone acetate	
Gambacciani, 1995	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	None	9

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Franke, 2006	Vaginal bleeding: Normal bleeding: Placebo: Cycle 1 (n=16), 6 (n=15), respectively: 6.5 ± 6.2, 1.4 ± 3.8 (p≤ 0.05 vs. cycle 1); CENT: cycle 1 (n=15), 6 (n=14), respectively, 10.1± 7.8, 5.7 ±7.6 (0.05 <p<0.10 vs. cycle 1); Severe bleeding: Placebo: Cycle 1 (n=16), 6 (n=15), : 1.7 ± 1.9, 0.4 ± 1.1 (0.05 <p<0.10 vs. cycle 1); CENT: cycle 1 (n=15), 6 (n=14), respectively, 1.6± 1.9, 0.2 ± 0.8 (0.05 <p<0.10 vs. cycle 1)	NR	NR	NR	NR	NR	NR	NR
Gambacciani, 1995	NR	NR	2	1	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Franke, 2006	NR	NR	NR	Avg. # of non-bleeding days/28-day cycle in first 6 months: P: 26 ± 3 days CENT: 21± 7 days; p=0.02 **Abdominal pain: Mild pain:** P: Cycle 1 (n=16), 6 (n=15), respectively: 3.3 ± 2.7, 3.1 ± 7.4 (p≤ 0.05 vs. cycle 1); CENT: cycle 1 (n=15), 6 (n=14), respectively, 5.0± 7.6, 3.1 ±4.6, **Severe pain:** Placebo: Cycle 1 (n=16), 6 (n=15), 23 respectively: 1.9 ± 5.8, 0.1 ± 1.5, CENT: cycle 1 (n=15), 6 (n=14), respectively, 0.6± 1.0, 1.0 ± 3.7. Double-layer endometrial thickness: BL to cycle 6: in both groups decreased by an average of 30% (P: mean 9.2 ± 3.2 mm at BL to 5.0 ± 3.2 mm after 6 months, CENT: 8.8± 4.9 at BL to 4.8 ± 3.4 mm after 6 months) Greene climacteric score (anxiety, depression, somatic complaints, vasomotor symptoms and loss of interest
Gambacciani, 1995	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Greenwald, 2005	E2 0.25 mg/day E2 0.5mg/day; E2 1mg/day; E2 1mg/day +NETA , E2 1mg/day +NETA or E2 2mg/day +NETA ; placebo for 26 months	NETA 0.25mg/day (with E2 1mg) NETA 0.5mg/day (with E2 1mg) NETA 1mg/day (with E2 2mg)	126/327 -(38.5%) - Discontinuation Rates to AE (n/total # randomized): placebo: (11/48), 23%; E2 0.25mg: (9/45), 20%; E2 0.5mg:(6/44)14%, E2 1mg (16/46), 35%; E2 1mg/NETA 0.25mg (7/49) 14%, E2 1mg/NETA 0.5mg (8/47) 17%, E22mg/NETA 1mg: (8/48) 17%
Jirapinyo et al, 2003	E2: 2mg/day	NETA 1mg/day	17/120
Lees, 2001	E2: 1 or 2 mg/day Canadian group encouraged to take 500 mg/day Ca	Dydrogesterone: 5, 10 or 20 mg/day cyclic	117

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Greenwald, 2005	For endometrial hyperplasia: placebo:1; E2 0.5mg: 1; E2 1mg: 9. E2 1mg/NETA 0.25mg: 0; E2 1mg/NETA 0.5mg: 0; E2 2mg/NETA 1mg: 0. Withdrawal due to of bleeding or uterine/endometrial disorders: E2 1mg: 12; combination therapy groups combined: 10 .	NR	NR	NR	NR	NR	NR	NR
Jirapinyo et al, 2003	1 in E2	1 in placebo	2 in E2, 1 in placebo	1 in E2 (died of pneumonia)	NR	NR	NR	NR
Lees, 2001	34 (6%) all in E2 group	NR	E2 2mg: 36% E2 1mg: 24% P: 12% Breast tenderness: worse with E2 2 mg than the E2 1mg.	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Greenwald, 2005	NR	NR	NR	No serious AE were reported during the trial, and the distribution of events was similar between treatment and placebo. Overall, 65 (20%) withdrew from the study because of an AE. The highest discontinuation rate was found in the unopposed E2 1mg group (56%), with the single most common reason being uterine bleeding. 37% of the withdrawals were contributed to endometrial disorder, endometrial hyperplasia, and bleeding.
Jirapinyo et al, 2003	1 in E2	NR	NR	One death occurred in an E2 patient whose condition had been diagnosed as tension headache and migraine; autopsy reported
Lees, 2001	NR	NR	NR	83 withdrawals due to 'other adverse events;" 11% in placebo, 62% in treatment groups. Nausea, abdominal pain were expected at greater than 10%. 13 fractures during the study: placebo: 3 (3%), E2:10 (4%).

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Liu, 2005	E2 1mg/day E2 1mg/day + progesterone placebo	micronized progesterone (P4) 300mg/day MPA 10mg/day (also used in combination with E2 1mg/day) norethindrone (NET) 1mg/day	109 (82.5%)
Mosekilde, 2000	E2: 1-2 mg/day; calcium NR	NETA: cyclic 1 mg/day 10 days (intact uterus); CCT 1 mg/day (without uterus)	89% completed study
Munk-Jensen, 1988	E2: 2 mg/day CCT vs. cyclic; calcium NR	NETA: 1 mg/day	86% completed (130)

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Liu, 2005	NR-see additional comments in other	0 (see additional comments in other)	NR (see additional comments in other)	NR	NR	NR-see additional comments in other	1 (thrombophlebitis)-see additional comments in other	NR
Mosekilde, 2000	NR	NR	NR	NR	NR	NR	NR	NR
Munk-Jensen, 1988	3 E2 0 placebo	NR	2 E2 0 placebo	NR	1 E2	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Liu, 2005	NR	NR	NR	"There were several minor AEs reported during the study, including breast tenderness, vaginal spotting, and increased drowsiness (especially during P4 tx)" Data not provided. 2 major AE reported to the Data Safety Monitoring Board. 1 subject developed thrombophlebitis (not taking an estrogen-containing preparation). A second subject reported a rapidly enlarging myoma that required a hysterectomy. No episodes of endometrial hyperplasia on surveillance endometrial bx were detected.
Mosekilde, 2000	NR	NR	NR	NR
Munk-Jensen, 1988	NR	NR	NR	Breast cancer: treatment 2, placebo 0; Confusion: treatment 0, placebo1; Cancer: treatment 3, placebo 0; Private reasons: 10; Technical errors: treatment 22, placebo 16; Paresthesia: treatment 1, placebo, 0

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Prestwood et al, 2003	E2: 0.25 mg/day E2 and placebo groups also received Calcium 1300 mg/day + Vitamin D 1000 IU/day	Progesterone (type not specified): 100 mg/day for 2 weeks every 6 months (unclear whether placebo group received progesterone or placebo)	E2: 29% withdrew; Placebo: 36% withdrew
Resch, 1990	E2: 2 mg/day cyclic + Ca 500 mg/day; placebo: Ca 500 mg/day	NETA: 1 mg/day CCT	E2: 6 placebo: 7
Riis, 1988	E2: 2 mg/day CCT; calcium NR	NETA: 1 mg/day CCT	E2: 3 placebo: 3

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Prestwood et al, 2003	1 E2 1 placebo	None	1 placebo	None	None	None	None	1 placebo
Resch, 1990	E2: 4	None	None	None	None	None	T: 1	None
Riis, 1988	E2: 1	None	None	None	None	None	None	None

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Prestwood et al, 2003	None	None	None	Total abnormal mammograms: 15 in E2 (1 withdrawal); 10 in placebo. (P=0.26) Other withdrawals due to medical reasons: 3 lung cancers (1 E2, 2 placebo), 2 GI-tract bleeding (1 E2, 1 placebo), 1 colon cancer (E2), 1 melanoma (E2), 1 meningioma (E2), 1 abnormal Pap (placebo), 1 fall (placebo), 1 hip replacement (placebo), 1 shingles (placebo), 3 unknown illness (placebo). 2 deaths (placebo)
Resch, 1990	None	None	None	E2: 1 transitory ischemic attack placebo: 7 lack of interest
Riis, 1988	None	None	None	E2: 2 lack of time placebo: 1 edema of legs & fingers 2 hot flashes

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Warming, 2004	1mg E2 + 1mg drospirenone, 1mg E2 + 2mg drospirenone, 1mg E2 + 3mg drospirenone, or placebo	Drospirenone: 1mg, 2mg, 3mg daily with E2 groups	Total randomized in all groups: 60 Total withdrawn due to AE/total withdrawals: P:6/13 (36%) E2 1mg + drospirenone: 18/21 (85%) E2 2mg + drospirenone: 10/11 (91%) E2 3mg + drospirenone: 12/15 (80%) Study had 75% completion rate.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Warming, 2004	Median Change in endometrial thickness (mm) (read off Figure 3) 6, 12, 18, 24 months respectively: P: -0.5, 0; -0.2; -0.5. E2 +1mg drospirenone: 0.5; 0.4, 0.8, 0.7. E2 + 2mg drospirenone (it appears that one data point for this group at 6 months may not be included in the graph line...?error) 0.0, 0.1, 0.15, -0.1. E2 + 3 mg drospirenone: 0.25, 0.25, 0.4, 0.0. Endometrial thickness decreased by: Placebo 0.5 ± 15 , (p<0.05), no change in 2mg and 3mg drospirenone groups; 1mg drospirenone group increased 0.7± 1.7 (p<0.05). Moderate or severe bleeding were recorded ≤2.5% per cycle after 1 year of treatment.	NR	NR	NR	NR	NR	E2 + 1 mg drospirenone: 1 (PE-54 y/o suffered from leg cramp X 20 years and had been on an airplane prior to the incident)	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Warming, 2004	NR	NR	NR	"significantly more participants withdrew from the study owing to bleeding episodes in the group treated with the lowest dose of drospirenone than in the 2 other groups." Authors included spotting in the category of mild bleeding disturbances. Authors state that HRT-related AE event = 35; not related to HRT n=11. Withdrawn due to lack of efficacy (n=2), breast cancer (n=1 in the group treatment with 2 mg drospirenone 20 months after randomization. Pt with no family history or other risk factors), pulmonary embolism (n=1) and other reasons (n=10). The end-of-study biopsies did not reveal any incidents of hyperplasia or cancer. In placebo, almost all 96.2-100% remain amenorrheic throughout the entire 2 year period. FIGURE 4 includes individual points for % of pts with no bleeding or spotting per cycle. In the active tx groups, the # of pts who did not bleed increased throughout the study. E2 + 2 mg drospirenone, 94% of the pts were amenorrheic in cycles 13 and 26. In E2 + 1mg drospirenone, 86% of the pts and in E2 + E3, 85% of the pts we

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Transdermal E2			
Adami, 1989	E2: 50 mg day + Ca 1200 mg/day + vitamin D 600-800 units/day; placebo: Ca 1200 mg/day + vitamin D 600-800 units/day	MPA: 10 mg/day (12 days)	None
Alexandersen, 1999	E2: 50 microgm/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	Oral NETA: 1 mg/day	5 had poor compliance; 68/100 completed study
Arrenrecht, 2002	E2: 50, 100 microgm/day; calcium NR	None	E2: 39
Bhattoa, 2003	E2: 50 microgm/day+ 500mg calcium carbonate + 400 IU vitamin D3	MPA 5mg daily	E2:8 placebo :3
Cagnacci, 1991	E2: 50 microgm/day cyclic; calcium NR	After 6 months, MPA 5 mg/day cyclic	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Transdermal E2								
Adami, 1989	NR	NR	NR	NR	NR	NR	NR	NR
Alexandersen, 1999	2	Reported	Reported	NR	Reported	NR	NR	2
Arrenrecht, 2002	NR	NR	5 (9%)	12 complaints	NR	NR	NR	NR
Bhattoa, 2003	E2: 4	NR	E2: 4	NR	NR	NR	E2: 1 (negative for antiphospholipid AB)	Placebo-1 (sudden AMI-1 day after BL visit)
Cagnacci, 1991	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Transdermal E2				
Adami, 1989	NR	NR	NR	NR
Alexandersen, 1999	NR	NR	NR	Mood changes reported
Arrenrecht, 2002	5 (9%) in E2	NR	NR	E2: 7 Edema (complaints) 4 hot flashes (withdrawal) 6 subject choice (withdrawal)
Bhattoa, 2003	E2: 2 ("allergic skin reaction")	NR	NR	Placebo: 1 had a CVA at visit M9--significant elevation in her anti-cardiolipin and anti-ß2 glycoprotein antibody titers)
Cagnacci, 1991	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Cooper, 1999	E2: 25, 50, 75 micrograms/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 20 mg/day cyclic	74-80% compliance in groups; 14% withdrew due to adverse events
Ettinger, 2004	unopposed 0.014 mg estradiol /day. placebo calcium 400mg twice daily (95% participants took it in both groups) vitamin D 400 IU once daily (95% of particpants took it in both groups)	None	E 191/208 (92%) completed trial compared to P:185/209 (89%). (patch counts showed that women who continued to use the study drug through 2 years, 84% used at least 75% of the expected number of patches). Incidence of serious AE: NS between group, p=1.0

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Cooper, 1999	NR	NR	37% reported symptoms	Reported	NR	NR	NR	NR
Ettinger, 2004	376/417 had endometrial bx-269 were adequate for dx: E:1 had "focal atypical hyperplasia" but after 2 years of tx, reported no uterine bleeding and had a bx after 1 year which was normal. After completing the study, the woman received 10mg medroxyprogesterone acetate bid x 3 months, subsequent bx showed atrophic endometrium. 107 had no endometrial bx, 101 of them underwent transvaginal US and 11 had endometrial thickness of 5 mm or greater--6 of which went on to have bx or D&C--found to be normal.	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Cooper, 1999	Reported	NR	NR	Back pain; flu syndrome
Ettinger, 2004	moderate to severe skin reaction to patch: P vs E: 6 vs.1; p= 0.12. Rash: (other site than patch application): E: 6/208 (2.9%) vs. P: 21/209 (10%), p=.003. Herpes zoster: E:1/208 vs. P: 9/209; p=.01	NR	NR	Authors state that the rate of endometrial hyperplasia in the E group, was, at worst, no more than 7.3% higher than in the P group. Endometrial bx: E: 1 had uterine adenosarcoma. Simple (nonhyperplastic) endometrial polyps (found at bx or by hysteroscopy) E: 3 (1.4%), vs. Placebo 2 (0.9%). Mammography was done in E: 188/191 and P: 178/185. E: 3/188 and 5/178 in the placebo group had abnormal mammograms. Breast cancer: E: 1, P: 2. Hernia: E :1/208 (0.5%) vs. P: 7/209 (3.3%); p=.03. Cervical polyp: E: 12/208 (5.8%) vs. P: 4/209 (1.9%); p<.04. Vaginal discharge: E: 22/208 (10.6%) vs. P: 3/209 (1.4%), p<.001. Cancer: E: 3/208 (1.4%, breast, lung, uterine adenosarcoma) vs. P: 5/209, (9.6%, 2 breast, 1 colon, 1 cervix, 1 liposarcoma); p=.5.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Filipponi, 1995	E2: 0.05 mg/day + Ca 1200-1500 mg/day; placebo: Ca 1200-1500 mg/day	MPA: 20 mg/day cyclic	92 of 124 completed study E2: 9 (21%) placebo: 12 (30%)
Gonnelli, 1997	E2: 0.05 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 10 mg/day cyclic	9
Hesley, 1998	E2: 0.025, 0.05, and 0.01 mg/day; calcium NR	None	NR
Lufkin, 1992	E2: 0.1 mg/day (1-21 days) + Ca 800 mg/day; placebo: Ca 800 mg/day	MPA: 10 mg/day, 10 days cyclic	9 total; 3 in E2 group; Over 50% of E2 group talked of adverse events
McKeever, 2000	E2: 0.025, 0.0375, 0.05, 0.1 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 2.5 mg/day CCT non-hysterectomized women	27 withdrew

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Filipponi, 1995	NR	NR	NR	NR	NR	NR	NR	NR
Gonnelli, 1997	1	NR	NR	NR	NR	NR	NR	NR
Hesley, 1998	NR	NR	NR	NR	NR	NR	NR	NR
Lufkin, 1992	8% E2 group	NR	56% of E2 group	NR	NR	NR	NR	NR
McKeever, 2000	34 reports	NR	43 reports	3	NR	NR	1	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Filipponi, 1995	E2: 3	NR	NR	E2: 2 fear of side effects (cancer); 2 loss to followup placebo: 5 dissatisfied with results; 3 had hot flashes; 4 loss to followup
Gonnelli, 1997	2	NR	NR	5 withdrawals for personal reasons; 1 withdrawal for side effects
Hesley, 1998	NR	NR	NR	NR
Lufkin, 1992	2 E2	NR	NR	1 withdrawal for no reason
McKeever, 2000	Reported	NR	NR	1 depression

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Notelovitz, 2002	E2: 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day	None	159/355
Perez-Jaraiz, 1996	E2: 50 microgm/day; calcium NR	MPA: 10 mg/day for 10 days	NR
Rubinacci, 2003	E2: 0.025 mg/day	norethisterone acetate 0.125 mg/day	32/124

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Notelovitz, 2002	NR	NR	14.6% E2 0.025 mg/day, 17.8% E2 0.05 mg/day, 34.8% E2 0.075 mg/day, 8% placebo; withdrawals not reported	11.2% E2 0.025 mg/day, 8.9% E2 0.05 mg/day, 5.6% E2 0.075 mg/day, 12.6% placebo; withdrawals not reported	NR	NR	NR	NR
Perez-Jaraiz, 1996	NR	NR	NR	NR	NR	NR	NR	NR
Rubinacci, 2003	36% of E2 and 24% of placebo had some bleeding; withdrawals not reported. Endometrial thickness increased by an average of 0.45 mm in E2, decreased by 0.18 mm in placebo; withdrawals not reported.	NR	36.7% E2, 22.2% placebo; withdrawals not reported	5% E2, 6.3% placebo; withdrawals not reported	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Notelovitz, 2002	application-site reactions 9% in E2, 0 placebo			1 case of breast cancer in E2 0.025 mg/day and 0.075 mg/day group.
Perez-Jaraiz, 1996	NR	NR	NR	NR
Rubinacci, 2003	erythema 9% E2, 14% placebo	NR	NR	2 cases of breast cancer in E2 group, one after 12 months and the other after 24 months.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Warming, 2005	E2: 45 microgram/day + 500mg CA	30 microgram levonorgestrel (LNG) 40 microgram levonorgestrel	45E2 + 30 LNG:36 (52%) 45E2 + 40 LNG 40 (56%) placebo: 26 (37%) completion rate was 52%.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Warming, 2005	# total AE/# bleeding (%) 45E2 + 30 LNG: 30/15 (50%) 45E2 + 40 LNG: 37/22 (59%) placebo: 0/17 (0%) bleeding was the reason for withdrawal (18%--all from HRT group). Bleeding/spotting at 3 months (n, %): 45E2 + 30 LNG, (34, 49%), 45E2+ 40 LNG: (33, 46%), Placebo: (1, 1%), overall (68, 32%). Bleeding/spotting at 12 months (n, %): 45E2 + 30 LNG, (17, 41%), 45E2+ 40 LNG: (12, 32%), Placebo: (0, 0%), Overall (29, 22%). Bleeding/spotting at 24 months (n, %): 45E2 + 30 LNG, (9, 27%), 45E2+ 40 LNG: (7, 22%), Placebo: (0, 0%), Overall (16, 15%). Change in endometrial	Mastalgia: 45E2 +30 LNG: 0 45E2 +40 LNG: 0 placebo: 0	45E2 +30 LNG: 15 (22%) 45E2 +40 LNG: 22 (31%) placebo: 0	NR	chg (kg) 45E2 + 30 LNG:-0.5 ± 2.97 45E2 +40 LNG: 0.38 ± 2.82; placebo: -0.13 ±3.13	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Warming, 2005	Patch Reaction: 45E2 + 30 LNG: 8 (125), 45E2 +40 LNG: 12 (17%), Placebo: 14 (20%). Overall: 34 (16%): local skin reactions: second most frequent withdrawal reasons being local skin reactions to the patch (16%). However, skin tolerance was good in 84% of the women with no difference between the study groups…thought related more to	NR	NR	45E2 1 +30LNG-1 died (autopsy showed no cause of death although it was assumed she died from alcohol intoxication). Reasons for withdrawal: Other AE: 45E2 +30 LNG: 7 (10%), 45E2 + 40 LNG: 3 (4%), placebo: 3 (4%), overall: 13 (6%). Lack of efficacy 45E2 +30 LNG: 1 (1%), 45E2+ 40 LNG: 1 (1%), placebo 6 (9%). Other (not related to AE): 45E2 + 30 LNG: 4 (6%), 45E2 + 40 LNG: 2 (3%), placebo 3 (4%), overall: 9 (4%).

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Oral E2V			
Doren, 1995	E2V: 2 mg/day + Ca 1000 mg/day; E2: 2 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	NETA: 5 mg/day cyclic; 1 mg/day CCT	NR
Heikkinen, 1997	E2V: 2 mg/day; calcium NR	MPA: 2 mg/day cyclic	8 in E2V
Isaia, 1989	E2V: 2 mg/day cyclic; calcium NR	MPA: 10 mg/day for 40 days	NR
Komulainen, 1997	T1: E2V 2 mg/day cyclic; T2: vit D 300 IU day + Ca 500 mg/day; T3: T1 + T2; placebo: Ca 500 mg/day	T1 & T3: CPA 1 mg/day cyclic	73: 55 from HT groups 84% completed study/99% compliance
Marslew, 1992	E2V: 2 mg/day CCT or cyclic; calcium NR	Cyproterone acetate (1 mg/day) or levonorgestrel (75 microgrm/day)	13: 12 in HT 1 in placebo

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Oral E2V								
Doren, 1995	E2V: 24% -reason for discontinuing of drug	NR	2	NR	2	NR	NR	NR
Heikkinen, 1997	2	NR	Reported	NR	NR	NR	1	NR
Isaia, 1989	NR	NR	NR	NR	NR	NR	NR	NR
Komulainen, 1997	17	None	None	12	None	None	None	None
Marslew, 1992	4	NR	NR	2	1	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Oral E2V				
Doren, 1995	NR	NR	NR	10 (missed appointments or misc.)
Heikkinen, 1997	NR	NR	NR	4 Hot flashes 1 Psychiatric syptoms 1 Personal reasons 1 Breast cancer 1 Death
Isaia, 1989	NR	NR	NR	NR
Komulainen, 1997	None	None	None	6 withdrawals from diagonisis of osteoporosis; 3 withdrawal disruptions in medication adherence
Marslew, 1992	NR	NR	NR	4 withdrawal due to anxiety, unrelated illness

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Oral CEE			
Agnusdei, 1990	CEE: 0.625 mg/day (days 1-20) + Ca 800-1200 mg/day; placebo: Ca 800-1200 mg/day	MPA: cyclic 5 mg/day	NR
Agnusdei, 1995	T1: CEE 0.3 mg/day alone; T2: CEE 0.3 mg/day + progestin; placebo: Ca carbonate 1000 mg/day; All subjects: Ca carbonate 1000/day	All patients, 10 mg/day MPA 15 days every 3 months.	27 (33%): 19 for personal reasons, 8 for adverse effects
Aloia, 1994	T1: CEE 0.65 mg + CA 1700 mg/day + vitamin D 400 IU /day T2: CA 1700 mg/day + vitamin D 400 IU /day; P: vitamin D 400 IU /day	MPA: cyclic 10 mg/day (days16-25)	17: 6 due to disease; 5 wanted change in HT; 3 no reason given

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Oral CEE								
Agnusdei, 1990	NR	NR	NR	NR	NR	NR	NR	NR
Agnusdei, 1995	3 with endometrial modification	5	NR	NR	NR	NR	NR	NR
Aloia, 1994	NR	1	2	2	2	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Oral CEE				
Agnusdei, 1990	NR	NR	NR	NR
Agnusdei, 1995	3 cases	NR	NR	NR
Aloia, 1994	NR	NR	NR	2 mood, 1 cramps, 1 libido, 1 eructation, 1 constipation

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Anderson, 2005 WHI Study	CEE: 0.625 mg/day placebo X average 6.8 years	None	Withdrew: 321 CEE: 136 placebo: 185 Lost to follow-up:242 CEE: 126 placebo: 116 Deceased: 580 CEE: 291 placebo: 289

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Anderson, 2005 WHI Study	NR	NR	NR	NR	NR	NR	CEE (n=5310) vs. P (n=5429): n, (annualized %), HR, (95% C) . VTE: 101 (0.28) vs. 78 (0.21). HR 1.33; (0.99-1.79). DVT: 77 (0.21) vs. 54 (0.15), HR 1.47, (1.04-2.08). PE 48 (0.13) vs. 37 (0.10) HR 1.34 (0.87-2.06). Removing the women with a history of PE: 47 vs. 37; HR 1.31; (0.85-2.01)	(CHD includes: acute MI requiring hospitalization, silent MI determined from serial ECG, and coronary death.) CEE (n=5310) vs. P (n=5429): n, (annualized %), HR, (95% C) . CHD: 177 (0.49) vs. 199 (0.54). HR 0.91; (0.75-1.12). CHD Death: 54 (0.15) vs. 59 (0.16), HR 0.94, (0.65-1.36). Nonfatal

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Anderson, 2005 WHI Study	NR	NR	NR	8.6% subsample at BL and year 1: reduction in LDL (-13.7% vs. -1.0%, p<.001) and a larger increase in HDL (15.1% vs. 1.1%, p<.001) in the CEE group vs. placebo group. Cholesterol reduction: NS. TG increase: CEE 25% vs. placebo 3%, p<.001. Systolic BP at 1 year was higher by a mean (SE) of 1.1 (0.4) mm HG with CEE vs. placebo p=.003. DBP-NS (data not shown). Incidence of stroke: CEE (n=5310) vs. placebo (n=5429): 158 (0.44) vs. 118 (0.32) HR 1.39 (95% CI 1.10-1.77). Fatal stroke: 15 (0.04) vs. 14 (0.04) HR 1.13 (95% CI 0.54-2.34). Nonfatal Stroke: 114 (0.32) vs. 85 (0.23) HR 1.39, (95% CI 1.05-1.84).In 168 women with prior stroke, the HR for subsequent stroke (6 vs. 6; HR 1.67; (95%CI, 0.52-5.36 did not differ from the HR in women without a history of stroke (152 vs. 112; HR 1.39; 95% CI 1.09-1.78; p=.77). Invasive breast cancer: 94 (0.26) vs. 124 (0.33) HR 0.77 95% CI 0.59-1.01. Colorectal cancer-NS. Total Cancer: 372 (1.03) vs. 408 (1.10) HR 0.93; 95% CI 0.81-1.07.Global Index: defined as time to the first event (CHD, stroke, PE, breast CA, colorectal CA, hip fracture

0

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Cauley, 2003	CEE: 0.625 mg/day	medroxy-progesterone acetate 2.5 mg/day	541/16608
Civitelli, 1988	CEE: 1.25 mg/day + Ca 800-1000 mg/day; placebo: Ca 800-1000 mg/day	None	NR
Civitelli, 2002	CEE: 0.625 mg/day	medroxy-progesterone acetate 2.5 mg/day	49/135 (45% placebo, 28% CEE)
Gallagher, 1991	T1: CEE 0 .625 mg/day; T2: progestin only; T3: CEE 0.3 mg/day + progestin; All subjects: Ca 1000 mg/day; placebo: Ca 1000 mg/day	NETA: 2, 10 mg/day cyclic	16
Gambacciani, 1997	CEE: 0.3 mg/day; All subjects: Ca 500 mg/day	None	7: 4 poor compliance

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Cauley, 2003	NR	NR	NR	NR	NR	NR	NR	NR
Civitelli, 1988	NR	NR	NR	NR	NR	NR	NR	NR
Civitelli, 2002	vaginal bleeding 2 CEE, 3 placebo; endometrial cancer 1 CEE, 0 placebo.	none	none	at least 1 (combined with other events in "other" category)	none	none	none	none
Gallagher, 1991	2 bleeding	NR	NR	NR	NR	NR	NR	NR
Gambacciani, 1997	NR	NR	1	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Cauley, 2003	NR	NR	NR	
Civitelli, 1988	NR	NR	NR	NR
Civitelli, 2002	none	none	none	1 withdrawal in CEE group due to breast cancer, 0 placebo; 1 withdrawal in placebo group due to ankle fracture, 0 CEE; 1 withdrawal in placebo group due to excessive decrease in BMD, 0 CEE.
Gallagher, 1991	NR	NR	NR	2 hot flashes
Gambacciani, 1997	NR	NR	NR	1 menopausal symptoms

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Gambacciani et al, 2003	CEE: 0.3 mg/day + Ca 1g/day Control: Ca 1g/day	MPA 2.5 mg/day, or dydrogesterone 5mg/day, or nomegesterol 2.5 mg/day	50% of control group, 30% of CEE group
Genant, 1982	CEE: 0.15, 0.30, 0.45, 0.60 mg/day; calcium NR	None	NR
Greenspan, 1998	CEE: 0.625 mg/day; calcium NR	None	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Gambacciani et al, 2003	11 CEE (withdrew due to), 3 control group (not clear if withdrew)	NR	NR	NR	Significant change from baseline in weight and BMI in control group, not CEE; withdrawals NR	NR	NR	NR
Genant, 1982	NR	NR	NR	NR	NR	NR	NR	NR
Greenspan, 1998	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Gambacciani et al, 2003	NR	NR	NR	40% of control group and 8% of CEE group withdrew because climacteric symptoms requiring treatment (or higher dosage)
Genant, 1982	NR	NR	NR	NR
Greenspan, 1998	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Greenspan, 2003	CEE 0.625mg with or without MPA alendronate (ALN) 10mg daily, HRT (CEE 0.625mg/day) + ALN 10mg daily placebo Calcium and Vitamin D if needed	MPA 2.5mg/day with CEE in women with intact uterus)	placebo: 10 HRT: 9 ALN: 8 HRT + ALN: 9
Hosking, 1998	US group: CEE 0.625 mg/day cyclic; UK: E2 1 to 2 mg/day cyclic; calcium NR	US: MPA 5 mg/day CCT UK: NETA 1 mg/day cyclic	NR Compliance to regimen was >75%

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Greenspan, 2003	n (%) that experienced menstrual spotting: (not clear how many contributed to actual withdrawal) placebo: 9 /93 (10) HRT: 29/93 (31) p<.05 vs. placebo ALN: 7/93 (8), p<.05 vs. HRT HRT + ALN: 31 /94 (33) p<.05 vs. placebo; p <.05 vs. ALN	indigestion: n (%) that experienced AE (not clear how many contributed to actual withdrawal) placebo: 4 /93 (4) HRT: 5/93 (5) ALN: 6/93 (6), HRT + ALN:1 /94 (1). Heartburn: placebo: 15 /93 (16) HRT:11/93 (12) ALN: 17/93 (18), HRT + ALN:16 /94 (17).	(%) that experienced breast tenderness: (not clear how many contributed to actual withdrawal) placebo: 16 /93 (17) HRT: 52/93 (56) p<.05 vs. placebo ALN:22/93 (24), p<.05 vs. HRT HRT + ALN: 50 /94 (53) p<.05 vs. placebo; p <.05 vs. ALN	NR	Weight gain n,(%) : placebo: 8 /93 (9) HRT: 8/93 (9) ALN:6/93 (6), HRT + ALN: 8/94 (9)	NR	DVT: n, (%) : placebo: 0 /93 HRT: 2/93 (2) ALN:1/93 (1), HRT + ALN: 0/94	NR
Hosking, 1998	99 complaints	51%	None	None	None	None	None	14%

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Greenspan, 2003	NR	NR	NR	Menstrual cramps: n,(%) : placebo: 0 /93 HRT: 6/93 (6), p<.05 vs. placebo ALN:0/93 p<.05 vs. placebo, HRT + ALN: 5/94 (5). endometrial bx: :n,(%) : placebo: 1 /93 (1) HRT: 12/93 (13), p<.05 vs. placebo ALN:2/93 (2)p<.05 vs. HRT, HRT + ALN: 11/94 (12), p<.05 vs. placebo, p<.05 vs. ALN. Other AE: Bloating; peripheral edema; dysphagia, high blood pressure, hospitalizations, falls, height loss, clinical fractures---All NS.
Hosking, 1998	28%	None	None	Nervous system, psychiatric 33%

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Hulley, 1998	CEE: 0.625 mg/day; Ca NR	MPA: 2.5 mg/day CCT	82% compliance
Hulley, 2002 (HERS II)	CEE: 0.625 day Calcium NR	MPA: 2.5 mg/day CCT	NR
Jackson, 2006 WHI substudy	CEE: 0.625 day placebo	none	NR
Leung, 1999	CEE: 0.625, 0.3 mg/day; calcium NR	MPA: 5 mg/day (if uterus present) cyclic	13: 6 in 0.3 group; 5 in 0.625; 2 in control
Lindsay, 1984	CEE: 0.15, 0.3, 0.625, 1.25 mg/day; calcium NR	None	33 CEE

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Hulley, 1998	NR	NR	NR	NR	NR	NR	Reported	Not significant between groups
Hulley, 2002 (HERS II)	NR	NR	NR	NR	NR	NR	Reported	NR
Jackson, 2006 WHI substudy	NR	NR	NR	NR	NR	NR	NR	NR
Leung, 1999	Reported	Reported	Reported	Reported	Reported	None	None	None
Lindsay, 1984	NR	NR	6	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Hulley, 1998	NR	Reported	NR	VTE (2.89; 1.50-5.58). Cholecystitis (1.38; 1.00-1.92).
Hulley, 2002 (HERS II)	NR	NR	NR	VTE (2.08; 1.28-3.40). Biliary tract surgery (1.48; 1.12-1.95)
Jackson, 2006 WHI substudy	NR	NR	NR	None
Leung, 1999	None	None	None	CEE: 4 withdrawals due to fear of side effects; 5 withdrawals due loss of fu; 2 felt they did not need the treatment. 2 in placebo group lost to fu.
Lindsay, 1984	NR	NR	NR	12 withdrawals due to poor control of menopausal symptoms; 5 illness; 11 moved.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Lindsay, 1990	CEE: 0.625 mg/day + 1500 mg Ca/day; placebo: 1500 mg Ca/day	MPA: 5 or 10 mg/day cyclic (if uterus present)	10: 4 fractures 4 lost to follow-up 2 moved away
Lindsay, 2002	CEE: 0.625, 0.45, 1.5, 0.3 mg/day + Ca 600 mg/day; placebo: Ca 600 mg/day	MPA: 2.5, 1.5 mg/day CCT	Adverse effects reported by 95% of subjects Drop outs: 8/94 (9%) placebo 103/655 (16%) treatment CEE
Meschia, 1993*	CEE: 0.3 and 0.625 mg/day; calcium NR	MPA: 2.5 mg/day	24% year 1 45% year 2 Investigators say not due to CEE
Mizunuma, 1997	CEE: 0.3 and 0.625 mg day calcium NR	2.5 mg MPA day MPA: 2.5 mg/day	3 in year 1 13 in year 2
PEPI, 1996	T1: CEE 0.625 mg/day only; T2 - T 3: CEE 0.625 mg/day + progestin; calcium NR	T2: MPA 10 mg/day cyclic, 12 days T3: MPA 2.5 mg/day daily T4: MP (micronized) 200 mg/day 12 days	Compliance: At 36 months: Taking assigned medications: Combination CEE 78% CEE only 56% Placebo 74%

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Lindsay, 1990	NR	NR	NR	NR	NR	NR	NR	NR
Lindsay, 2002	Reported in CEE groups (p<0.05)	NR	Reported in CEE groups (p<0.05)	NR	NR	NR	NR	NR
Meschia, 1993*	NR	NR	NR	NR	NR	NR	NR	NR
Mizunuma, 1997	6 vaginal bleeding (CEE group)	NR	NR	NR	NR	NR	NR	NR
PEPI, 1996	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Lindsay, 1990	NR	NR	NR	NR
Lindsay, 2002	NR	NR	NR	Vaginal dryness reported more with placebo ($p<0.05$)
Meschia, 1993*	NR	NR	NR	NR
Mizunuma, 1997	NR	NR	NR	CEE groups: 1 fear of cancer, 1 fatigue; placebo group: *2* loss of interest
PEPI, 1996	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Recker, 1977	CEE: 0.625 mg/day; Ca 2600 mg/day	MPA: 5 mg/day cyclic	NR
Recker, 1999	CEE: 0.3 mg day + Ca 1000 mg/day + vitamin D 75 nmol/L/day; placebo: Ca 1000 mg/day + vitamin D 75 nmol/L/day	MPA: 2.5 mg/day CCT	CEE: 11 placebo: 10 complaints also listed

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Recker, 1977	NR	NR	NR	NR	NR	NR	NR	NR
Recker, 1999	CEE: 31 compliants placebo: 1 complaint	None	CEE: 49 complaints placebo: 27 complaints	None	None	None	None	None

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Recker, 1977	NR	NR	NR	NR
Recker, 1999	None	None	None	Stroke: CEE 1, placebo 1; Hip fracture: placebo 1; Death: CEE 2, placebo 1; HT side effects: CEE 2, placebo 1; 17% of subjects had symptoms last more than 12 months.

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Reid, 2004	CEE 0.625 Raloxifene (SERMS) 60mg/day Raloxifene (SERMS) 150mg/day All groups: 400-600mg CA	None	placebo: 62 Raloxifene 60mg :61 Raloxifene 150mg: 55 CEE: 56
Rosen, 1997	CEE: 0.625 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 2.5 mg/day CCT, 5 mg/day cyclic	9; reasons not provided

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Reid, 2004	NR	NR	Breast pain: placebo: 10/152 (6.6%) raloxifene 60mg: 11/152 (7.2%) Raloxifene 150mg 1/157 (0.6%) CEE 25/158 (15.8% (p=009) Breast enlargement: placebo: 1/152 (0.7%) Raloxifene 60 1/152 (0.7%) Raloxifene 150: 1/157 (0.6%) CEE 7/158 (4.4%) (p<.001). [Breast pain and enlargement were more with CEE vs. other groups, p≤.02]	NR	NR	NR	MI: Placebo,0; Raloxifene 60mg, 1; raloxifene 150mg, 1; CEE, 1; (p=NS)	NR
Rosen, 1997	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Reid, 2004	NR	NR	NR	Urinary incontinence: P: 2 (1.3); Raloxifene 60mg: 1 (0.7%); R 150mg: 1 (0.6%); CEE: 11:(7.0%); p<.001. [CEE vs. other groups, p≤.01] Hernia: P: 7 (4.6%); R 60mg: 5 (3.3%); R 150mg 1 (0.%); CEE 1 (0.6%); p=.04. Leg cramps: P: 2 (1.3%), R 60mg 15 (9.9%), R 150mg 14 (8.9%), CEE: 5 (3.2%), p=.001. {R (either doses) vs. placebo or CEE, p≤.03) Hot flashes: P: 41 (37%), R 60mg 51 (33.6%), R 150mg 70 (44.6%), CEE 17 (10.8%), p<.001. [R 150mg vs. others, p≤.04, P vs. R 60mg, NS]
Rosen, 1997	NR	NR	NR	4 subjects moved away; CEE: 1 stopped taking treatment,1 removed by physician; placebo: 1 stopped taking treatment, 2 removed by physician

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Villareal, 2001	CEE: 0.625 mg/day + Ca 1200 mg/day	MPA: 5 mg/day cyclic	CEE: 11, placebo: 2; 86% compliance in CEE group; 9 HT regimen changed due to adverse events; 141 eligible subjects did not want to participate
WHI, 2002	CEE: 0.625 mg/day; calcium NR	MPA: 2.5 mg/day CCT	583 (3.5%) lost to follow-up; CEE: 42% stopped treatment placebo: 38% stopped treatment
Wimalawansa, 1998	CEE: 0.625 mg/day + Ca 1000 mg/day + vit D 400 units/day; placebo: Ca 1000 mg/day + vit D 400 units/day	Norgestrel: 150 micrograms/day cyclic	CEE: 3 placebo: 3
Oral esterified estrogen			
Genant, 1997	Esterified estrogens: 0.3, 0.625, 1.25 mg day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	None	49 withdrawals 188 discontinued 94% compliance

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Villareal, 2001	1 CEE	None	2 CEE	None	None	None	None	None
WHI, 2002	CEE: 248 hysterectomy placebo: 183 hysterectomy	NR	NR	NR	NR	NR	DVT: 167 cases PE: 101 cases	286 cases
Wimalawansa, 1998	NR	None	None	None	None	None	None	None
Oral esterified estro								
Genant, 1997	Placebo = 3 HT: 0.3 mg=1 0.625 mg = 17	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Villareal, 2001	None	None	None	CEE: 7 medical, unrelated to study;1 death due to car crash; placebo: 2 withdrew consent
WHI, 2002	NR	NR	NR	Breast cancer: 1.26 (1.00-1.59), 290 cases Stroke: 1.41 (0.86- 2.31), 212 cases Endometrial cancer: 0.83 (0.29-2.32), 47 cases
Wimalawansa, 1998	None	None	None	Placebo: 1 withdrawal due to inability to take meds; 2 for other medical conditions; CEE: Some complaints about calcium supplementation, however did not result in withdrawals.
Oral esterified estro				
Genant, 1997	NR	NR	NR	Adverse event 49

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Gozansky, 2005	placebo , raloxifene 60mg/d, or conjugated estrogen (0.625mg/d)	Women with intact uterus received trimonthly MPA (5mg/day x 13 consecutive days)	Weight loss arm: placebo: 5 raloxifiene: 7 HT: 2 Wt-stable arm: raloxifiene: 2 HT: 1
Lindsay, 2005 (substudy HOPE)	all doses mg/d CE 0.625, CE 0.625 +MPA, CE 0.45, CE 0.45 + MPA, CE 0.3, CE 0.3 + MPA, placebo	MPA: 2.5mg/day with CE 0.625mg and CE 0.45mg/day and MPA 1.5mg/day with CE 0.45mg and CE 0.3mg	127

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Gozansky, 2005	NR	NR	NR	NR	(see other) wt loss group vs. wt stable group: p<0.001. fat-mass:wt loss group vs. wt stable group: p<0.001. Changes were not different among the drug treatment groups.	NR	NR	NR
Lindsay, 2005 (substudy HOPE)	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Gozansky, 2005	NR	NR	NR	"text states that "2 participants did not tolerate drug treatment." on entry into the study, women who were recruited for the weight loss arm weighted more (79.2 ±12.0 vs. 71.1 ± 13.1 kg, p=0.005 and had more fat mass 35.3± 8.7 vs. 29.4 ± 10.7 kg; p=0.008) and fat-free mass 43.9 ± 4.7 vs. 41.7 ± 5.3 kg, p=0.047) than those in the wt-stable arm. Pair diet records were available for only 56 subjects (60%). Text states that the magnitude of weight loss was modest and was induced primarily through exercise training.
Lindsay, 2005 (substudy HOPE)	NR	NR	NR	"Previous results form the Women's HOPE study indicate that lower doses of CE and CE/MPA provide effective vasomotor symptom relief and prevent vaginal atrophy with favorable bleeding profiles (Utian, 2001, Archer,2001)"

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals
Utian, 2004 substudy HOPE	CE 0.625mg/day, CE 0.625mg/day +MPA, CE 0.45mg/day, CE 0.45mg/day + MPA, CE 0.3mg/day, CE 0.3mg/day + MPA, placebo	MPA: 2.5mg/day with CE 0.625 and CE 0.45mg/day and MPA 1.5mg/day with CE CE 0.3	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects							
Study/Year	Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness	Headache	Weight change	Dizziness	VTE	CVD events
Utian, 2004 substudy HOPE	Endometrial hyperplasia: after 1 year with lower doses of CE and MPA (n=2153): 32 cases: unopposed CE 0.625 or CE 0.45 treatment groups: 29 . Bleeding: (n=1555): # of bleeding cycles to amenorrhea: tx vs. placebo, p<0.001 Mean # of bleeding days: tx vs. placebo, p<0.001.	NR	Breast pain: (already reported in Utian 2001) after 1 year: CE 0.625/MPA 2.5: 26% incidence	NR	Mean change from BL: (partially read off of Fig 1) CE 0.625 (n=212):0.59 ± .21 kg vs placebo; p=≤0.05. CE 0.45 (n=231) 0.75 kg; CE 0.3mg: (n=235) 0.9 kg. CE .625/MPA 25: (n=241) 0.73kg; CE 0.45/MPA 25 (n=232) 0.95kg; CE 0.45/MAP 1.5 (n=228) 0.53 ± 0.19 (SE) kg; vs placebo p=0.054. CE.3/MPA 1.5mg: 1.0kg. Placebo: 1.15 ± 0.21 (SE) kg.	NR	NR	NR

Evidence Table 10. Adverse effects reported in placebo-controlled trials with bone density or fracture outcomes

	Withdrawals due to specific adverse effects			
Study/Year	Rash & pruritis	Chole-cystitis	Liver effects	Other
Utian, 2004 substudy HOPE	NR	NR	NR	"lower-dose regimens of CE and MPA produced significantly higher rates of amenorrhea and no bleeding compared with CE 0.625/MPA 2.5". Hot flush frequency: As early as 3 wk of therapy, all active tx groups significantly decrease compared with baseline and placebo (p<.05) and remained SS throughout the 12 month study period. Vasomotor symptoms: (n=188) Mean # of flushes per day: tx effects vs. placebo; p<0.05. severity of hot flushes: tx vs. placebo; p<0.001. Vaginal maturation index: increased from baseline to the two subsequent measurements (cycles 6 and 13) in all CE and CE/MPA groups (p <0.001) but not in placebo.