Oregon Health Resources Commission

Hormone Replacement Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

Update #3, April, 2008

This report is the third update of the initial Estrogen Subcommittee Report of January 2003. All revisions are highlighted.

Produced by:
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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-Managed Prescription Drug Plan. Statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

Through spring and fall of 2002 the HRC appointed a subcommittee to perform an evidence-based review of ESTROGEN THERAPY. Members of the subcommittee consisted of physicians, pharmacists, nurse practitioners, other health care professionals, consumers and advocates.

Subcommittee members worked with the Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the OHSU-EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU-EPC's draft report titled '*Drug Class Review on Estrogen for Treatment of Menopausal Symptoms and Prevention of Low Bone Density and Fractures*" was completed the week of November 13, 2002, circulated to subcommittee members, and posted on the web. The subcommittee met on November 20, 2002 to begin review of the document and other relevant materials. Three additional meetings were held. Time was allotted at each meeting for public comment, questions and testimony. All available sources of information were considered in the conclusions drawn by the Estrogen Subcommittee, which comprise the body of this report.

The HRC appointed a Pharmaceutical subcommittee to perform an evidence-based review of the EPC's October 2007 "Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage" (which supersedes the previous report on Estrogens) for new information or changes in the FDA package inserts. Members of the Pharmaceutical subcommittee consisted of one HRC Commissioner (who is a physician), two additional physicians, one Nurse Practitioner, one Pharm D. and one RPh/PhD. This report is the third update of the initial January 2003 Subcommittee Report. All revisions are highlighted.

The OHSU-EPC's update report "Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage" was completed in October 2007, circulated to the Pharmaceutical subcommittee members and posted on the HRC's website at:
http://www.oregon.gov/OHPPR/HRC/Subcommittee_Reports_HRT.shtml

The Pharmaceutical subcommittee held a meeting to review the document and additional evidence. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment, questions, and written and oral testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony, were considered.

This report is prepared to facilitate the HRC in providing recommendations to the Oregon Medical Assistance Program (OMAP) for the Plan Drug List (PDL). This report was presented to the HRC on April 18, 2008 at which time public testimony was heard and due consideration given. On April 18, 2008 this report was approved by the HRC.

This report does not recite or characterize all the evidence that was considered by the OHSU-EPC, the Pharmaceutical subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials.

The Pharmaceutical subcommittee of the HRC, working together with the OHSU-EPC, and the OSU College of Pharmacy will continue to monitor medical evidence for new developments in this drug class. On a periodic basis new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and FDA changes in indications and safety recommendations will be evaluated. The Hormone Replacement Therapy report will be updated if indicated

The full OHSU-EPC's report, "*Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage*", is available on the Office for Oregon Health Policy & Research Practitioner-Managed Prescription Drug Plan web site; http://www.oregonrx.gov . Additional information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Health Resources Commission website:
http://www.oregon.gov/OHPPR/HRC/index.shtml

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from the Office for Oregon Health Policy & Research and from OSHU Center for Evidence-based Policy.

Critical Policy:

- *Senate Bill 819:*
    - "The Department of Human Services shall adopt a Practitioner-Managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission:*

    - "Clinical outcomes the most important indicator of comparative effectiveness;
    - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Key Questions

1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?
2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for preventing low bone density and fractures?
3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?
4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?
5. Are there subgroups of patients based on demographics, other medications, comorbidities, length of use, or initiation of use relative to onset of menopause, for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion criteria

Populations

• Study participants include women recruited from any health care setting or a populationbased sample experiencing menopause. When possible, data are considered separately for women with natural versus surgical menopause (oophorectomy) and for postmenopausal women versus women in the menopausal transition stage.
• Women in the menopausal transition stage are those transitioning through natural menopause who have had irregular menstrual periods within the last 12 months.
• Postmenopausal women are those with surgical or natural menopause and amenorrhea for more than 12 months.

Interventions

Interventions include oral and transdermal estrogen monotherapy or estrogen plus progestin/progesterone preparations listed below for all symptoms, bone density and fracture outcomes, and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens. Included products are shown in **Table 1**.

Effectiveness Outcomes

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

Safety Outcomes

• Withdrawals
• Withdrawals due to adverse effects
• Withdrawals due to specific adverse effects

For short-term use

• Atypical bleeding; endometrial hypertrophy
• Nausea and vomiting
• Breast tenderness
• Headaches
• Weight changes
• Dizziness
• Thrombosis (including relationship to estradiol levels)
• Cardiovascular events
• Rash and pruritus
• Cholecystitis
• Effects on the liver

For long-term use

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

Study Designs

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

Data Synthesis
Treatment effects were defined as the difference in outcomes between the estrogen and placebo groups, or between estrogen groups for head-to-head comparisons. For crossover trials, only results from the end of the first phase were used because of the potential for carry-over effects.

Subcommittee Considerations Regarding Estrogen Therapy Studies

- Almost all studies were rated "fair" because of high dropout rates. Otherwise, they were generally of "good" quality; well conducted and designed.
- Most head-to-head trials compared another estrogen derivative(s) to CEE.
- Quality trials that report on potential differences among special populations do not exist.

Abbreviations and Acronyms

WHI: Women's Health Initiative
HERS: Heart, Estrogen/Progestin Replacement Study
PEPI: Postmenopausal Estrogen/Progestin Interventions Trial
ET: Estrogen Therapy
CEE: Conjugated Equine Estrogen
E2: Oral Estradiol
E2V: Estradiol Valerate
EE: Esterified Estrogen
MPA: Medroxyprogesterone Acetate

Drugs:
Table 1 Included Estrogen Products

Drug	**Trade names**	**FDA-approved indications**
Oral estrogens		
17b Estradiol	Estradiol (generic) Estrace	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar or vaginal atrophy, topical vaginal products should be considered. 3. Treatment of Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen dependant carcinoma of the prostate (for palliation only). 6. Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

Estradiol acetate	Femtrace	Treatment of moderate to severe vasomotor symptoms associated with the menopause
Esterified estrogens	Menest Neo-Estrone	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Atrophic vaginitis. 3. Kraurosis Vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. 7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 8. Prostatic carcinoma-palliative therapy of advanced disease.
Estropipate	Estropipate (generic) Ogen Ortho-est	1. Signs and symptoms of naturally occurring or surgically induced estrogen deficiency states associated with menopausal and postmenopausal symptoms, e.g., hot flashes, sleep disturbances and urogenital atrophy. 2. Osteoporosis induced by estrogen deficiency states in conjunction with other pertinent measures.
Conjugated equine estrogens (CEE)	Premarin	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). 6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Synthetic conjugated estrogens	Cenestin Enjuvia C.E.S Congest PMS-Conjugated	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause: 0.45mg, 0.625mg, 0.9mg, 1.25mg 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 0.3 mg
Estrogen-progestin combinations		
CEE, medroxyprogesterone	Prempro Premplus Premphase	1. Treatment of moderate to severe symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
17b-estradiol, norgestimate	Ortho-Prefest	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

		3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17-b estradiol, norethindrone acetate	Activella	1.0 mg/0.5mg and 0.5mg/0.1mg 1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. 1.0mg/0.5mg 3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
17b-estradiol, drospirenone	Angeliq	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Ethinyl estradiol, norethindrone acetate	FemHRT	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered
Transdermal estrogens		
17b-estradiol matrix patch	Alora Climara Esclim Vivelle Vivelle-Dot Menostar Estradot Oesclim 17-b estradiol (generic)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol reservoir patch	Estraderm	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risks of osteoporosis and non-estrogen medications should be carefully considered
17b-estradiol, norethindrone acetate	Combi-Patch Estalis	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

patch	Estalis Sequi Estracomb	2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
17b-estradiol, levonorgestrel patch	Climara Pro	Treatment of moderate to severe vasomotor symptoms associated with menopause
17b-estradiol transdermal gel	EstroGel Elestrin Divigel	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate topical emulsion	Estrasorb	Estrasorb is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause.
Topical products		
17b-estradiol vaginal cream	Estrace vaginal cream	Treatment of vulvar and vaginal atrophy.
CEE cream	Premarin vaginal cream	Treatment of atrophic vaginitis and kraurosis vulvae.
Esterified estrogen cream	Neo-Estrone vaginal cream	1. Treatment of menopausal and post menopausal symptoms. 2. Should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.
17-b estradiol intravaginal ring	Femring Estring	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered
Estradiol hemihydrate vaginal tablet	Vagifem	Treatment of atrophic vaginitis

New Findings:

- Since the last update one estrogen product has been added: Ethinyl estradiol, norethindrone acetate
- When prescribing solely for the prevention of postmenopausal osteoporosis, the FDA recommends that therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
- The FDA added health warnings to its label including new data on health harms from the WHI Memory Study (WHIMS) published in 2003.[1]
- Forty-four new studies were included: 6 head-to-head trials with hot flash or other symptom outcomes, 16 placebo-controlled trials with hot flash or other symptom outcomes, 9 placebo controlled trials with bone mineral density outcomes, 4 placebo-controlled trials with data about harms, 7 reports from the Women's Health Initiative, and 2 recent systematic reviews. Dossiers were submitted by one pharmaceutical company (Wyeth, for Prempro, Premarin, and Premarin Vaginal Cream), but these dossiers did not contain any new studies not previously identified..

[1] Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *Jama.* 2003;289(20):2651-2662

Amended Summary of Results:

Key Question 1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?

Women's Health Initiative Hormone Replacement Study

The Women's Health Initiative (WHI), begun in 1993, was designed to examine major causes of morbidity and mortality in postmenopausal women. Details of hormone replacement studies from the WHI are shown in the DERP report in Evidence Tables 3 (outcomes) and 4 (quality assessment). It encompasses two large, randomized, controlled, double-blind studies of estrogen therapy in postmenopausal women. Women between the ages of 50 and 79 years were recruited from 40 clinical centers in the U.S. The WHI estrogen plus progesterone trial randomized 16,608 postmenopausal women with an intact uterus assigned to 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg medroxy progesterone acetate (MPA) (Prempro, Wyeth) or to placebo. This trial was stopped early due to an unfavorable global risk-benefit profile at 5.2 years, rather than the planned 8.5 years of duration. The WHI CEE-only trial involved 10,739 women who had had a hysterectomy. This study was also stopped early (at 6.8 years) due to a lack of overall health benefit and an increased risk of stroke similar to that seen in the estrogen-only trial.

Barnabei and colleagues[2] reported that women with an intact uterus and moderate-to severe hot flashes, night sweats, or vaginal or genital dryness at baseline who took CEE and MPA had improvements in these symptoms, as well as improvements in joint pain and stiffness ($p<0.001$ for each of these outcomes) at 1-year follow-up. Women who were younger, thinner, and closer to the menopause experienced more relief of hot flushes and night sweats. Among women asymptomatic at baseline, treatment-related beneficial effects included prevention of hot flushes ($p<0.001$), night sweats ($p=0.003$), and vaginal or genital dryness ($p<0.001$) and reduction in the incidence of new musculoskeletal symptoms ($p<0.001$).

A subgroup (8.6% of randomized population, oversampled for minorities) of women was examined at 3-year follow-up.[2] Among women who had moderate-to-severe symptoms at baseline, there were no significant differences between treatment groups for hot flashes or for various genital and musculoskeletal symptoms. Among women who were asymptomatic at baseline, vasomotor symptoms

[2] Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment related effects of estrogen and progestin in the Women's Health Initiative. *Obstetrics & Gynecology*. May 2005;105(5 Pt 1):1063-1073.

were not prevented, but these women were less likely to report vaginal or genital dryness and joint pain or stiffness than women on placebo.

The WHI was a good-quality study with high follow-up rates for most outcomes, intention-to-treat analyses, and baseline comparability of treatment groups. Adherence rates were low, however. In the CEE/MPA study, 42% of the treatment group and 38% of the placebo group stopped taking the study drug during the follow-up period. In the estrogen-only study, 54% stopped the study medication.

Data informing the question of the applicability of the study to broad U.S. population are reported by Stefanick and colleagues[3]. The hormone replacement therapy study of the WHI involved a very large and diverse cohort: over 16,000 women in the estrogen/progesterone study and over 10,000 in the estrogen-alone cohort. The ethnic distribution of participants was similar to that of the U.S. census for women aged 50 to 79 years.

There were important differences between study participants and the general U.S. population, however.[3] Family household income and percentage with a college degree were higher in the study population than among general populations. The WHI hormone therapy participants contained fewer smokers and fewer women reporting no leisure time physical activity each week. There were more obese women in the study and the average intake of dietary calcium was above average. Study participants also appeared to be at fairly low risk for coronary heart disease, including low rates of hypertension, diabetes, and elevated cholesterol requiring drug therapy.

In addition, there are important differences between the populations of the estrogen-only study (post hysterectomy) and the estrogen/medroxyprogesterone study (intact uterus).[3] The estrogen-only study subjects were at higher risk for coronary heart disease, were more obese and less active, and had a slightly higher incidence of pre-existing cardiovascular disease than the estrogen/progesterone study subjects.[3] It is not possible to determine if the differences between the two study groups is due to uterine status, and data are not available to determine if demographic and other characteristics vary between women with and without a uterus.

- **Hot Flashes/Flushes**

  - The terms ‘flashes’ and ‘flushes’ refer to descriptions of vasomotor symptoms used in estrogen trials. Although the term “flash” indicates a prodromal phase and “flush” the vasomotor dilation phase, they are combined in this report because they were reported inconsistently among the trials. It is the predominant symptom evaluated in clinical trials of symptoms. Multiple outcome measures were used in reporting.
  - Head-to-head trials: Twelve head-to-head trials variously reporting comparisons of CEE to oral E2, CEE compared to E2 acetate and micronized E2, oral E2 to E2V, conjugated synthetic estrogen compared to E2 intravaginal delivering systemic levels of E2 ring compared to oral E2, and five trials comparing transdermal E2 to oral CEE (one rated poor quality), reported improved number and/or severity of flashes/flushes. No statistically significant differences between the agents were determined.

[3] Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: Overview and baseline characteristics of participants. *Ann. Epidemiol.* 2003;13(9 SUPPL.):S78-S86.

- Two studies described an intravaginal ring delivering systemic levels of E2 ring compared to oral E2 in head-to-head studies with both preparations being equally effective. [4,5]

- Placebo comparisons:
- Among 16 new trials added for Update #3,13 were rated fair quality, 1 was fair to poor, and 2 were rated poor.
- Except for one trial of oral E2 vs. placebo, all other trials of oral E2 (11 studies), transdermal E2 (11 studies), E2V (3 studies), CEE (6 studies), estropiptate (1 study), and synthetic conjugated estrogen B (1 study)[6] reported statistically significant decreases in frequency and/or severity of hot flash symptoms.
- There is one fair quality placebo-controlled trial of a transdermal vaginal ring releasing E2 for treatment of vasomotor symptoms (N=333).[7] The efficacy analysis was not intention-to-treat; it included only women with a baseline measurement of moderate to severe vasomotor symptoms who had a vaginal ring inserted and who had at least one evaluation during the study (325/333 randomized). At 13 weeks, the percentage reduction from baseline in number of moderate to severe vasomotor symptoms per week was 79.9% in women randomized to the E2 50 mcg ring, 90.6% in those randomized to the E2 100 mcg ring, and 49.1% in those using a placebo vaginal ring ($p<0.05$ for both E2 groups compared to placebo).
- There were 8 new fair-quality studies for this update which examined symptoms. All of the new studies focused on postmenopausal women except one which examined a mix of postmenopausal women and women in the menopausal transition. This latter study did not examine these two population subgroups separately. The number of flushes and/or the severity of symptoms decreased in all fair-quality studies of oral estrogen preparations: estradiol acetate, conjugated equine estrogen, estradiol with norethisterone, oral estradiol with drospirenone, and ethinyl estradiol with norethindrone. Transdermal estradiol 50mcg/day with norethindrone acetate decreased hot flashes compared to placebo, whereas the UltraLow Transdermal estRogen Assessment trial (ULTRA) (n=417) did not demonstrate an improvement in postmenopausal symptoms among older, asymptomatic women compared with placebo at 2-year follow-up
- Meta-analyses of E2 and of CEE versus placebo studies showed similar reduction of hot flashes/flushes. Including trials with E2 plus progestins/progesterone did not alter the result. Multiple trials, including three of E2V versus placebo, did not meet criteria for inclusion in the meta-analysis because they did not provide data on frequency of hot flashes were presented in graph form or did not report standard deviations.

[4] Al-Azzawi F. Buckler HM. Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. Climacteric 2003;6(2):118-127.
[5] Buckler H, Al-Azzawi F, UK Vaginal Ring Multicentre Trial Group. The effect of a novel vaginal ring delivering estradiol acetate on climacteric symptoms in postmenopausal women. BJOG: An International Journal of Obstetrics & Gynecology. 2003;110(8):753-759.
[6] Utian WH, Lederman SA, Williams BM, et al. Relief of hot flushes with new plant-derived 10-component synthetic conjugated estrogens. Obstet & Gynecol. 2004;103(2):245-253.
[7] Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. *Obstetrics & Gynecology.* 2003;102:823-834.

- A Cochrane meta-analysis of trials of oral estrogens published before 2000 was compared with the more current Oregon EPC's meta-analysis of trials of oral and transdermal forms. Results of the two reports were consistent. The Cochrane review also reported reduction of hot flashes by treatment with estrogens both with and without progestins/progesterone. Interpreting results of this meta-analysis, it is possible to conclude that symptom severity may be better decreased by estrogens with progestins/progesterone. Differences between clinical trials included in the meta-analysis could also explain this finding.

Consensus

- *The Pharmaceutical subcommittee agrees by consensus that estrogen preparations improve symptoms of hot flashes/flushes.*
- *Head-to-head clinical trials and placebo-controlled trials do not identify a clinically significant difference in estrogen preparations for the treatment of hot flashes/flushes except for the Ultra low dose transdermal estrogen study which appears to be less effective.*

- **Sleep Disturbances/Night Sweats**

- In three trials of transdermal E2 and one trial of oral CEE with progestins, participants reported reduction in sleep disturbance and alleviation of vasomotor symptoms at night, compared to placebo. Multiple sleep outcome measures made comparisons difficult. No studies of other eligible estrogens were identified. No head-to-head comparisons of estrogen products for sleep disturbances/night sweats were identified.
- The WHI reported night sweats, as noted at the beginning of the KQ1 section above. For Update #3, four new studies were identified. A small, fair-quality trial of postmenopausal women taking oral conjugated equine estrogens did not find significant improvement in sleep symptoms and a study of transdermal estradiol found an improvement in sleep at 12 weeks (p=0.046).[8] Two other studies were of poor quality.

Consensus

The Pharmaceutical subcommittee agrees by consensus that estrogen preparations reduce sleep disturbances, primarily nighttime vasomotor symptoms. Evidence is insufficient to distinguish between estrogen preparations. Women with more symptoms tended to have more of a response.

- **Mood Changes**

[8] Levine DW, Dailey ME, Rockhill B, Tipping D, Naughton MJ, Shumaker SA. Validation of the Women's Health Initiative Insomnia Rating Scale in a multicenter controlled clinical trial. *Psychosom. Med.* 2005;67(1):98-104.

- Trials of E2 compared to E2V (1 study), and oral E2 (1), transdermal E2 (3) and CEE (5) compared to placebo met entry criteria. Whether or not there was symptom improvement was mixed, with some, but not all, identifying improvement in mood with estrogen treatment. Baseline characteristics and measurement instruments in the different studies were not consistent or directly comparable. In the HERS study, whether or not there was mood improvement with treatment was influenced by whether there were vasomotor symptoms at baseline. Studies of 'well-adjusted women' on CEE versus placebo showed symptom improvement with CEE on some scales but not on others. The PEPI trial has shown no difference between treatment with CEE and treatment with placebo for anxiety and affective symptoms.

Consensus
The Pharmaceutical subcommittee agrees by consensus that different entry and measurement criteria make trial comparisons difficult. Those with estrogen alone largely showed some effect. Trials of estrogen with progestins/progesterone are not interpretable due to the potential mood effects of progestins/progesterone. Information from current trials is insufficient to draw firm conclusions about estrogen treatment of mood changes and no comparisons between estrogens can be made.

- **Urogenital Symptoms/Sexual Function**
  - A head-to-head trial comparing oral CEE with transdermal E2, and three trials comparing E2 released from a vaginal ring or tablet with CEE vaginal cream all showed no differences in clinical efficacy. Both self-reported and objective measures of improvement were identified with all of the preparations. Participants preferred using the E2 vaginal ring and tablet over CEE vaginal creams.
  - Trials of transdermal E2 and oral CEE versus placebo for treatment of sexual function were inconclusive. Measurement instruments were not comparable and participant improvement was variable or was not described.
  - The WHI reported on genital symptoms, as noted above at the beginning of the section on Key Question 1.
  - For this Update, the ULTRA study found no differences between treatment with low-dose transdermal estradiol on vaginal dryness or on urinary incontinence.
  - There was a reduction in investigator-assessed vaginal atrophy, dryness, and friability for estradiol acetate compared with placebo ($p<0.05$) in a large, fair-quality study[9]

[9] Speroff L, Haney AF, Gilbert RD, Ellman H, Estradiol Acetate Investigator G. Efficacy of a new, oral estradiol acetate formulation for relief of menopause symptoms. *Menopause (New York, N.Y.).* 2006;13(3):442-450.

- A Cochrane systematic review compared efficacy and safety of intra-vaginal estrogen preparations (creams, pessaries, tablets, and estradiol-releasing ring) for the relief of symptoms of vaginal atrophy (vaginal dryness, itching, discomfort, and painful sexual intercourse).[10] Overall, the author concluded that the preparations appear to be equally effective for the symptoms of vaginal atrophy. For the comparison of the estradiol ring to CEE vaginal cream, there was no difference between groups in patient assessment of vaginal dryness or withdrawals due to adverse events, but there was more improvement in pruritus with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets, but there was no difference between groups in genital pruritus or withdrawals due to adverse events. Symptom improvement was similar for tablet versus cream. There was no difference among all treatment comparisons for dysuria, nocturia, urgency, urge incontinence, participant symptom improvement in dryness, soreness, and irritation, loss of libido, and vaginitis.

Consensus

- The Pharmaceutical subcommittee agrees by consensus that some women experience reduced symptoms of urogenital atrophy with estrogen use.
- Adequate trials evaluating sexual function do not exist for any eligible estrogen product and measures of sexual dysfunction are inadequate.
- For the comparison of the estradiol ring to CEE vaginal cream there was more improvement in pruritus with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets
- There is inadequate evidence to identify a difference in estrogen preparations for treatment of other urogenital symptoms/sexual function. ??

- **Quality of life**
  - A head-to-head study of CEE versus transdermal E2 showed improvement in quality of life measures with no differences between agents.
  - Studies of oral E2 (2), transdermal E2 (4), and esterified estrogen (1) versus placebo indicated improvement on dissimilar measures of quality of life. Women with 'high well-being' and no vasomotor symptoms showed no improvement versus placebo, as did women in the HERS study that were older and otherwise had complicating health issues. One poor comparison trial was identified.
  - Oral E2 was superior to placebo in Greene and Beck scores for 7 of 8 trials.
  - HRQL was also examined in the WHI estrogen-only study (n=10,739). At 1-year follow-up, there was a small positive effect of CEE on sleep disturbance (0.4 on a 20-point scale, $p<0.001$) and a negative effect on social functioning (1.3 on a 100-

[10] Suckling, Lethaby, Kennedy. Local oestrogen for vaginal atrophy in postmenopausal women [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2007;1:1.

point scale, p=0.003). At 1- year follow-up of women who had moderate-to-severe vasomotor symptoms at baseline, 72.4% of the CEE group no longer reported these symptoms, compared to 55.6% of the placebo group (p<0.001). In a subsample (n=1,189) examined at 3-year follow-up there were no significant differences in any HRQL measure between treatment groups.

- For this update none of the three new studies reporting HRQL or related outcomes showed significant effects between the treatment and placebo groups.

Consensus
The Pharmaceutical subcommittee agrees by consensus that it is unclear how consistently estrogen therapy improves quality of life. Measures to capture it are inadequate. There is no evidence to identify a difference in estrogen preparations to improve quality of life.

KQ 1 Consensus:

The Pharmaceutical Subcommittee agrees by consensus that:

- *Estrogen preparations were found to reduce hot flashes/flushes, sleep disturbances/night sweats, mood changes, and urogenital atrophy symptoms.*
- *For the comparison of the estradiol ring to CEE vaginal cream there was more improvement in pruritis with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets.*
- *Studies measuring sexual dysfunction and quality of life and other urogenital symptoms were inadequate to determine any clinical relevance*

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

- **Bone Density**
  - Four head-to-head trials compared different estrogen preparations. Results were comparable for all estrogen preparations studied: CEE vs. transdermal E2 of transdermal E2 vs. E2V. All showed an increase or no change in bone density over the duration of the trials.
  - One trial comparing oral CEE (0.625 mg/day) with transdermal E2 (0.05 mg twice weekly) further evaluated the addition of alendronate to each form of estrogen treatment.[11] Although the addition of alendronate to either form of hormone therapy increased BMD significantly more than

[11] Davas I, Altintas A. Yoldemir T, et al. Effect of daily hormone therapy and alendronate use on bone mineral density in postmenopausal women. Feril Steril. 2003;80(3):536-540.

did hormone therapy alone, the increases did not differ significantly between the CEE and E2 groups.

- Sixty-four trials (nine new studies) meeting criteria compared an estrogen preparation to placebo. Estrogens studied included oral E2 (16 studies), transdermal E2 (15), oral E2V (5), CEE (26), esterified estrogen (1), and one trial of conjugated synthetic estrogen plus medroxyprogesterone. In one small (N=135) trial CEE increased bone density over 3 years at the femoral neck, total femur, and trochanter, but not at the lumbar spine. The addition of calcium and vitamin D to the treatment and placebo regimens became standard after 1995. All estrogen preparations studied increased bone density or slowed its loss compared to placebo. Differences in estrogens versus placebo were statistically significant. Higher doses of estrogen were more effective than lower doses, although a minimally effective dose of estrogen to prevent bone density loss remains yet to be established.
- A good-quality trial comparing combination treatment with CEE (with or without medroxyprogesterone) plus alendronate to either treatment alone, patients on combination therapy had a significantly greater increase in total hip BMD than those on either ALN or HRT alone after 3 years ($p<.01$)[12]
- A more recent substudy of the Women's HOPE trial found that most women on lower doses of CE with or without Medroxyprogesterone had less continued bone loss over 2 years than women randomized to placebo.[13]
- A Cochrane review and meta-analysis was published in August 2002. Fifteen trials of estrogens not meeting Oregon's inclusion criteria were included in this review rendering the two reports not directly comparable. Overall, however, results were consistent.
    - Trials included in the Cochrane review studied women with and without established osteoporosis.
    - Women received estrogen preparations with and without progestins/progesterone and were compared to women given placebo.
    - All estrogen groups had statistically significant improvements in bone density compared to placebo groups.
    - Estrogen improved bone density for both women with established osteoporosis as well as those without osteoporosis. There was no difference between groups treated with an estrogen alone and groups treated with an estrogen with progestins/progesterone.
    - A dose-response relationship was determined, with higher doses showing greater improvement.

[12] Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. *Jama.* 2003;289(19):2525-2533

[13] Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos. Int.* Apr 2005;16(4):372-379.

- A more recent meta-analysis published in 2003, [14] found that different estrogen preparations, including CEE, oral and transdermal E2, E2V and EE were equally effective in the maintenance or gain of BMD at the lumbar spine and hip. The two year mean changes in lumbar spine BMD are summarized as follows:
  - 7.6% (range 1.5% -13.4%) for CEE
  - 7.2% (range 1.5% - 20.0%) for oral E2, E2V, EE and estrone sulfate
  - 7.5% (range 3.4% - 14.4%) for non-oral estrogens
- Effect on bone density from discontinuation of estrogen was reported in two new independent studies and a follow-up study that concluded:
  - The rate of bone loss after stopping estrogen was similar to that of women who did not receive estrogen treatment.
  - After an average of 4 years (from the PEPI trial) there was no evidence of accelerated bone loss.

Consensus
The Pharmaceutical subcommittee agrees by consensus that:
All estrogen preparations studied improve bone density compared to placebo.
A limited number of head-to-head trials do not identify any differences between estrogen preparations.
Decreasing doses of CE with or without MPA resulted in decreasing preservation of bone density however it is unclear if lower doses of estrogen will sufficiently preserve bone density in a manner to affect outcomes.

- **Fractures**
  - No head-to-head trials comparing estrogen preparations were identified; eleven studies included fracture outcome data comparing estrogens and placebo. A single study of E2V showed a statistically significant decrease in non-vertebral fractures.
  - The Women's Health Initiative (WHI), the largest randomized controlled trial of estrogen treatment, published results from the treatment arm receiving CEE plus MPA compared to placebo. After five years of follow-up, WHI showed a statistically significant reduction in total fractures compared to placebo, but no statistically significant reduction in site-specific fractures.
  - The WHI study of CEE use in women post hysterectomy also reported a decrease in total fracture rates at mean follow-up interval of 6.8 years (HR 0.70, 95% CI, 0.63-0.79, 95% CI adjusted for multiple comparisons 0.59-0.83) ($p<0.001$). Hip

[14] Doren M, Nilsson JA, Hohnell O. effects of specific post-menopausal hormone therapies on bone mineral density in post-menopausal women: A meta-analysis. Hum Reprod. 2003;18(8):1737-1746.

fractures and clinical vertebral fractures were also decreased, although 95% confidence intervals adjusted for multiple comparisons overlapped a HR of 1.0 [hip fractures HR: 0.61 (adjusted 95% CI, 0.33 – 1.11); vertebral fractures HR 0.62 (adjusted 95% CI, 0.34-1.13)]. Additional data on fractures recorded through the study termination (average 7.1 years of follow-up)173 also showed a reduction in incident fractures at the hip, spine, and wrist. These positive effects occurred largely irrespective of baseline risk factors for osteoporosis or fracture. The global index of overall health risks and benefits was balanced, however, with no evidence of overall benefit or risk noted even for women in the highest tertile of risk for fracture.

- The above-mentioned August 2002 Cochrane review and meta-analysis of seven studies reporting fracture outcomes found no statistically significant reduction in vertebral and non-vertebral fractures compared to placebo. WHI data were not included in the Cochrane review.
- No randomized clinical trials about fracture prevention or treatment for greater than five years duration were identified.

Consensus
The Pharmaceutical subcommittee agrees by consensus that:

- ***The WHI indicates that combined estrogen therapy improves overall and hip and vertebral and wrist fracture outcomes in post-menopausal women.***
- ***Most studies other than the WHI are too small and underpowered to draw any firm conclusions about other site-specific fractures.***
- ***No comparisons between estrogen products could be made with available evidence.***

Key Question 2 Consensus:

The Pharmaceutical subcommittee agrees by consensus that:

- *No significant differences between types of estrogens could be determined.*
- *No significant differences between estrogen preparations could be determined*
- *All estrogen preparations improve bone density; some studies demonstrate a dose-response effect.*
- *Use of estrogen replacement therapy reduces fractures*

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

A. For short-term use (<5 years)?

- Most trials evaluating symptoms and osteoporosis outcomes were small.

- Reports of adverse effects in trials of symptoms and of osteoporosis were unevenly described with inadequate numbers in any group to combine in summary statistics.
- Estrogen treatment was associated with venous thromboembolic and coronary heart disease events early in both the WHI and the HERS studies.
- Various reports showed no difference in the rate of headache[15] and dizziness or disorientation[16,15] and weight gain[16] was reported at similar rates between estrogen users and the placebo group.
- Greenspan and colleagues[16] reported that the incidence of venous thromboembolic disease, endometrial and colon cancer, hospitalizations, myocardial infarction, and clinical fractures was similar between subjects receiving conjugated equine estrogen with medroxyprogesterone and placebo.
- Speroff and colleagues[17]38 reported that rates of headache, breast tenderness, vaginal bleeding, and palpitations were evenly distributed between treatment with ethinyl estradiol/norethindrone acetate and placebo (n=266).
- A Cochrane systematic review[10] concluded that CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation). In the comparison of estradiol ring vs. CEE vaginal cream and estradiol ring vs. estradiol tablet there was no difference in withdrawals due to adverse effects.
- The highest numbers of withdrawals from estrogen-treated groups were related to breast tenderness and uterine bleeding. Withdrawals for many other reasons were common in both treatment and placebo groups, potentially compromising trial data and conclusions. It is unclear how use of progestins/progesterone contributed to withdrawals in those studies where it was included.
- Women using higher doses of estrogen had increased symptoms compared to placebo regardless of which estrogen preparation was being evaluated.
- Transdermal estrogen use is associated with local skin reactions.
- Though multiple adverse outcomes in the short-term use of estrogen treatment have been reported, study data available are inadequate to effectively compare different estrogen preparations either with or without progestins/progesterone. Many symptoms reported in both treatment and placebo groups may be due to symptoms related to menopause itself.
- For this update six new trials were identified which examined the effects of hormone therapy on cognitive function with follow-up between 12 weeks and 3 years, demonstrating no differences between groups at up to 2-year followup
- The WHI study did show an increase in "probable dementia" at 4 years in the CEE+MPA group. There was NSD in the CEE alone group at up to 6.8 years follow up. The

[15] Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial.[summary for patients in Ann Intern Med. 2006 Dec 19;145(12):I25; PMID: 17179054]. *Ann. Intern. Med.* Dec 19 2006;145(12):869-879.

[16] Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am. J. Med.* Nov 2005;118(11):1232-1239

[17] Speroff L, Symons J, Kempfert N, Rowan J, femhrt Study I. The effect of varying lowdose combinations of norethindrone acetate and ethinyl estradiol (femhrt) on the frequency and intensity of vasomotor symptoms. *Menopause.* 2000;7(6):383-390.

incidence of probable dementia among participants with an intact uterus taking CEE and MPA for mean duration 4 years (n=4532) was increased (HR 2.05, 95% CI, 1.21 – 3.48). Risk increased with age and with lower Mini Mental State exam scores at baseline

KQ 3 Consensus

The Pharmaceutical Subcommittee agrees by consensus that:

- ***Estrogen treatment was associated with venous thromboembolic and coronary heart disease events early in both the WHI and the HERS studies however Greenspan and colleagues[16] reported that the incidence of venous thromboembolic disease, endometrial and colon cancer, hospitalizations, myocardial infarction, and clinical fractures was similar between subjects receiving conjugated equine estrogen with medroxyprogesterone and placebo.***
- ***Various reports showed no difference in the rate of headache[1] and dizziness or disorientation[1,15] and weight gain[16] was reported at similar rates between estrogen users and the placebo group***
- ***Evidence suggests that nuisance side effects can be associated with hormone therapy however there is no evidence of comparative difference between preparations..***
- ***CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation***).
- ***Risk of probable dementia increased with age and with lower Mini Mental State exam scores at baseline with CEE+MPA***

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

- No head-to-head studies are available that compare adverse effects after five or more years of estrogen use. WHI and HERS studies provide the best evidence of long-term adverse effects for post-menopausal estrogen use, and both use continuous regimens of CEE/MPA compared with placebo.
- Coronary Heart Disease & Stroke
  - WHI identified a statistically significant increase in coronary heart disease among CEE + MPA users without known existing heart disease.
  - Among women in the WHI using CEE alone (post hysterectomy),[18] no significant effect on CHD rates was observed compared with placebo at a mean follow-up of

[18] Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* Apr 14 2004;291(14):1701-1712.

6.8 years (5 fewer events per 10,000 person-years with CEE, HR 0.91, 95% CI, 0.75 – 1.12).
    - There was no statistically significant elevation of stroke risk in HERS.
    - In the CEE-only WHI study[18] the risk for stroke was increased by 39% in the CEE group (p=0.007; HR 1.39, 95% CI, 1.10 - 1.77). A greater risk of stroke was estimated among study participants who complied with study medications, taking more than 80% of study drugs, compared to the intention-to-treat population.
- Venous Thrombosis/Thromboembolism
    - Increased risk of venous thrombosis has been observed in WHI, HERS, and a meta-analysis of other studies. However, during follow-up to a mean of 6.8 years in HERS II, this elevated risk decreased (p-value for time trend =0.08). The overall risk for all 6.8 years was 1.08 (95% CI, 1.28 – 3.4)
    - Risk of venous thromboembolism was elevated with long-term use of CEE/MPA in the WHI (HR 2.11, 95% CI, 1.26 -3.55). In the CEE-only WHI trial,[18] active treatment increased venous thromboembolic disease (p = 0.03, HR 1.47, 95% CI, 1.04 – 2.08; adjusted 95% CI, 0.87 – 2.47).
- Cholecystitis
    - Evidence indicates an increased incidence of cholecystitis and risk may increase with duration of estrogen use.

- Breast Cancer
    - There are conflicting reports from WHI and HERS in patients taking CEE/MPA. The WHI of CEE/MPA reported increased risks for invasive breast cancer at 5.2 years of follow-up (HR 1.26; 95% CI, 1.00 - 1.59). Meta-analyses of other studies indicate increased risk. This was not seen in HERS/HERSII which indicated no increased risk at 6.8 years after 6.8 years (RR=1.27; 95% CI: 0.84, 1.94). Mortality is not increased. No comparisons between estrogen preparations are available. In the WHI study of CEE alone, the incidence of invasive breast cancer, the primary safety outcome for this trial, was decreased[18] over a mean follow-up duration of 6.8 years (HR 0.77, 95% CI, 0.59 – 1.01; 26 versus 33 cases per 10,000 person-years, p=0.06). This differential effect became apparent beginning in year 2.
    - A large cohort study of French women comparing users and non-users of estrogen over 8.9 years showed that the relative risk of breast cancer was 0.98 (95% CI 0.73-1.75) compared to non-users.

- Ovarian Cancer/Endometrial Cancer
    - No conclusive evidence indicates an increase in ovarian cancer with estrogen therapy. There is increased risk of endometrial cancer in women who have not had an hysterectomy and are using an estrogen product without progestins/progesterone.

- Cognition and Dementia

- The WHI Memory Study (WHIMS), an ancillary study to the WHI study, examined the effect of postmenopausal CEE with and without MPA on dementia and cognitive impairment in healthy women 65 years of age and older. The incidence of probable dementia among participants with an intact uterus taking CEE and MPA is discussed in Key Question 3 as it occurs before 5 years of treatment. Mild cognitive impairment was not significantly increased (HR 1.07, 95% CI, 0.74 – 1.55). Global cognitive function increased in both treatment and placebo groups for year 1 through 4 (likely due to a practice effect repeated testing) and then decreased in both groups with no significant differences between groups at year 5 and 6. In the CEE-only study of the WHI, the incidence of probable dementia was not significantly increased at mean follow-up of 5.2 years (HR 1.49, 95% CI, 0.83 – 2.66) and was not significantly different from rates with CEE/MPA. Rates of mild cognitive impairment were also not significantly increased.

Systematic Review:

A recent Cochrane systematic review assessed the effect of long-term hormone therapy on mortality, heart disease, venous thromboembolism, stroke, transient ischemic attacks, breast cancer, colorectal cancer, ovarian cancer, endometrial cancer, gallbladder disease, cognitive function, dementia, fractures, and quality of life.[19] Searches were conducted through November 2004. Fifteen randomized controlled trials were included, but the WHI and HERS, the largest trials, contributed most of the data. This review concluded that combined continuous hormone therapy significantly increased the risk of both venous thromboembolism and coronary events after one year, stroke after 3 years, breast cancer after 5 years, and gallbladder disease. In women over age 65, the incidence of dementia was also increased. In younger women (age 50 to 59 years) taking either combined regimens or estrogen-only hormone therapy, there was an increased risk of venous thromboembolism, but the absolute risk was low.

Key Question 4 Consensus:

The Pharmaceutical subcommittee agrees by consensus that:

- ***Evidence suggests that serious and nuisance side effects can be associated with hormone therapy.***
- ***There are no comparison studies between estrogen products.***
- ***There are conflicting results for Breast cancer rates and CHD events.***
- ***There is an increased rate of probable dementia in CEE/MPA treated patients vs. patients treated with CEE alone.***

[19] Farquhar, CM, Marjoribanks, et al. Long term hormone therapy for perimenopausal and postmenopausal women [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2007;1:1.

Key Question 5. Are there subgroups of patients based on demographics, other medications, comorbidities, length of use, or initiation of use relative to onset of menopause, for which one medication or preparation is more effective or associated with fewer adverse effects?

- Age Groups
  - Studies such as HERS and WHI and some osteoporosis and fracture trials enrolled older women (mean age mid-sixties). HERS/HERS II did not report results by age. In WHI there was no evidence that the effect of CEE in reducing fracture risk differed by age or time since menopause. For this update several studies examined older women and results were found to be similar to studies in younger women.
- Racial and Ethnic Groups
  - Most studies have been done in Caucasian women in North America and Western Europe. The WHI reported a sub analysis by race. Among black women (N=1124), CEE plus medroxyprogesterone acetate reduced the risk of total fractures by 42%; however, this was not statistically significant because of the small number of fractures in this subgroup.

- Co-Morbidities

No trials separately consider smokers, women at high-risk for ovarian and/or breast cancer, or other risk factors and co-morbidities. HERS enrolled only women with previous coronary artery disease (CAD); however, they are not compared with women without CAD, making it difficult to know how risks/benefits vary. As previously noted, both women with and without established osteoporosis demonstrated bone density benefits with estrogen use, though no comparisons between different estrogen preparations can be made. In the WHIMS study the increased incidence of probable dementia among participants taking CEE (+/-_ MPA) was positively related to increasing age and lower Mini Mental State exam scores at baseline.

- Early oophorectomy (<45 years) or premature menopause (<35 years)
  - No trials compare estrogen treatment for women with early oophorectomy or premature menopause with women undergoing menopause at an older age.

Key Question 5 Consensus:

The Pharmaceutical subcommittee agrees by consensus that:

- ***There is insufficient evidence to identify subgroups of patients for which one medication or preparation is more effective.***
- ***An increased incidence of probable dementia among participants taking CEE (+/-_ MPA) was positively related to increasing age and lower Mini Mental State exam scores at baseline.***

Conclusion:

It is the conclusion of the Pharmaceutical subcommittee that:

1. *Estrogens reduce some menopausal symptoms and have been shown to improve bone density and reduce fracture risk.*
2. *Decreasing doses of CE with or without MPA resulted in decreasing preservation of bone density however it is unclear if lower doses of estrogen will sufficiently preserve bone density in a manner to affect outcomes.*
3. *The majority of studies are of estradiol and conjugated equine estrogen. For many estrogen preparations, clinical trials are few and evidence is insufficient to conclude they are equal to estrogens that have been studied more extensively.*
4. *Evidence suggests that serious and nuisance side effects can be associated with hormone therapy.*
5. *For the comparison of the estradiol ring to CEE vaginal cream there was more improvement in pruritus with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets*
6. *CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation).*
7. *There are conflicting results for Breast cancer rates and CHD events.*
8. *At the present time there is no comparative evidence to evaluate estrogen use in subgroup populations of race or ethnicity.*
9. *An increased incidence of probable dementia among participants taking CEE (+/-_ MPA) starting after 4 years, was positively related to increasing age and lower Mini Mental State exam scores at baseline.*
10. *The subcommittee feels that additional properly controlled comparative evidence is needed to better address these questions in the future.*

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the

commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.