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DERP VI Update Scan 8: Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

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OHSU

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Objectives

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on hormone therapy for postmenopausal women or women in the menopausal transition stage. The literature search for this scan focuses on new randomized controlled trials (RCTs) and systematic reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last update report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participating organizations agreed to proceed with a full report update or other research product.

Topic History

Scan 7: September 2016

Scan 6: September 2015

Scan 5: July 2014

Scan 4: September 2013

Scan 3: November 2011

Scan 2: June 2010

Scan 1: May 2009

Update report 3: October 2007, searches through March 2007

Background and Context

Menopause is defined as the permanent cessation of menstruation after ovarian activity stops.[1] Most women begin the physiological changes associated with menopause in the years preceding the final menstrual period.[1] This interval is called perimenopause or the climacteric or menopausal transition.[2] The menopausal transition usually begins in the mid-to-late 40s, and lasts about 4 years; menopause occurs at a median age of 51 years.[2]

Women report experiencing a variety of menopausal symptoms, including breast tenderness and vasomotor (hot flashes) and vaginal symptoms, which are closely associated with hormonal changes during menopausal transition.[3] In the U.S., a variety of systemic estrogen therapies are approved to treat symptoms associated with the menopause.[4]

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?

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 (less than 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 a medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Using the PICO outlined below, we screened our search results for eligible systematic reviews and meta-analyses and RCTs published since the implementation of the search strategy in the most recent scan, which occurred in September 2016. Systematic reviews were only included if their search strategy occurred after or included a period of time following the search date in the most recent scan.

Populations

- Women 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 are oral and transdermal estrogen monotherapy or estrogen plus progestin/progesterone preparations for all symptoms; bone density and fracture outcomes; and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens (Table 1). Interventions had to be evaluated for at least 3 months for symptom control, or for at least 12 months for the prevention of osteoporosis.

Table 1. Included Interventions

Generic Name	Brand Name	Product Type
Estrogen Only		
17b Estradiol	Estradiol (generic)	Oral, transdermal patch; vaginal cream; vaginal tablet
Conjugated Estrogens	Premarin	Oral; vaginal cream
Esterified Estrogen	Menest	Oral
Estradiol	Alora	Patch
Estradiol	Climara	Patch
Estradiol	Divigel	Gel
Estradiol	Elestrin	Gel
Estradiol	Estrace	Oral; vaginal cream
Estradiol	Estring	Vaginal insert
Estradiol	EstroGel	Gel
Estradiol	EvaMist	Skin spray (transdermal)
Estradiol	Menostar [a]	Patch
Estradiol	Minivelle	Patch
Estradiol	Vagifem	Vaginal tablet
Estradiol	Vivelle-Dot	Patch
Estradiol Acetate	Femring	Vaginal ring
Estropipate	Ogen	Oral; vaginal cream
Combined Estrogen and Progestin		
Conjugated Estrogen/ Medroxyprogesterone	Prempro	Oral
Conjugated Estrogen/ Medroxyprogesterone	Premphase	Oral
Conjugated Estrogen/ Medroxyprogesterone	Prempro/Premphase	Oral
Conjugated Estrogen/ Medroxyprogesterone	Premphase 14/14	Oral
Estradiol/Drospirenone	Angeliq	Oral
Estradiol/ Levonorgestrel	Climara Pro	Patch
Estradiol/ Norethindrone Acetate	Activella	Oral
Estradiol/ Norethindrone Acetate	Combipatch	Patch
Norethindrone Acetate/ Ethinyl Estradiol	Femhrt	Oral
Combined Estrogen and Hormone		
Conjugated Estrogen/ Bazedoxifene	Duavee	Oral

Note. [a] *Only used to prevent osteoporosis. Source. Adapted from the FDA website.*[5]

Comparators

- Another FDA-approved hormone therapy
- No treatment
- Placebo

Outcomes

- Hot flashes or flushes
- Other symptoms such as sleep disturbances, night sweats, mood changes (depression), sexual function, urogenital atrophy, and quality of life
- Osteoporosis
- Withdrawals
- Adverse events
- Short-term outcomes, including atypical bleeding, weight change, and cardiovascular events
- Long-term outcomes, including cardiovascular events; breast, ovarian, or endometrial cancer; and thrombosis

Methods

We searched the FDA website to identify newly approved drugs and indications, any first generic approvals, and new serious harms (e.g., boxed warnings) for included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information. To identify relevant literature, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from August 2016 to July 2018, using terms for included drugs and limits for English language and human participants. We also conducted an internet search using Google and Google Scholar with key words for included drugs.

Findings

New Drugs or Formulations

Since the search was conducted in the last update report in October 2007,[4] 7 new hormone therapy drugs and formulations (Table 2) have been approved by the FDA. Since scan 7 in September 2016,[6] 1 first generic and 1 new formulation were approved.

Table 2. Newly Approved Hormone Therapy Drugs, First Approved Generics, and Formulations Since the Update Report[4]

Generic Name	Brand Name	Date of FDA Approval	Formulation	Indication
Estradiol	Imvexxy	May 2018	Vaginal insert (4 mcg)	• Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Estradiol		December 2017 *First approved generic product	Vaginal cream (.01%)	• Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause
Conjugated Estrogen/ Bazedoxifene	Duavee	March 2013	Oral tablet	For women with a uterus: • Treatment of moderate to severe vasomotor symptoms associated with menopause • Prevention of postmenopausal osteoporosis
Estradiol	Minivelle	October 2012	Extended-release transdermal patch	• Treatment of moderate to severe vasomotor symptoms due to menopause • Prevention of postmenopausal osteoporosis
Synthetic Conjugated Estrogens, A	SCE-A Vaginal Cream	November 2008	Vaginal cream	• Treatment of moderate to severe vaginal dryness due to menopause • Treatment of moderate to severe dyspareunia due to menopause
Estradiol	EvaMist	July 2007	Transdermal spray	• Treatment of moderate to severe vasomotor symptoms due to menopause
Estradiol	Divigel	June 2007	Transdermal gel (.1%)	• Treatment of moderate to severe vasomotor symptoms due to menopause

Abbreviation. FDA: Food and Drug Administration.

Some formulations have been discontinued since the last update report[4] and are not included in the interventions considered for this scan (Table 2). However, previous scans might have included studies evaluating interventions that are now discontinued.

New Indications

We did not identify any new indications since the completion of the last update report in October 2007.[4]

New Serious Harms

In 2017, the FDA instructed manufacturers of estrogen-only and estrogen and progesterone hormone therapy drugs for menopause to include safety information on the risk of ovarian cancer in the labeling of their products. Prescribing information was updated for several hormone therapy drugs[7-26] to include the results from a meta-analysis of 17 prospective and 35 retrospective epidemiology studies, which showed an increased risk of ovarian cancer in women using hormonal therapy for menopausal symptoms.[27]

We did not identify any recent label changes to the following hormone therapy drugs that were not discontinued at the time of this scan:

- Estrace
- Estradiol (generic)
- Femring
- Menest
- Ogen
- Premarin
- Prempro

Systematic Reviews

Since the last update report on this topic,[4] we have identified 8 systematic reviews on the efficacy and safety of hormone therapy for postmenopausal women or women in the menopausal transition stage.[28-35]

- A comparative effectiveness review of bioidentical hormone replacement therapy for menopausal symptoms[28]
- A systematic review and meta-analysis evaluating the association of postmenopausal hormone replacement therapy with the risk of developing cataracts[29]
- A Cochrane review assessing the effect of hormone replacement therapy for women with type 1 diabetes mellitus[30]
- A review of how hormone therapy affects quality of life after menopause[31]
- A systematic review and meta-analysis of the effect of hormone replacement therapy on cardiovascular outcomes in postmenopausal women[32]
- A comparative effectiveness review of treatments for menopausal symptoms, including long-term benefits and harms[33]
- A review of hormone therapy for the primary prevention of chronic conditions in postmenopausal women[34]
- A Cochrane review assessing the effects of long-term hormone therapy in perimenopausal and postmenopausal women, during and after cessation of treatment[35]

Of these, we have identified 2 new systematic reviews in this scan (Table 3).

Table 3. Characteristics of New Systematic Reviews

Author, Year Aim	Population	Intervention	Study Designs	Outcomes
Gartlehner et al., 2017[34] To update evidence for the U.S. Preventive Services Task Force on the benefits and harms of hormone therapy in reducing risks for chronic conditions	Generally healthy perimenopausal and postmenopausal women who were eligible for hormone therapy	Systemic therapy (pill, patch, or injection) with estrogen-only formulations or combination preparations of estrogen plus progestin	RCTs, controlled trials, systematic reviews, and large controlled cohort studies	Beneficial or harmful changes in risks for various chronic conditions
Marjoribanks et al., 2017[35] To assess effects of long-term hormone therapy (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment	Perimenopausal or postmenopausal women recruited from any health care setting or a population-based sample	All estrogens, with and without progestogens, administered by oral, transdermal, subcutaneous, or intranasal routes, and given as perimenopausal or postmenopausal therapy for any reason for 12 months or longer	RCTs	Mortality Coronary events Stroke VTE Cancer Gallbladder disease Fractures Cognitive function

Abbreviations. RCT: randomized controlled trial; VTE: venous thromboembolism.

Randomized Controlled Trials

Since the last report on this topic,[4] we have identified 74 publications[36-109] from 58 relevant trials.

- 10 head-to-head trials
- 48 placebo or no treatment controlled trials

Of these, we have identified 10 publications[49,50,59,65-67,73,74,98,108] from 5 new placebo-controlled trials in this scan (Table 4).

- 1 trial evaluating an estrogen alone[50]
- 4 trials evaluating a combination of estrogen and progestin or progesterone[59,65,67,108]

Table 4. Characteristics of New Trials

Author, Year Study Name NCT Number	Population	Intervention	Comparator	Outcomes
Estrogen Only				
Constantine et al., 2017[49,50,73,74,98] REJOICE NCT02253173	764 postmenopausal women, aged 40 to 75, with a self-identified most bothersome symptom of moderate-to-severe dyspareunia	Estradiol, a vaginal estradiol soft-gel capsule (4 mcg, 10 mcg, or 25 mcg)	Placebo	Vaginal cell health Vaginal pH Severity of dyspareunia Severity of vulvar and vaginal atrophy-related symptoms Sexual dysfunction Patient acceptability and satisfaction Safety
Combined Estrogen and Progestin or Progesterone				
Gordon et al., 2018[59] PERT NCT01308814	172 perimenopausal and early postmenopausal women, aged 45 to 60, with euthymia	Transdermal estradiol patch and intermittent oral micronized progesterone	Placebo	Depression Vasomotor symptoms Adverse events
Henderson et al., 2016[65,66] ELITE-Cog NCT00114517	643 women, aged within 6 years of menopause or 10 years after menopause	Oral estradiol + vaginal micronized progesterone gel 4% (45 mg) per day or oral estradiol alone, depending on uterine status	Placebo	Cognitive function, including memory and stress Safety
Honisett et al., 2016[67] Not reported	15 postmenopausal women athletes, aged 45 to 60, competing at masters level	Transdermal estradiol patch + oral MPA	Placebo	Aerobic capacity Hormone levels Bone turnover markers Bone formation markers
Yoon et al., 2018[108] Not reported	37 postmenopausal women with mild cognitive impairment	Percutaneous estradiol gel + oral micronized progesterone	Placebo	Cognitive function Activities of daily living Quality of life Depression and behavior Progression to dementia

Abbreviation. MPA: medroxyprogesterone acetate.

Long-term results and secondary analyses from key trials, such as the Women's Health Initiative,[110] continue to be published. We did not include any secondary analyses or long-term reports in this scan; however, any relevant reports would be included in a full update report.

Summary

- We identified 7 newly approved hormone therapy drugs and formulations since the last update report. We identified 1 new first generic approval and 1 new formulation in this scan:
    - 1 first generic approval for estradiol vaginal cream (.01%)
    - 1 new formulation of estradiol vaginal insert (4 mcg)
- We did not identify any new indications since the last update report.
- We identified new prescribing information in this scan on the increased risk of ovarian cancer associated with the use of hormonal therapy.
- We identified 8 systematic reviews since the last update report, of which 2 are new in this scan:
    - A review of hormone therapy for the primary prevention of chronic conditions in postmenopausal women
    - A Cochrane review assessing the effects of long-term hormone therapy in perimenopausal and postmenopausal women, during and after cessation of treatment
- We identified 58 trials since the last update report, of which 5 are new in this scan:
    - 1 placebo-controlled trial evaluating an estrogen alone
    - 4 placebo-controlled trials evaluating a combination of estrogen and progestin or progesterone

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Appendix A. Abstracts of Relevant Systematic Reviews

Gartlehner G, Patel SV, Feltner C, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2017;318(22):2234-2249.

Importance: Postmenopausal status coincides with increased risks for chronic conditions such as heart disease, osteoporosis, cognitive impairment, or some types of cancers. Previously, hormone therapy was used for the primary prevention of these chronic conditions. Objective: To update evidence for the US Preventive Services Task Force on the benefits and harms of hormone therapy in reducing risks for chronic conditions. Data Sources: MEDLINE, Cochrane Library, EMBASE, and trial registries from June 1, 2011, through August 1, 2016. Surveillance for new evidence in targeted publications was conducted through July 1, 2017. Study Selection: English-language randomized clinical trials reporting health outcomes. Data Extraction and Synthesis: Dual review of abstracts, full-text articles, and study quality; meta-analyses when at least 3 similar studies were available. Main Outcomes and Measures: Beneficial or harmful changes in risks for various chronic conditions. Results: Eighteen trials (n=40058; range, 142-16608; mean age, 53-79 years) were included. Women using estrogen-only therapy compared with placebo had significantly lower risks, per 10000 person-years, for diabetes (-19 cases [95% CI, -34 to -3]) and fractures (-53 cases [95% CI, -69 to -39]). Risks were statistically significantly increased, per 10000 person-years, for gallbladder disease (30 more cases [95% CI, 16 to 48]), stroke (11 more cases [95% CI, 2 to 23]), venous thromboembolism (11 more cases [95% CI, 3 to 22]), and urinary incontinence (1261 more cases [95% CI, 880 to 1689]). Women using estrogen plus progestin compared with placebo experienced significantly lower risks, per 10000 person-years, for colorectal cancer (-6 cases [95% CI, -9 to -1]), diabetes (-14 cases [95% CI, -24 to -3), and fractures (-44 cases [95% CI, -71 to -13). Risks, per 10000 person-years, were significantly increased for invasive breast cancer (9 more cases [95% CI, 1 to 19]), probable dementia (22 more cases [95% CI, 4 to 53]), gallbladder disease (21 more cases [95% CI, 10 to 34]), stroke (9 more cases [95% CI, 2 to 19]), urinary incontinence (876 more cases [95% CI, 606 to 1168]), and venous thromboembolism (21 more cases [95% CI, 12 to 33]). Conclusions and Relevance: Hormone therapy for the primary prevention of chronic conditions in menopausal women is associated with some beneficial effects but also with a substantial increase of risks for harms. The available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev.* 2017;1:CD004143.

BACKGROUND: Hormone therapy (HT) is widely provided for control of menopausal symptoms and has been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005. OBJECTIVES: To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment. SEARCH METHODS: We searched the following databases to September 2016: Cochrane Gynaecology and Fertility

Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO. We searched the registers of ongoing trials and reference lists provided in previous studies and systematic reviews. SELECTION CRITERIA: We included randomised double-blinded studies of HT versus placebo, taken for at least 1 year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via the oral, transdermal, subcutaneous or intranasal route. DATA COLLECTION AND ANALYSIS: Two review authors independently selected studies, assessed risk of bias and extracted data. We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data, along with 95% confidence intervals (CIs). We assessed the quality of the evidence by using GRADE methods. MAIN RESULTS: We included 22 studies involving 43,637 women. We derived nearly 70% of the data from two well-conducted studies (HERS 1998; WHI 1998). Most participants were postmenopausal American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (i.e. generally fit, without overt disease), combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000), stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000), breast cancer (after 5.6 years' use: from 19 per 1000 to between 20 and 30 per 1000), gallbladder disease (after 5.6 years' use: from 27 per 1000 to between 38 and 60 per 1000) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000).Oestrogen-only HT increased the risk of venous thromboembolism (after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000; after 7 years' use: from 16 per 1000 to 16 to 28 per 1000), stroke (after 7 years' use: from 24 per 1000 to between 25 and 40 per 1000) and gallbladder disease (after 7 years' use: from 27 per 1000 to between 38 and 60 per 1000) but reduced the risk of breast cancer (after 7 years' use: from 25 per 1000 to between 15 and 25 per 1000) and clinical fracture (after 7 years' use: from 141 per 1000 to between 92 and 113 per 1000) and did not increase the risk of coronary events at any follow-up time. Women over 65 years of age who were relatively healthy and taking continuous combined HT showed an increase in the incidence of dementia (after 4 years' use: from 9 per 1000 to 11 to 30 per 1000). Among women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism (at 1 year's use: from 3 per 1000 to between 3 and 29 per 1000). Women taking HT had a significantly decreased incidence of fracture with long-term use. Risk of fracture was the only outcome for which strong evidence showed clinical benefit derived from HT (after 5.6 years' use of combined HT: from 111 per 1000 to between 79 and 96 per 1000; after 7.1 years' use of oestrogen-only HT: from 141 per 1000 to between 92 and 113 per 1000). Researchers found no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analysed subgroups of 2839 relatively healthy women 50 to 59 years of age who were taking combined continuous HT and 1637 who were taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: Their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded, as this study was not designed to have the power to detect differences between groups of women within 10 years of menopause. For most studies, risk of bias was low in most domains. The overall quality of evidence for the main comparisons

was moderate. The main limitation in the quality of evidence was that only about 30% of women were 50 to 59 years old at baseline, which is the age at which women are most likely to consider HT for vasomotor symptoms. AUTHORS' CONCLUSIONS: Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented. HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for prevention of deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women and in postmenopausal women younger than 50 years of age.

Appendix B. Abstracts of Relevant Randomized Controlled Trials

Head-to-Head Trials

None identified in this scan

Placebo or No Treatment Controlled Trials

Note. Some trials may also have active or head-to-head arms, as well as placebo arms.

Constantine GD, Bouchard C, Pickar JH, et al. Consistency of effect with a low-dose, estradiol vaginal vapsule (TX-004HR): evaluating improvement in vaginal physiology and moderate-to-severe dyspareunia in subgroups of postmenopausal women. *J Womens Health (Larchmt)*. 2017;26(6):616-623.

BACKGROUND: The 12-week, randomized, double-blind, placebo-controlled, multicenter, phase 3 REJOICE trial demonstrated that TX-004HR, an investigational, applicator-free, low-dose vaginal softgel capsule containing solubilized 17beta-estradiol, effectively and rapidly treats symptoms of vulvar and vaginal atrophy (VVA) with negligible to very low systemic absorption. The aim of this analysis was to assess whether the efficacy of TX-004HR varies with age, body mass index (BMI), uterine status, pregnancy status, and vaginal delivery. METHODS: The REJOICE trial evaluated the efficacy of 4-, 10-, and 25-mug doses of TX-004HR in postmenopausal women (40-75 years) with VVA and a self-identified most bothersome symptom of moderate-to-severe dyspareunia. Prespecified subgroup analyses of the four co-primary endpoints (percentages of superficial cells and parabasal cells, vaginal pH, and severity of dyspareunia) were analyzed with respect to age, BMI, uterine status, pregnancy status, and vaginal births. Each dose was compared with placebo for change from baseline to week 2 through week 12, respectively. RESULTS: TX-004HR significantly improved superficial cells, parabasal cells, and vaginal pH from baseline to weeks 2 and 12 in most subgroups. All TX-004HR doses numerically reduced the severity of dyspareunia by 2 weeks and maintained efficacy over 12 weeks, with many of the subgroups having statistically significant improvement relative to placebo. CONCLUSIONS: TX-004HR was efficacious for treating symptomatic VVA, and it demonstrated a consistency of effect when women's age, BMI, uterine status, pregnancy status, and vaginal births were evaluated. Clinical Trial Identifier: NCT02253173.

Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause*. 2017;24(4):409-416.

OBJECTIVE: To evaluate the safety and efficacy of TX-004HR vaginal estradiol soft-gel capsules for moderate-to-severe dyspareunia associated with postmenopausal vulvar and vaginal atrophy. METHODS: In this randomized, double-blind, placebo-controlled, phase 3 study, postmenopausal women with a self-identified most bothersome symptom of dyspareunia received 4, 10, or 25 mug TX-004HR or placebo for 12 weeks. Four co-primary efficacy endpoints were change from baseline to week 12 in percentages of superficial and parabasal cells, vaginal pH, and severity of dyspareunia. Secondary endpoints included severity of vaginal dryness and vulvar and/or vaginal itching or irritation. Endometrial histology and adverse events (AEs) were included in the safety endpoints. RESULTS: In all, 764 women were randomized (modified intent-

to-treat population, n = 747; mean age 59 y). Compared with placebo, all three doses of TX-004HR significantly improved the four co-primary endpoints (P < 0.0001 for all, except dyspareunia with 4 mug, P = 0.0149). Changes in cytology, pH, and dyspareunia were also significant at weeks 2, 6, and 8. Vaginal dryness and vaginal itching/irritation improved. Sex hormone binding globulin concentrations did not change with treatment. TX-004HR was well-tolerated, with no clinically meaningful differences in treatment-emergent AEs versus placebo, and no treatment-related serious AEs or deaths. CONCLUSIONS: TX-004HR (4, 10, and 25 mug) was safe, well-tolerated, and effective for treating moderate-to-severe dyspareunia within 2 weeks with minimal systemic estrogen exposure. This novel product may be a potential new treatment option for women experiencing postmenopausal vulvar and vaginal atrophy.

Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):149-157.

Importance: The menopause transition and early postmenopausal period are associated with a 2- to 4-fold increased risk for clinically significant depressive symptoms. Although a few studies suggest that hormone therapy can effectively manage existing depression during this time, to our knowledge, there have been no studies testing whether hormone therapy can prevent the onset of perimenopausal and early postmenopausal depressive symptoms. Objective: To examine the efficacy of transdermal estradiol plus intermittent micronized progesterone (TE+IMP) in preventing depressive symptom onset among initially euthymic perimenopausal and early postmenopausal women. A secondary aim was to identify baseline characteristics predicting TE+IMP's beneficial mood effects. Design, Setting, and Participants: Double-blind, placebo-controlled randomized trial at the University of North Carolina at Chapel Hill from October 2010 to February 2016. Participants included euthymic perimenopausal and early postmenopausal women from the community, aged 45 to 60 years. Interventions: Transdermal estradiol (0.1 mg/d) or transdermal placebo for 12 months. Oral micronized progesterone (200 mg/d for 12 days) was also given every 3 months to women receiving active TE, and identical placebo pills were given to women receiving placebo. Main Outcome Measures: Scores on the Center for Epidemiological Studies-Depression Scale (CES-D), assessed at baseline and months 1, 2, 4, 6, 8, 10, and 12 after randomization, and the incidence of clinically significant depressive symptoms, defined as a CES-D score of at least 16. Results: Of 172 participants, 130 were white (76%), and 70 were African American (19%), with a mean household income of $50000 to $79999. The mean age was 51 years, and 43 developed clinically significant depressive symptoms. Women assigned to placebo were more likely than those assigned to TE+IMP to score at least 16 on the CES-D at least once during the intervention phase (32.3% vs 17.3%; odds ratio [OR], 2.5; 95% CI, 1.1-5.7; P = .03) and had a higher mean CES-D score across the intervention period (P = .03). Baseline reproductive stage moderated the effect of treatment (beta, -1.97; SEM, 0.80; P for the interaction = .03) such that mood benefits of TE+IMP vs placebo were evident among women in the early menopause transition (beta, -4.2; SEM, 1.2; P < .001) but not the late menopause transition (beta, -0.9; SEM, 0.3; P = .23) or among postmenopausal women (beta, -0.3; SEM, 1.1; P = .92). Stressful life events in the 6 months preceding enrollment also moderated the effect of treatment on mean CES-D score such that

the mood benefits of TE+IMP increased with a greater number of events (beta, 1.22; SEM, 0.40; P = .003). Baseline estradiol levels, baseline vasomotor symptoms, history of depression, and history of abuse did not moderate treatment effects. Conclusions: Twelve months of TE+IMP were more effective than placebo in preventing the development of clinically significant depressive symptoms among initially euthymic perimenopausal and early postmenopausal women. Trial Registration: clinicaltrials.gov Identifier: NCT01308814.

Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology*. 2016;87(7):699-708.
OBJECTIVE: To test the hypothesis that effects of estrogen-containing hormone therapy on cognitive abilities differ between postmenopausal women near to, and further from, menopause. METHODS: In this randomized, double-blind, placebo-controlled trial, healthy women within 6 years of menopause or 10+ years after menopause were randomly assigned to oral 17beta-estradiol 1 mg/d or placebo. Women with a uterus received cyclic micronized progesterone vaginal gel or placebo. The primary outcome assessed at 2.5 and 5 years, compared between treatment groups, was change in a standardized composite of neuropsychological test scores assessing verbal episodic memory. Secondary outcomes assessed executive functions and global cognition. RESULTS: A total of 567 women were included in modified intention-to-treat analyses after a mean treatment duration of 57 months. For verbal memory, the mean estradiol minus placebo standardized difference in composite scores (-0.06, 95% confidence interval -0.22 to 0.09) was not significant (2-tailed p = 0.33). Differences were similar in early and late postmenopause groups (2-tailed interaction p = 0.88). Interactions between postmenopause groups and differences between treatment groups were not significant for executive functions or global cognition. CONCLUSIONS: Estradiol initiated within 6 years of menopause does not affect verbal memory, executive functions, or global cognition differently than therapy begun 10+ years after menopause. Estradiol neither benefits nor harms these cognitive abilities regardless of time since menopause. CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that estradiol initiated within 6 years of menopause does not affect cognition at 2.5 years differently than estradiol initiated 10+ years after menopause. Copyright © 2016 American Academy of Neurology.

Herrera AY, Hodis HN, Mack WJ, Mather M. Estradiol therapy after menopause mitigates effects of stress on cortisol and working memory. *J Clin Endocrinol Metab*. 2017;102(12):4457-4466.
Context: Postmenopausal estradiol therapy (ET) can reduce the stress response. However, it remains unclear whether such reductions can mitigate effects of stress on cognition. Objective: Investigate effects of ET on cortisol response to a physical stressor, cold pressor test (CPT), and whether ET attenuates stress effects on working memory. Design: Women completed the CPT or control condition across two sessions and subsequently completed a sentence span task. Setting: General community: Participants were recruited from the Early vs Late Intervention Trial with Estradiol (ELITE). Participants: ELITE participants (mean age = 66, standard deviation age = 6.8) in this study did not suffer from any major chronic illness or use medications known to affect the stress response or cognition. Interventions: Participants had received a median of randomized 4.7 years of estradiol (n = 21) or placebo (n = 21) treatment at time of participation

in this study. Main Outcome Measures: Salivary cortisol and sentence span task performance. Results: Women assigned to estradiol exhibited blunted cortisol responses to CPT compared with placebo (P = 0.017) and lesser negative effects of stress on working memory (P = 0.048). Conclusions: We present evidence suggesting ET may protect certain types of cognition in the presence of stress. Such estrogenic protection against stress hormone exposure may prove beneficial to both cognition and the neural circuitry that maintains and propagates cognitive faculties. Copyright © 2017 Endocrine Society

Honisett SY, Pagliaro D, Tangalakis K, et al. Hormone therapy reduces bone resorption but not bone formation in postmenopausal athletes. *Prilozi.* 2016;37(2-3):15-21.
INTRODUCTION: Independently, hormone therapy and exercise have well-established protective effects on bone parameters. The combined effects of hormone therapy and exercise, however, are less clear. We, therefore, examined the effects of hormone therapy on bone turnover markers in postmenopausal women undergoing regular high intensity exercise. METHODS: In a randomised, double blind study, postmenopausal athletes competing at Masters level, received either hormone therapy (50 mug transdermal oestradiol, 5 mg MPA, n = 8) or placebo (n = 7) for 20 weeks. Women were tested before and after treatment for plasma concentrations of oestradiol, FSH, LH, and serum bone formation marker -osteocalcin (OC); and urine bone resorption markers-pyridinoline (PYD) and deoxypyridinoline (DPD). RESULTS: As a result of treatment with hormone therapy there were significant reductions in levels of FSH (73.3 +/- 13.7 to 48.6 +/- 10.5 mmol/L, p = 0.01) and bone resorption markers (PYD, 81.9 +/- 7.7 to 57.8 +/- 3.7 nmol/mmol Cr, p = 0.001, and DPD, 18.5 +/- 3.1 to 11.8 +/- 2.1 nmol/mmol Cr, p = 0.01). Oestradiol and bone formation markers were not significantly altered as a result of hormone therapy. There were no changes to any variables with placebo treatment. CONCLUSION: Hormone therapy reduced bone resorption, but not bone formation, in postmenopausal athletes. These favorable reductions in bone turnover; therefore, provide an effective treatment in combination with high intensity exercise to further reduce the subsequent risk of osteoporosis and associated fractures.

Kingsberg SA, Derogatis L, Simon JA, et al. TX-004HR improves sexual function as measured by the Female Sexual Function Index in postmenopausal women with vulvar and vaginal atrophy: the REJOICE trial. *J Sex Med.* 2016;13(12):1930-1937.
INTRODUCTION: TX-004HR is an investigational, applicator-free, vaginal soft gel capsule containing low-dose solubilized 17beta-estradiol. The phase 3, randomized, double-blinded, placebo-controlled, multicenter REJOICE trial has shown TX-004HR to be safe and effective for the treatment of moderate to severe dyspareunia in postmenopausal women with vulvar and vaginal atrophy (VVA). AIM: To evaluate the effect of TX-004HR on female sexual dysfunction in postmenopausal women with VVA. METHODS: The REJOICE study compared the effects of 12-week treatment with TX-004HR (4, 10, or 25 mug) with placebo in postmenopausal women (40-75 years old) with VVA and a most bothersome symptom of moderate to severe dyspareunia. Changes in the percentage of superficial and parabasal cells, vaginal pH, and dyspareunia were measured as co-primary end points. Female sexual dysfunction was evaluated as a secondary end point using the Female Sexual Function Index (FSFI) patient self-report inventory. MAIN OUTCOME MEASURES: Changes from baseline to week 12 in total and individual domain FSFI

scores for each TX-004HR dose were compared with those for placebo. RESULTS: All three TX-004HR doses increased the baseline total FSFI score after 12 weeks, with 10 mug (P < .05) and 25 mug (P = .0019) having a significantly greater effect than placebo. A similar trend was observed for the individual FSFI domains, with 10 and 25 mug significantly improving baselines scores for pain and lubrication at 12 weeks (P <= .015 for all vs placebo). Changes from baseline to week 12 in arousal (P = .0085) and satisfaction (P = .0073) were significantly greater for TX-004HR 25 mug vs placebo. All three TX-004HR doses were comparable to placebo in their effect on desire and orgasm. CONCLUSION: TX-004HR improved FSFI scores in a dose-dependent manner. The observed improvements in sexual function suggest that TX-004HR is a promising treatment option for postmenopausal VVA with a potential added beneficial effect on female sexual dysfunction. Copyright A© 2016 The Authors. Published by Elsevier Inc. All rights reserved.

Kingsberg SA, Kroll R, Goldstein I, et al. Patient acceptability and satisfaction with a low-dose solubilized vaginal estradiol softgel capsule, TX-004HR. *Menopause.* 2017;24(8):894-899.

OBJECTIVE: TX-004HR is an investigational, muco-adhesive, vaginal, softgel capsule containing low-dose, solubilized, 17beta-estradiol designed to treat postmenopausal vulvar and vaginal atrophy (VVA) and improve user experience without an applicator and less mess. METHODS: As part of the 12-week, placebo-controlled, double-blind, phase 3 REJOICE trial evaluating the efficacy/safety of 4-, 10-, and 25-mug TX-004HR in 764 postmenopausal women with VVA, a five-question product survey was administered. Pearson correlation coefficients were used to evaluate correlations between clinical endpoints (vaginal physiology, dyspareunia, and vaginal dryness) and patient acceptability and satisfaction. RESULTS: Majority of the women receiving TX-004HR or placebo reported that the product was easy to use (85.4%-92.1%) and rated ease of capsule insertion as "good" to "excellent" (75.0%-82.6%). A significantly greater percentage of women reported being "very satisfied" or "satisfied" with TX-004HR (68.6%-76.3%) than with placebo (56.8%, P < 0.05 for all). A greater percentage of women "somewhat" or "very much" preferred TX-004HR over their previous treatment versus those taking placebo (P < 0.05). Significantly more women receiving TX-004HR (72.8%-80.5%) versus placebo (62.5%, P < 0.05) would "probably" or "definitely" consider using the product again. Dyspareunia and vaginal dryness reductions were correlated with higher product satisfaction and the percentage of women who would consider re-using TX-004HR. CONCLUSIONS: TX-004HR had a high level of product acceptability, and more women were satisfied with TX-004HR, preferred it over their previous treatment, and would consider using it again versus placebo. Women may find TX-004HR to be a more acceptable product than current options to treat their dyspareunia associated with postmenopausal VVA.

Simon JA, Archer DF, Kagan R, et al. Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. *Menopause.* 2017;24(9):1003-1010.

OBJECTIVE: To evaluate the response of the vaginal mucosa with TX-004HR and its correlation with vulvar and vaginal atrophy (VVA) symptoms, and whether visual examination is a useful measure for assessing VVA. METHODS: REJOICE was a 12-week, phase 3, multicenter,

randomized, double-blind, placebo-controlled study of a vaginal, muco-adhesive, 17beta-estradiol softgel capsule (TX-004HR 4, 10, and 25 mug) in postmenopausal women with VVA and moderate-to-severe dyspareunia. Treatments were self-administered vaginally once per day for 2 weeks, then twice per week for 10 weeks. The vagina was visually examined at baseline and at weeks 2, 6, 8, and 12; changes were evaluated using a 4-item scale for vaginal color, vaginal epithelial integrity, vaginal epithelial surface thickness, and vaginal secretions. RESULTS: Significant improvements were observed with all three TX-004HR doses versus placebo in vaginal color (least square mean score changes of -0.96 to -1.06 for TX-004HR doses vs -0.60 for placebo at week 12), epithelial integrity (-0.97 to -1.07 vs -0.60), epithelial surface thickness (-0.94 to -1.03 vs -0.61), and secretions (-1.01 to -1.06 vs -0.64) ($P < 0.001$ for all comparisons at all time points). Both Pearson's correlations and logistic regression receiver-operating characteristic curve analyses significantly correlated the sum of the individual visual assessment scores with dyspareunia ($P < 0.0001$) and vaginal dryness ($P < 0.0001$) at 12 weeks. CONCLUSIONS: Greater improvements in the vaginal mucosa of postmenopausal women with VVA and moderate-to-severe dyspareunia were observed with TX-004HR versus placebo, and vaginal mucosa assessment scores correlated with vaginal symptoms of dyspareunia and dryness. Visual vaginal assessment by healthcare professionals is a useful measure for diagnosing VVA and assessing response to treatment.

Yoon BK, Chin J, Kim JW, et al. Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. *Menopause*. 2018;25(8):870-876.
OBJECTIVE: The aim of the study was to explore the therapeutic potential of menopausal hormone therapy (MHT) in women with mild cognitive impairment (MCI). METHODS: Thirty-seven postmenopausal women (age range: 57-82 y) with multiple-domain, amnestic subtype MCI were randomly assigned to either placebo (n = 18) or MHT (n = 19) for 24 months (percutaneous estradiol [E2] gel [0.1%, 2 mg/d] and oral micronized progesterone [MP4] [100 mg/d]). All participants received donepezil, and apolipoprotein E genotype was determined. The primary endpoint was general cognitive function: Alzheimer's disease Assessment Scale, cognitive subscale, the Korean version of Mini-Mental State Examination (K-MMSE), and the Korean version of the Montreal Cognitive Assessment (MoCA_K) were performed in-person every 6 months. RESULTS: Twenty-one participants (placebo 13, MHT 8) completed the trial (56.8%). Progression rates to dementia were 52.9% (9/17) in the placebo group and 44.4% (8/18) in the MHT group. Within-group analysis showed that all three tests significantly worsened during the trial in the placebo, but not the MHT groups. Analysis adjusted for epsilon4 allele demonstrated that MHT significantly reduced deterioration of MoCA_K score, a sensitive tool for assessing global cognition in MCI ($P = 0.0261$). Compared with the control group, both MoCA_K ($P = 0.043$; mean difference, 3.85; 95% CI, -0.46 to 8.16) and K-MMSE ($P = 0.0319$; mean difference, 3.26; 95% CI, 0.04-6.48) scores were significantly better at 24 months in the MHT group. CONCLUSIONS: Long-term MHT using percutaneous E2 gel and oral MP4 might attenuate cognitive decline in postmenopausal women with MCI.