

Hormone Replacement Therapy – A Focus on the Benefits and Risks of Estrogen

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Hormone replacement therapy (HRT) is used by over 6 million women to manage symptoms of menopause.¹ Estrogen, used with or without progestin products, comprise most HRT regimens. Estrogen is FDA-approved for the treatment of menopausal conditions such as vasomotor symptoms and vaginal atrophic changes, and prevention of osteoporosis.² Estrogen is also used off-label for gender dysphoria disorder and palliative care in metastatic breast and prostate cancer.³ Evidence has demonstrated benefits of HRT beyond symptom management; however, risks associated with HRT have also been identified. This newsletter will focus on the most recent findings of the benefits and risks of HRT, and provide reviews of two new estrogen products.

Background

Decreased estrogen levels with corresponding cessation of menstrual cycle and vasomotor, musculoskeletal, urogenital and psychological symptoms are associated with menopause.⁴ These symptoms can be associated with decreased quality of life affecting families and work environments.² Approximately 60% to 80% of women experience menopausal symptoms, 20% of them are considered severe. Reported prevalence varies by ethnicity, with a higher incidence in Black and Hispanic women.⁵ Menopause has also been identified as an independent risk factor for cardiovascular disease (CVD).²

Treatment recommendations for menopausal symptoms include the use of lubricants and gels as well as lifestyle modifications (e.g., weight loss, smoking cessation). Estrogen products are considered the most effective treatment for vasomotor symptoms and should be considered in women who need additional treatment and do not have contraindications. In women with an intact uterus, oral estrogen is given in combination with progestins to avoid hyperplasia or carcinoma.⁵ Estrogen is available as the following dosage formulations: oral, vaginal, intranasal, transdermal or subcutaneous implant. Estrogen derivatives include estradiol, estradiol valerate synthetic conjugated estrogens, ethinyl estradiol, or conjugated equine estrogen.

Evidence for the Use of HRT

There is substantial evidence for the use of HRT for the management of menopausal symptoms; however evidence for the long-term benefits and risks of HRT for other indications has been mixed. Findings from the Women’s Health Initiative (WHI) found HRT prevented fractures and colon cancer, but noted an increased risk of cardiovascular (CV) events and breast cancer.⁶ Mixed evidence has also suggested the use of HRT in

older women for prevention of CV disease, osteoporosis and cognitive decline. Observational studies of HRT have demonstrated a reduced risk of coronary heart disease (CHD); however, findings from randomized controlled trials (RCTs) failed to demonstrate CHD benefits.² The United States Preventative Services Task Force (USPSTF) recommends against the use of HRT for the primary prevention of chronic conditions.⁷

New Evidence

Two high quality systematic reviews, from the Agency for Healthcare Research and Quality (AHRQ) and Cochrane Database for Systematic Reviews, evaluated the benefits of HRT.^{2,8} Hormone therapy for the primary prevention of chronic conditions in postmenopausal women was the focus of the AHRQ review. Estrogen use alone was found to reduce the risk of diabetes and fractures, while combination estrogen and progestin therapy was found to decrease the risk of colorectal cancers, diabetes and fractures (Table 1).² Evidence demonstrated estrogen use was not associated with developing or preventing dementia. Long-term (at least 1 year) HRT resulted in reductions in the risk of fracture for perimenopausal and menopausal women.⁸

Table 1. Benefits of HRT*²

Outcome	Results
<i>Estrogen Monotherapy</i>	
Diabetes	137 fewer cases per 10,000
Fractures	382 fewer cases per 10,000
<i>Estrogen and Progestin Therapy</i>	
Colorectal cancer	33 fewer cases per 10,000
Diabetes	77 fewer cases per 10,000
Fractures	222 fewer cases per 10,000

* Compared to placebo or no treatment

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) recommends the use of estrogens for management of vasomotor symptoms based on low- to moderate-quality evidence.⁴ Counseling the patient on the short and longer-term benefits and risks should be a part of the discussion with women considering HRT. The use of vaginal estrogens are also recommended for women with urogenital atrophy, in patients taking systemic HRT still experiencing symptoms, or in those in which systemic therapy is contraindicated.⁴

Risks of HRT

Some of the harms associated with the use of HRT is founded on substantial evidence while others are less clearly

elucidated. The use of HRT has been shown to increase the risk of breast cancer when used as estrogen alone or in combination therapy with progestins. Compared to placebo, there is an increased risk of breast cancer with combination therapy with a relative risk [RR] of 1.27 (95% confidence interval [CI], 1.03 to 1.56) and an increased risk of invasive breast cancer with an incidence of 52 more cases than placebo for every 10,000 women treated.^{2,8} Guidelines advise of an increased risk of breast cancer with all HRT preparations except for vaginal estrogens.⁴ The increased risk persists for more than 10 years after HRT is discontinued.⁴

There is also a notable increased risk of venous thromboembolism (VTE) with oral HRT, which can present early in treatment and increases with age.⁴ A retrospective review found an increased risk with oral estrogens (e.g. conjugated estrogens and estradiol used alone and in combination with progestins), compared to no exposure, OR 1.58 (95% CI, 1.52 to 1.64).⁹ The risk of VTE is not significantly increased with the use of transdermal products. If HRT is discontinued the increased risk of VTE is eliminated. Guidelines recommend that for women who are at increased risk of VTE or who have a body mass index greater than 30 kg/m² should consider transdermal HRT instead of oral therapy.⁴

Other harms associated with HRT include: gallbladder disease, stroke, and urinary incontinence.^{2,8} The evidence on an increased risk of stroke with the use of HRT is low to very low-quality, preventing strong conclusions. There is no additional CV risk noted with HRT use in women under the age of 60 years and no evidence of an increased risk of CV mortality. Recently, there has also been an association of an increased risk of ovarian cancer with the use of HRT.¹⁰

While the risks with estrogen therapy appear to be dose related, there is insufficient evidence to direct optimal doses or suggest lower doses are without risk. Oral estrogens should be avoided in women who are at high risk of CV disease, thromboembolic disease or certain cancers (e.g., breast, uterine).⁸

New Estrogen Formulations

Bijuva®: In 2018 a new drug approval was granted for the estradiol/progesterone 0.5 mg/100 mg and 1 mg/100 mg combination oral capsule indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.¹¹ Combination estradiol/progesterone was shown to reduce moderate to severe vasomotor symptoms, frequency and severity, more than placebo in one, 12-week, randomized study (n=726). Women included in the study had at least 50 moderate to severe vasomotor symptoms per week and severity score was 2.55 at baseline. At 12 weeks, reduction in mean weekly frequency of symptoms were reported as clinically meaningful with a difference from placebo in the

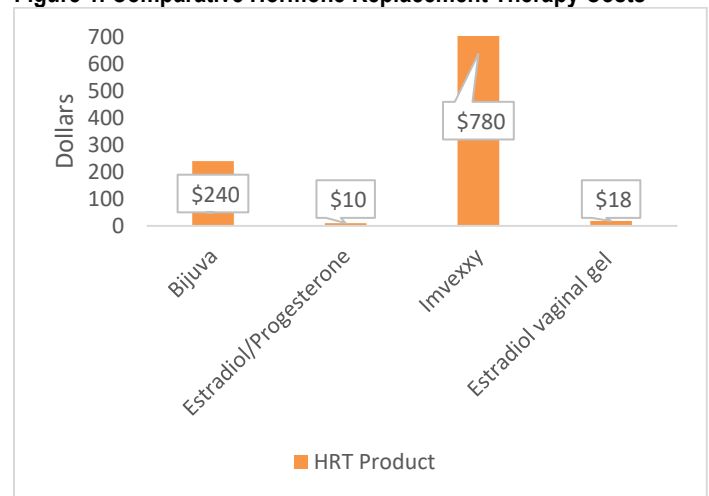
estradiol/progesterone arm of -16.58 episodes; p<0.001.¹¹ The severity of weekly moderate to severe vasomotor symptoms was reduced with estradiol/progesterone by -0.57 (p<0.001) compared to placebo at week 12. Four cases of breast cancer were diagnosed over the year-long safety study, 2 in patients treated with estradiol/progesterone 0.5 mg/100 mg, 2 in the estradiol/progesterone 1 mg/100 mg group and none in the placebo group.

Imvexxy®: Estradiol vaginal inserts 4 mcg and 10 mcg were approved in 2018 for the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.¹² Evidence for approval was from one, 12-week, double-blind, placebo-controlled, study of 574 women who were postmenopausal. For moderate to severe symptoms of dyspareunia, associated with postmenopausal vulvar and vaginal atrophy, improvements at 12 weeks compared to baseline were the following; estradiol 4 mcg, estradiol 12 mcg and placebo, -1.52 (p = 0.0149 compared to placebo), -1.69 (p<0.0001 compared to placebo) and -1.28, respectively.^{11,12}

As with other estrogen products both Bijuva® and Imvexxy®, have a black box warning for an increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.¹² There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

Limitations to the evidence for both new products include no direct comparisons to currently available treatment options and only short-term data on efficacy and safety findings. Current evidence supports utilization of more cost-effective generic options over the new formulations (Figure 1).

Figure 1. Comparative Hormone Replacement Therapy Costs*



* Costs are for a 30-day supply of selected therapies based on Meyers and Stauffers Average Actual Acquisition Cost (AAAC) Accessed 11.4.22.

Conclusion

Estrogens are an integral component of HRT. The demonstrated benefits of estrogen on menopausal symptoms are supported by high quality evidence; however, there are important potential risks of therapy that should be discussed with those considering HRT.

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