Drug Class Review

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

Preliminary Scan Report #7

September 2016

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

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OBJECTIVE

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

Date of Last Update Report

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

Date of Last Preliminary Update Scan Report

Scan #6: September 2015

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

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

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

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

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

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

Inclusion Criteria

Populations

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

Interventions

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

Table 1. Included estrogen products

Drug	Trade names
Oral estrogens	
17b Estradiol	Estradiol (generic)
Estradiol acetate	Femtrace
Esterified estrogens	Menest Neo-Estrone
Estropipate	Estropipate (generic) Ogen .625, 1.25, 2.5, 5
Conjugated equine estrogens (CEE)	Premarin
Synthetic conjugated estrogens	C.E.S Congest Enjuvia PMS-Conjugated
Estrogen-progestin combinations	
CEE, medroxyprogesterone	Premphase 14/14 Premplus Prempro Prempro/Premphase
17b-estradiol, norgestimate	Ortho-Prefest
17-b estradiol, norethindrone acetate	Activella
17b-estradiol, drospirenone	Angeliq
Ethinyl estradiol, norethindrone acetate	FemHRT
Transdermal estrogens	
17b-estradiol matrix patch	17-b estradiol (generic) Alora

Drug	Trade names
	Climara Estradot Menostar Minivelle Oesclim Vivelle Vivelle-Dot
17b-estradiol reservoir patch	Estraderm
17b-estradiol, norethindrone acetate patch	Combi-Patch Estalis Estalis Sequi Estracomb
17b-estradiol, levonorgestrel patch	Climara Pro
17b-estradiol transdermal gel	Divigel Elestrin EstroGel
Estradiol hemihydrate topical emulsion	Estrasorb
Topical products	
17b-estradiol vaginal cream	Estrace vaginal cream
CEE cream	Premarin vaginal cream
Esterified estrogen cream	Neo-Estrone vaginal cream
Synthetic conjugated estrogens A, vaginal cream	Synthetic conjugated estrogens A (generic)
17-b estradiol intravaginal ring	Estring Femring
Estradiol hemihydrate vaginal tablet	Vagifem
Estradiol transdermal spray	EvaMist
Other combination products	
Conjugated estrogens/bazedoxifene	Duavee

Note: norethindrone is also known as norethisterone.

Effectiveness Outcomes

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

Harms Outcomes

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

For short-term use

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

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

For long-term use

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

Study Designs

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

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from July 2015 through August 2016 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
No new drugs or formulations found.

Identified in previous Preliminary Update Scans
New Drugs
Conjugated estrogens/bazedoxifene (Duavee®): FDA approved on 10/3/2013 for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis.

Synthetic conjugated estrogens A, vaginal cream: Approved for the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia (11/28/2008).

Estradiol transdermal spray (EvaMist®): Approved for the treatment of moderate to severe vasomotor symptoms due to menopause (7/27/2007).

New Formulations
Estradiol extended-release transdermal patch (Minivelle®): FDA approved on 10/29/2012 for the treatment of moderate to severe vasomotor symptoms due to menopause and the prevention of postmenopausal osteoporosis.

Estradiol 0.1% transdermal gel (Divigel®): Approved for the treatment of moderate to severe vasomotor symptoms due to menopause (6/4/2007).

New Populations

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
None.

New Serious Harms (e.g. Boxed Warnings)

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans

Estradiol vaginal ring (Estring): Updated the Boxed Warning to include a revised general heading and two specific subheadings: Estrogen-Alone Therapy and Estrogen Plus Progestin Therapy; updated the text in the Boxed Warning to reflect the current recommended estrogen-class labeling (August 2014). (See Appendix A).

Estradiol topical emulsion (Estrasorb): Boxed Warning updated to include warning of endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (March 2015). (See Appendix A).

Synthetic conjugated estrogens, B (Enjuvia): Boxed Warning updated to include warning of endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (March 2015). (See Appendix A).

Premarin (oral, topical, injectable), Prempro, Premphase (oral): Updated to include warning of endometrial cancer, cardiovascular disorders, breast cancer and probable dementia (October 2011, February 2012, April 2012). (See Appendix A).

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

We identified 1 potentially relevant comparative effectiveness review that covers the entire scope of this scan (see Appendix B for abstract):

1. Grant MD, Marbella A, Wang AT, Pines E, Hoag J, Bonnell C, Ziegler KM, Aronson N. Menopausal Symptoms: Comparative Effectiveness of Therapies. Comparative Effectiveness Review No. 147. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 15-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

We have identified 5 reviews that could answer pieces of an update report (see Appendix B for abstracts):

1. Hayes, Inc. Bioidentical hormone replacement therapy for menopausal symptoms. 2013. http://www.hayesinc.com/hayes/htareports/directory/bioidentical-hormone-replacement-therapy-for-menopausal-symptoms/

2. Lai K, Cui J, Ni S, Zhang Y, He J, Yao K. The effects of postmenopausal hormone use on cataract: a meta-analysis. *PLoS ONE.* 2013;8(10):e78647. http://www.ncbi.nlm.nih.gov/pubmed?term=24205286

3. Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;6:CD008613. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008613.pub2/abstract

4. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. *Menopause.* Oct 2013;20(10):1098-1105. http://www.ncbi.nlm.nih.gov/pubmed?term=23799357

5. Yang D, Li J, Yuan Z, Liu X. Effect of hormone replacement therapy on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS ONE.* 2013;8(5):e62329. http://www.ncbi.nlm.nih.gov/pubmed?term=23667467

Randomized Controlled Trials

Trials identified since the most recent Full Report

The Medline search for this scan resulted in 96 citations. Of those, 3 were potentially relevant publications of new trials, including 1 head-to-head trial, 1 placebo-controlled trial, and 1 publication of 2 placebo-controlled trials. The head-to-head trial compared the combination of estradiol/norethisterone with the combination of estradiol/drospirenone (also compared with placebo) with a focus on weight change. The first placebo-controlled trial studied the effect of conjugated equine estrogen with medroxyprogesterone on endometrial cancer in the Women's Health Initiative randomized trial. The second placebo-controlled trial publication documented 2 trials: 1 studying the combination of conjugated equine estrogens and medroxyprogesterone in comparison to placebo on breast cancer and the other trial studying the effect of conjugated equine estrogens alone in comparison to placebo on breast cancer. Both were randomized placebo-controlled trials of the Women's Health Initiative.

In addition to trials identified in previous scans, there are now 48 potentially relevant new trials for this drug class, including 10 primary head-to-head trials and 38 placebo-controlled trials. Table 2 summarizes the study characteristics of the potentially relevant new head-to-head trials (see Appendix C for abstracts). The number of placebo-controlled trials is tabulated for each drug or drug combination of study. Abstracts of placebo-controlled trials are available upon request.

Table 2. Potentially relevant head-to-head trials of hormone therapy* (N=10)

Author, Year	Comparison(s)	N Duration	Focus
Cieraad, 2006	**17-beta estradiol/dydrogesterone** vs. conjugated equine estrogen/norgestrel	169 6 months	Lipids, vasomotor symptoms, bleeding, tolerability
De Franciscis, 2007	**17-beta estradiol/dydrogesterone** vs. dydrogesterone	120 4 weeks	Vasomotor symptoms, bleeding
Pinkerton, 2014	**Bazedoxifene** 20 mg**/conjugated estrogens** 0.45 mg* vs. bazedoxifene 20 mg/conjugated estrogens 0.625 mg* vs. bazedoxifene 20 mg, conjugated estrogens 0.45 mg/medroxyprogesterone acetate 1.5 mg* vs. placebo	459 1 year	Sleep parameters and menopause-specific health-related quality of life
Mizunuma, 2010	**Oral estradiol** 0.5 mg or 1.0 mg, with or	152	Bone mineral density

Table 2. Potentially relevant head-to-head trials of hormone therapy* (N=10)

Author, Year	Comparison(s)	N Duration	Focus
	without levonorgestrel 40 mcg vs. placebo	52 weeks	
Paoletti, 2015	**Oral estradiol** 1 mg + **norethisterone** 0.5 mg vs. **oral estradiol** 1 mg + **drospirenone** 2 mg (also vs. placebo)	100 12 months	Weight change
Long, 2006	**Conjugated equine estrogen** (oral vs. vaginal)	57 3 months	Sexual function
Prior, 2007	**Conjugated equine estrogen** vs. medroxyprogesterone	41 12 months	Vasomotor symptoms
Hassa, 2010	**Conjugated equine estrogen** 0.625 mg vs. transdermal 17 beta-estradiol patch 3.9 mg every other week vs. placebo	NR 6 months	Vasomotor symptoms
Cameron, 2006	**Continuous transdermal estradiol/levonorgestrel** vs. interrupted estradiol patch x 4 days followed by estradiol/levonorgestrel patch	59 6 months	Incidence of amenorrhea and relief of vasomotor symptoms
Samsioe, 2007	**Transdermal estradiol/norethisterone** vs. oral estradiol/norethisterone	677 1 year	Harms (safety), tolerability

Note: shading indicates new trials identified in the present scan.
*Indicates combination product

Potentially relevant placebo-controlled trials of hormone therapy (N=38)

Oral estrogens

- 17b-estradiol (N=3)
- Conjugated equine estrogens (N=4; 1 this scan)
- Synthetic conjugated estrogens (N=1)

Estrogen-progestin combinations

- Estrogen, progestin (N=2)
- Estrogen, progesterone (N=1)
- Conjugated equine estrogen, medroxyprogesterone (N=5; 2 this scan)
- 17b-estradiol, drospirenone (N=3)
- 17b-estradiol, dydrogesterone (N=1)
- 17b-estradiol, norethisterone (N=3)
- Estradiol valerate, dienogest (N=1)
- Ethinyl estradiol, norethindrone acetate (N=1)

Transdermal estrogens

- 17b-estradiol patch (N=1)
- Transdermal estradiol (N=2)
- 17b-estradiol, levonorgestrel patch (N=1)
- 17b-estradiol transdermal gel (N=2)
- Estradiol topical emulsion (N=1)

Topical products

- Vaginal estradiol (N=1)
- Conjugated estrogens vaginal cream (N=2)

- Estradiol transdermal spray (N=1)

Other combinations or therapies

- Oral conjugated estrogens + conjugated estrogens vaginal cream (N=1)
- Continuous combined HRT (N=1)

Note: shading indicates new trials identified in the present scan.

SUMMARY

Since the last update report, we have identified 3 new drugs (estradiol transdermal spray [EvaMist®], synthetic conjugated estrogens A, vaginal cream, and conjugated estrogens/bazedoxifene [Duavee®]), and 2 new formulations (estradiol 0.1% transdermal gel [Divigel®], and estradiol extended-release transdermal patch [Minivelle®]), none of which were identified in the current scan. We have identified 4 new serious harms/boxed warnings; 2 for conjugated estrogens, 1 for the estradiol vaginal ring, and 1 for the estradiol topical emulsion, none of which were identified in the current scan. Since the last update report, we have identified 1 new comparative effectiveness review that encompasses the entire scope of the scan, and 5 potentially relevant reviews that could be used to answer specific pieces of an update report, none of which were identified in this scan. Since the last update report, we have identified 48 potentially relevant new trials for this drug class, including 10 primary head-to-head trials (1 this scan) and 38 placebo-controlled trials (3 this scan).

APPENDIX A. NEW SERIOUS HARMS (E.G. BOXED WARNINGS) OF HORMONE THERAPY

*Shading indicates new serious harms identified in the current scan.

ESTRING (ESTRADIOL VAGINAL RING)

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

August 2014

BOXED WARNING

- *Updated the Boxed Warning to include a revised general heading and two specific subheadings: Estrogen-Alone Therapy and Estrogen Plus Progestin Therapy; updated the text in the Boxed Warning to reflect the current recommended estrogen-class labeling.*

CONTRAINDICATIONS

- Known anaphylactic reaction or angioedema or hypersensitivity to Estring …
- Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders.

WARNINGS

Cardiovascular Disorders-Stroke

- Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

Cardiovascular Disorders - Coronary Heart Disease

- Subgroup analyses of women 50 to 59 years of age suggest a statistically nonsignificant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

Malignant Neoplasms-Breast Cancer

- *updated to reflect the current recommended estrogen-class labeling.*

Probable Dementia

- *updated to reflect current recommended estrogen-class labeling.*

Hereditary Angioedema

- Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

PRECAUTIONS
Geriatric Use

- *updated to reflect the findings in The Women's Health Initiative Studies and The Women's Health Initiative MemoryStudy; accompanying text was modified to reflect current recommended estrogen-class labeling.*
- *Updated PRECAUTIONS Section to reflect current recommended estrogen-class labeling*

ADVERSE REACTIONS
Postmarketing Experience

- *addition of Cases of Hypersensitivity

PATIENT INFORMATION

- *Updated*

ESTRASORB (ESTRADIOL TOPICAL EMULSION)

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

March 2015

BOXED WARNING (edited)

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

Estrogen-Alone Therapy

Endometrial Cancer

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.2)].

Cardiovascular Disorders and Probable Dementia

- Estrogens-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.2, 14.3)].
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [see Warnings and Precautions (5.1), and Clinical Studies (14.2)].

- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.3)].
- In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
- Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.2, 14.3)].
- The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg] relative to placebo [see Warnings and Precautions (5.1), and Clinical Studies (14.3)].
- The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment withdaily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.3)].

Breast Cancer

- The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.2), and Clinical Studies (14.3)].
- In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.
- Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

CONTRAINDICATIONS

- Known anaphylactic reaction or angioedema with ESTRASORB
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

WARNINGS AND PRECAUTIONS

Estrogen class labeling text updated in the following sub-sections:

- Cardiovascular Disorders

- Malignant neoplasms
- Probable Dementia
- Laboratory Tests
- Drug- Laboratory Test Interactions

Hereditary Angioedema section added

- Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

ADVERSE REACTIONS

Clinical Trials Experience table updated

Postmarketing Experience section added

USE IN SPECIFIC POPULATIONS

- Estrogen class labeling text updated in the following sub-sections: Pregnancy, Nursing Mothers

Geriatric Use section updated

Renal Impairment section added

Hepatic Impairment section added

PATIENT PACKAGE INFORMATION (PPI) updated with the Estrogen class labeling text

ENJUVIA (SYNTHETIC CONJUGATED ESTROGENS, B) TABLETS

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

June 2015

BOXED WARNING (edited)

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

- Estrogens-alone therapy should not be used for the prevention of cardiovascular disease or dementia.
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years

of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

- In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
- Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.
- The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA).
- The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Breast Cancer

- The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.
- In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.
- Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

CONTRAINDICATIONS

- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

WARNINGS AND PRECAUTIONS

- Hereditary Angioedema: Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

ADVERSE REACTIONS

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of ENJUVIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Gastrointestinal Disorders: abdominal discomfort, abdominal distension, nausea
- Immune System Disorders: anaphylactic reaction, hypersensitivity
- Musculoskeletal and connective tissue disorders: muscle spasms
- Nervous System Disorders: headache, dizziness
- Psychiatric disorders: insomnia
- Reproductive system and Breast Disorders: breast pain, breast tenderness

- Skin and Subcutaneous Tissue Disorders: alopecia, rash, urticaria
- Vascular Disorders: deep vein thrombosis, thrombosis

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

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

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

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

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

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

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

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

APPENDIX B. POTENTIALLY RELEVANT NEW COMPARATIVE EFFECTIVENESS REVIEWS OF HORMONE THERAPY

*Shading indicates reviews identified in the current scan.

Menopausal Symptoms: Comparative Effectiveness of Therapies

Structured Abstract

Objectives. To systematically review and synthesize evidence evaluating the comparative effectiveness of treatments for menopausal symptoms, along with potential long-term benefits and harms of those treatments.

Data sources. The following electronic databases were searched through January 2014: MEDLINE®, Embase®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine. Gray literature searches included clinicaltrials.gov, the Food and Drug Administration Web site, and relevant conference abstracts.

Review methods. Menopausal symptom outcomes included: vasomotor, quality of life, psychological, sexual function, urogenital, and sleep disturbance. Randomized controlled trials provided the evidence base for symptom relief. Standardized mean differences were calculated to allow pooling of outcomes from varied measures. Network meta-analyses were performed when possible, along with pairwise comparisons. Systematic reviews, cohort studies, and case-control studies provided evidence for the following long-term benefits and harms: breast, colon, endometrial, and ovarian cancer; coronary heart disease and venous thromboembolic events; gallbladder disease; and osteoporotic fractures.

Results. Evidence from 283 trials provided results for vasomotor symptoms (211 trials), quality of life (125 trials), psychological symptoms (108 trials), sexual function (94 trials), urogenital atrophy (71 trials), and sleep disturbance (56 trials). The most commonly studied agents were estrogens, isoflavones, and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs). Estrogens appeared to be the most effective treatment in relieving vasomotor symptoms and were accompanied by better quality-of-life scores. SSRIs/SNRIs relieve vasomotor symptoms less effectively than estrogens but were accompanied by the largest improvement in global measures of psychological well-being. Estrogens administered vaginally diminished pain during sex and testosterone increased sexual activity. Measures of urogenital atrophy were improved with ospemifene and vaginal or oral estrogens. Estrogens also improved sleep, but the effect appeared to be modest. Over the long term, estrogen combined with progestogen has both beneficial effects (fewer osteoporotic fractures) and harmful effects (increased risk of breast cancer, gallbladder disease, venous thromboembolic events, and stroke). Estrogens given alone do not appear to increase breast cancer risk, although endometrial cancer risk is increased. There is limited evidence on the long-term effects of most nonhormone treatments. No studies were identified that examined the efficacy or safety of compounding practices for hormone therapies.

Conclusions. Women experiencing symptoms of menopause can consider a number of potential treatments of varying efficacy. From a large body of evidence, there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. For other common symptoms—psychological, urogenital, and sleep disturbance—although estrogens are effective, some nonhormonal agents compare favorably. Estrogens are accompanied by potential long-term harms that require consideration. There is limited evidence on the potential consequences of long-term use of nonhormonal agents when those agents are used to treat menopausal symptoms.

1. Hayes, Inc. Bioidentical hormone replacement therapy for menopausal symptoms. 2013.

Key Questions:

- Are FDA-approved bioidentical estrogen hormonal products (e.g., estradiol, estrone) or progesterone hormonal products (e.g., micronized oral progesterone, progesterone creams) safer or more effective than nonbioidentical hormonal products for the treatment of menopausal symptoms?
- Is compounded BHRT safe and effective for the treatment of menopausal symptoms?
- Have definitive patient selection criteria been established for use of bioidentical hormones for treatment of menopausal symptoms?

2. Lai K, Cui J, Ni S, Zhang Y, He J, Yao K. The effects of postmenopausal hormone use on cataract: a meta-analysis. *PLoS ONE*. 2013;8(10):e78647.

Abstract:

BACKGROUND

Cataract is the leading cause of blindness worldwide. Many observational studies assessed the relationship between postmenopausal hormone replacement therapy (HRT) and risk of cataract development, but the reported results were controversial. The aim of present meta-analysis was to evaluate the association of postmenopausal hormone replacement therapy with risk of cataract development.

METHODS

The eligible observational studies, including cross-sectional, case-control and cohort studies, were identified by searching PubMed and Embase during March of 2013. Either a fixed- or a random-effects model was used to calculate the pooled odds ratio (OR) with its 95% confidence interval (95%CI). Subgroup analysis on cataract types was performed.

RESULTS

A total of four cohort and five case-control or cross-sectional studies were finally included into this meta-analysis. Overall, a significant decreased risk of developing any type of cataract was found in ever HRT group as compared with non-HRT group among cohort studies (OR 0.83; 95% CI: 0.71,0.97) and case-control or cross-sectional studies (OR 0.74; 95% CI: 0.59,0.93). Subgroup analysis on cataract types determined that the significantly decreased risk of nuclear cataract in current HRT group (OR 0.72; 95% CI: 0.61,0.85) and also a critically reduced risk of nuclear cataract in ever HRT group (OR 0.80; 95% CI: 0.64,1.01) were found among case-control or cross-sectional studies, as compared with non-HRT group. No association of HRT with risk of cortical and posterior subcapsular cataract was observed.

CONCLUSIONS

The results of present meta-analysis indicate that postmenopausal hormone use may play a protective role in cataract development.

3. Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;6:CD008613.

Abstract:

BACKGROUND
There is conflicting information about the impact of the menopause on glycaemic control amongst women with type 1 diabetes. Some menopausal women with type 1 diabetes are treated with hormone replacement therapy (HRT) but the effects of this treatment have, to date, not been established.

OBJECTIVES
To assess the effects of HRT for women with type 1 diabetes mellitus.

SEARCH METHODS
We searched *The Cochrane Library*, MEDLINE, EMBASE, CINAHL and PsycINFO from their inception to June 2012. The last search was run for all databases on 18 June 2012.

SELECTION CRITERIA
We selected randomised controlled trials or controlled clinical trials that involved peri- or postmenopausal women with type 1 diabetes undergoing HRT as an intervention.

DATA COLLECTION AND ANALYSIS
Two researchers independently applied the inclusion criteria to the identified studies and assessed risk of bias. Disagreements were resolved by discussion or by intervention by a third party. Descriptive analysis was conducted for the review.

MAIN RESULTS
Ninety-two publications were screened. No studies met the inclusion criteria exclusively but one study that included both type 1 and type 2 diabetes participants was considered. This randomised clinical trial (RCT) compared HRT (N = 27) with placebo (N = 29) over 12 months. The outcome measures were cardiovascular risk factors, including lipid profile, glycaemic control, blood pressure and body weight. No significant differences between placebo and HTR were detected. Patient-important outcomes like all-cause mortality, cardiovascular disease, diabetic complications or health-related quality of life were not investigated.

AUTHORS' CONCLUSIONS
There is a lack of evidence around the use of HRT in women with type 1 diabetes. The one study that has been undertaken in this area is underpowered. More RCTs are required in the area to examine the impact of HRT on glycaemic control and cardiovascular outcomes.

4. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. *Menopause.* Oct 2013;20(10):1098-1105.

Abstract:

OBJECTIVE
Given the complexity of the literature on quality of life (QOL) and hormone therapy (HT) among women in the menopausal transition and postmenopause, the purposes of this integrative review were to (1) define QOL as a multidimensional construct; (2) review validated instruments for measurement of QOL; (3) review results of HT and QOL clinical trials that have used validated instruments; and (4) assess the effectiveness of HT on QOL, including health-related QOL (HRQOL), menopause-specific QOL (MSQOL), and global QOL (GQOL).

METHODS
The literature on HT and QOL was searched for definitions of QOL and validated instruments for measuring QOL, and the results were summarized. The purposes of this integrative review were to evaluate the effects of HT on HRQOL, differentiating the effects of HT on GQOL, HRQOL, and MSQOL. As a basis for this review, we searched for published controlled clinical trials in which the effects of HT on QOL were studied using validated QOL instruments, in particular menopause-specific validated instruments.

RESULTS
Clear definitions are elucidated. Validated instruments for the measurements of HRQOL, GQOL, and MSQOL are summarized, and the necessity of their incorporation into future research and clinical practice is emphasized. The published effects on QOL of estrogens and progestogens administered to symptomatic and nonsymptomatic women in the menopausal transition and beyond are reviewed.

CONCLUSIONS
The impact of various health state-related symptoms on HRQOL and GQOL is now an integral component of contemporary health care. Effects of HT include GQOL and HRQOL and should be menopause-specific. There is clearly a need for further studies on menopause and menopause-related therapies using appropriate and validated instruments. Literature review shows that HT provides a significant benefit for MSQOL in midlife women, mainly through relief of symptoms, but treatment also may result in a global increase in sense of well-being (GQOL). HRQOL benefits are contingent on symptom status, as are MSQOL outcomes. Women who are severely symptomatic experience a significant improvement in HRQOL and MSQOL, although this improvement is not significant among women without severe symptoms at baseline measures in clinical trials.

5. Yang D, Li J, Yuan Z, Liu X. Effect of hormone replacement therapy on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS ONE*. 2013;8(5):e62329.

Abstract:

BACKGROUND

Hormone replacement therapy (HRT) is widely used to controlling menopausal symptoms and prevent adverse cardiovascular events. However, the benefit and risk of HRT on cardiovascular outcomes remains controversial.

METHODOLOGY AND PRINCIPAL FINDINGS

We systematically searched the PubMed, EmBase, and Cochrane Central Register of Controlled Trials databases for obtaining relevant literature. All eligible trials reported on the effects of HRT on cardiovascular outcomes. We did a random effects meta-analysis to obtain summary effect estimates for the clinical outcomes with use of relative risks calculated from the raw data of included trials. Of 1903 identified studies, we included 10 trials reporting data on 38908 postmenopausal women. Overall, we noted that estrogen combined with medroxyprogesterone acetate therapy as compared to placebo had no effect on coronary events (RR, 1.07; 95% CI: 0.91-1.26; P=0.41), myocardial infarction (RR, 1.09; 95% CI: 0.85-1.41; P=0.48), stroke (RR, 1.21; 95% CI: 1.00-1.46; P=0.06), cardiac death (RR, 1.19; 95% CI: 0.91-1.56; P=0.21), total death (RR, 1.06; 95% CI: 0.81-1.39; P=0.66), and revascularization (RR, 0.95; 95% CI: 0.83-1.08; P=0.43). In addition, estrogen therapy alone had no effect on coronary events (RR, 0.93; 95% CI: 0.80-1.08; P=0.33), myocardial infarction (RR, 0.95; 95% CI: 0.78-1.15; P=0.57), cardiac death (RR, 0.86; 95% CI: 0.65-1.13; P=0.27), total mortality (RR, 1.02; 95% CI: 0.89-1.18; P=0.73), and revascularization (RR, 0.77; 95% CI: 0.45-1.31; P=0.34), but associated with a 27% increased risk for incident stroke (RR, 1.27; 95% CI: 1.06-1.53; P=0.01).

CONCLUSION/SIGNIFICANCE

Hormone replacement therapy does not effect on the incidence of coronary events, myocardial infarction, cardiac death, total mortality or revascularization. However, it might contributed an important role on the risk of incident stroke.

APPENDIX C. ABSTRACTS OF NEW POTENTIALLY RELEVANT HEAD-TO-HEAD TRIALS OF HORMONE THERAPY

*Shading indicates new trials identified in the current scan.

Head-to-Head Trials (N=10)

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

OBJECTIVES: Pilot study to compare the effects of a continuous combined hormone replacement therapy (HRT) regimen with an interrupted progestogen regimen administered transdermally, upon the endometrium of postmenopausal women, the incidence of amenorrhoea and relief of menopausal symptoms. METHODS: Fifty-nine postmenopausal women aged 50-63 years were randomised to either (i) continuous combined regimen: combined oestrogen/progestogen skin patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) or (ii) interrupted regimen: oestrogen-only patches (releasing 80 microg estradiol/day) for 4 days followed by combined oestrogen/progestogen patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) for 3 days, for 6 months. An endometrial biopsy was performed at end of treatment for histological analysis. RESULTS: Thirty-three women (56%) completed the study. Significantly higher rates of amenorrhoea were observed with the interrupted than continuous combined regimen (P<0.0001; 25% versus 7% at 6 months). The interrupted regimen was also associated with fewer days of bleeding overall (total 20 versus 44 days during months 4-6; P=0.001). Both regimens improved vasomotor symptoms. No endometrial hyperplasia or atypical changes were observed in endometrial biopsies. CONCLUSIONS: Although significantly less bleeding was observed with the interrupted regimen, it did not have a sufficiently high incidence of amenorrhoea to render it clinically useful.

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

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

symptoms, but oestradiol/dydrogesterone showed some advantages in terms of lipid profile and incidence of bleeding.

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

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

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

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

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

OBJECTIVE: To compare the effects of oral and vaginal estrogen therapy (ET) on the vaginal blood flow and sexual function in postmenopausal women with previous hysterectomy. DESIGN: Fifty-seven women were randomized to receive either oral (0.625 mg of conjugated equine estrogens per tablet; n = 27) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 30) estrogen administered once daily. All women underwent estradiol measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire before and 3 months after ET. RESULTS: A higher serum level of estradiol was noted in the oral group compared with the topical group after 3 months of ET. There

were significant increases in the number of vaginal vessels and the minimum diastole (P < 0.01), and marked decreases of pulsatility index values (P < 0.01) in both groups after ET. Regarding the systolic peak, we found a significant decrease only in the topical group (P < 0.05). Although the post-ET prevalence of anorgasmia decreased significantly in both groups (P < 0.05), changes in other domains, including the rates of low libido and coital frequency, were not statistically significant (P > 0.05). In the topical group, ET improved sexual function on the vaginal dryness and dyspareunia domains in a statistically significant manner (P < 0.05), but this was not the case in the oral group (P > 0.05). However, the efficacy of oral ET for vaginal dryness and dyspareunia reached 80% and 70.6%, respectively. The corresponding figures of the topical ET were 79.2% and 75%. CONCLUSIONS: The results of our study suggest that ET alone in hysterectomized postmenopausal women increases the vaginal blood flow and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol.

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

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

Pinkerton, J. V., et al. (2014). "Sleep parameters and health-related quality of life with bazedoxifene/conjugated estrogens: a randomized trial." Menopause **21**(3): 252-259.

OBJECTIVE: The effects of bazedoxifene (BZA)/conjugated estrogens (CE) on sleep and health-related quality of life (HRQoL) were evaluated in nonhysterectomized postmenopausal women who were enrolled in a randomized, double-blind, placebo- and active-controlled phase 3 trial.

METHODS: The sleep/HRQoL substudy enrolled 459 women with bothersome moderate to severe vasomotor symptoms who were randomized to BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, BZA 20 mg, CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg, or placebo for 1 year. On months 3 and 12, sleep parameters were evaluated using the Medical Outcomes Study sleep scale, and HRQoL was assessed using the Menopause-Specific Quality of Life (MENQOL) questionnaire.

RESULTS: BZA/CE and CE/MPA significantly improved sleep and HRQoL compared with placebo. On month 3, most Medical Outcomes Study sleep parameter improvements with

BZA/CE and CE/MPA versus placebo were not significant. On month 12, both BZA/CE doses and CE/MPA significantly improved time to fall asleep and sleep disturbance ($P < 0.05$ vs. placebo); BZA 20 mg/CE 0.625 mg and CE/MPA also showed significant improvements in sleep adequacy and sleep problem indices I and II ($P < 0.01$ vs placebo). Both BZA/CE doses and CE/MPA significantly improved MENQOL vasomotor function score versus placebo at 3 and 12 months ($P < 0.001$). At 3 months, total MENQOL score was significantly improved with BZA 20 mg/CE 0.625 mg and CE/MPA versus placebo ($P < 0.05$); at 12 months, both BZA/CE doses and CE/MPA showed significant improvements ($P < 0.001$).

CONCLUSIONS: Symptomatic postmenopausal women who are treated with BZA/CE for 1 year demonstrate significant improvements in sleep and HRQoL, similar to women treated with CE/MPA.

Paoletti, A. M., et al. (2015). "Clinical effect of hormonal replacement therapy with estradiol associated with noretisterone or drospirenone. A prospective randomized placebo controlled study." Gynecological Endocrinology **31**(5): 384-387.

The study was performed to compare the clinical effect of a hormone replacement therapy (HRT) with two different progestins. Postmenopausal women (PMW) with climacteric symptoms (CS) randomly received for 12 months orally, either placebo (n = 20), 1mg estradiol (E) plus 0.5mg noretisterone acetate (NETA; n=40), or 2mg drospirenone (DRSP; n=40), a testosterone- and spironolactone-derived molecule, respectively. Weight (W) declined only during E/DRSP ($p<0.04$ versus placebo). Fat mass (FM) decreased, similarly, during E/NETA and E/DRSP. Intracellular water (ICW) did not change, while extracellular water (ECW) decreased during E/DRSP ($p<0.0001$) ($p<0.002$ versus E/NETA). During E/NETA and E/DRSP, similar decreases were observed for insulin resistance (IR) by the homeostatic model assessment for IR (HOMA-IR) ($p<0.0001$ versus placebo for both), systolic ($p<0.04$ versus placebo for both) and diastolic ($p<0.002$) blood pressure (BP). Lipids did not change. In comparison to placebo CS, by the Kupperman Index (KI), significantly declined ($p<0.0001$) during E/NETA or E/DRSP. Menopause-specific Quality of Life (MENQoL) significantly declined versus placebo ($p<0.04$) during both E/NETA and E/DRSP. In conclusion, differences between the two progestins are mainly limited to body composition (BC), where the addition of DRSP decreases ECW and body W (BW).

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

Oestrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and oestrogen/progestin are not suitable for all women. MPA (medroxyprogesterone acetate) reduces hot flushes, but its effectiveness compared with oestrogen is unknown. In the present study, oral oestrogen [CEE (conjugated equine oestrogen)] and MPA were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-year randomized double-blind parallel group controlled trial in an urban academic medical centre. Participants were healthy menstruating women prior to hysterectomy/ovariectomy for benign disease. A total of 41 women {age, 45 (5) years [value is mean (S.D.)]} were enrolled; 38 women were included in this analysis of daily identical capsules containing CEE (0.6 mg/day) or MPA (10 mg/day). Demographic variables did not differ at baseline. Daily data provided the number of night and day flushes compared by group. The vasomotor symptom day-to-day intensity change was assessed by therapy assignment. Hot flushes/night sweats were well controlled in both groups, one occurred on average every third day and every fourth night. Mean/day daytime occurrences were 0.363 and 0.187 with CEE and MPA respectively, but were not

significantly different (P=0.156). Night sweats also did not differ significantly (P=0.766). Therapies were statistically equivalent (within one event/24 h) in the control of vasomotor symptoms. Day-to-day hot flush intensity decreased with MPA and tended to remain stable with CEE (P<0.001). In conclusion, this analysis demonstrates that MPA and CEE are equivalent and effective in the control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

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

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