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Postmenopausal Hormone Therapy—Local and Systemic: A Pharmacologic Perspective

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Abstract

Every woman, if she lives long enough, will transition into menopause, and as the US population ages, women will be spending more time in a postmenopausal state than before. For postmenopausal women, the decision to initiate menopausal hormone therapy should be individualized. A thorough evaluation of the patient's cardiovascular, venous thromboembolic, cancer, and fracture risk should be considered along with the woman's quality of life. Hormone therapy exerts its therapeutic effects on vasomotor symptoms, the skeleton, and the genitourinary system independent of age since menopause and these benefits are lost once hormone therapy is stopped. Here we review the pharmacologic properties dose, formulation, mode of administration, timing of initiation, and duration of hormonal therapies in regard to optimizing benefit and minimizing risk to the patient. This discussion will focus on the effects of common hormonal therapies including estrogen (local and systemic), progesterone, estrogen receptor agonist/antagonist, and local dehydroepiandrosterone and include a brief review of compounded bioidentical hormone therapy.

Keywords

menopause, hormone therapy, estrogen, vaginal atrophy, dehydroepiandrosterone (DHEA), bazedoxifene

Every woman, if she lives long enough, will transition into menopause. According to the North American Menopause Society (NAMS), roughly 6000 US women transition to menopause each day. It has been estimated that >50 million women will be postmenopausal in 2020,[1] and as the US population ages, women will be spending more time in a postmenopausal state than before. In addition to bothersome vasomotor symptoms, postmenopausal women are at greater risk for genitourinary and sexual dysfunction, cognitive decline, cardiovascular disease, and significant bone loss.[2] Hormone therapy has repeatedly been shown to be the most effective treatment for problematic vasomotor symptoms of menopause while significantly decreasing the risk of postmenopausal bone loss.[3] However, following the Women's Health Initiative (WHI) trials, many questions regarding the safety of hormone therapy have arisen. The WHI trials were conducted to evaluate the risks and benefits of hormone therapy taken for primary prevention of chronic diseases among postmenopausal woman, whose average age was 63 years.[4] Women were stratified to either combined conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg if they had a uterus and conjugated equine estrogen alone if they had had a hysterectomy. The conjugated equine estrogen plus MPA arm was terminated after 5.6 years because of increased risk of breast cancer, whereas the conjugated equine estrogen-only arm was terminated after 7.2 years because of increased stroke risk.[4]

The results of the WHI trials cannot be applied to other hormone regimens, as each arm of the trials evaluated a single dose and formulation of orally administered hormone therapy. Since the publication of the WHI trials, experts have investigated how hormone therapy formulation, timing of administration, mode of hormone therapy delivery, and combination of hormones used impacts a woman's risk. New data have improved expert understanding, allowing for individualized hormone therapy regimens that optimally balance risk and benefit. This article reviews the available data regarding conventional and newer options for systemic and local hormone therapies.

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Systemic Hormone Therapy

Vasomotor symptoms have been associated with negative perceptions of sleep quality and quality of life as well as adverse effects on mood, work productivity, and interpersonal relationships.[5] Lifestyle modifications may be beneficial but do not always provide substantial relief of moderate to severe vasomotor symptoms. Based on previous research, estrogen-based hormone therapy has long been considered the gold standard for managing bothersome vasomotor symptoms.[3,6] Systemic hormone therapy has been US Food and Drug Administration (FDA)-approved for the treatment of bothersome vasomotor symptoms, hypoestrogenism, genitourinary syndrome of menopause, and prevention of postmenopausal bone loss. Although there is no time limit for using hormone therapy, patients should be evaluated annually, and dosing should be adjusted to the lowest effective dose for managing vasomotor symptoms.[6]

Estrogen

The most common menopausal estrogen formulations are conjugated equine estrogen, micronized 17 β-estradiol, synthetic conjugated estrogen, esterified estrogen, estradiol acetate, and ethinyl estradiol.[6] Systemic estrogen therapy can be administered orally, vaginally as a ring or as a transdermal patch, gel, or spray.[6] Estrogen therapy can be administered as a single agent in women without a uterus. In women with a uterus, estrogen must be administered in conjunction with a progestogen, known as estrogen/progestogen therapy, or with an estrogen receptor agonist-antagonist previously termed selective estrogen receptor modulator.[6]

Although conjugated and synthetic estrogens are only available orally, estradiol can be administered via vaginal ring, oral, and transdermal routes. Dosing equivalents between systemic estrogens has been defined as 0.625 mg conjugated equine estrogen /esterified estrogen = 5 μg ethinyl estradiol = 1 mg oral 17 β-estradiol = 50 μg transdermal estradiol.[7] Conjugated equine estrogens are composed of 10 sulfated estrogens extracted from horse urine.[6] Estrogen exerts it effects by acting on 2 different estrogen receptors (ERs) in the body, ER-α and ER-β.[8] Estrogen receptor-α is primarily located in the breast, ovaries, uterus, bone, liver, central nervous system, cardiovascular tissue, and adipose tissue.[8] Estrogen receptor-β is concentrated in the central nervous and cardiovascular systems, ovaries, lung, bladder, vascular endothelium, and colon.[8] Activation of these estrogen receptors initiates signaling pathways with varying downstream effects.[8]

Metabolism and Pharmacokinetics

In circulation, roughly 37% of estrogen is bound to sex hormone-binding globulin with high affinity, 61% is bound to albumin with low affinity, and 2% is free.[9] Both free estrogen and albumin-bound estrogen are biologically active. Oral estradiol, when used in a microcrystalline form, has rapid absorption and increased bioavailability. After administration of oral estradiol, serum estradiol peaks within 6 hours and is maintained for up 12 hours before starting to slowly decline.[9] With 2 mg of oral micronized estradiol, serum estradiol peaks around 40 pg/mL within 24 hours of administration. Over time a steady state is reached, and by day 21 serum estradiol reaches 80 pg/mL.

Oral estrogens undergo first-pass liver metabolism, with conjugated equine estrogen having greater effects on liver protein production compared with estradiol. In the liver, estradiol is converted to estrone and estriol, the major urinary metabolite. Following administration of oral conjugated equine estrogen, conjugated estrogens are hydrolyzed in the gut and small intestine, then converted to active estrogens in the liver and other tissues.[9] Because of liver metabolism, higher doses of oral estrogen are needed to achieve therapeutic effects compared with transdermal routes. With aging, women may experience changes in body composition and increased volume of distribution for lipophilic drugs with reduced volume of distribution for water-soluble drugs. Reduced renal clearance and polypharmacy my also impact drug therapy.[10] Therefore, dosing of hormone therapy may need to be adjusted over time.

Transdermal administration of estradiol circumvents first-pass metabolism in the liver, providing higher and more stable systemic levels of estradiol (3.5 to 7 days) compared with oral estrogen.[11] Sufficient skin permeability is necessary for the delivery and efficacy of transdermal formulations. Transdermal preparations are typically applied to the groin, lower abdomen, buttock, or lower back. After diffusing through the layers of skin, transdermal estradiol permeates capillaries over time based on the concentration gradient between the application site and capillaries.[9] The rate of hormone delivery varies by transdermal formulation. Matrix patches contain estradiol dispersed throughout a polymeric acrylate or vinyl acetate adhesive and penetration enhancers.[9] Delivery of estradiol is based on the area of the patch, peaks at 12 hours, and steadily declines over 7 days. The average maximal serum estradiol concentration with a 100-μg patch is around 90-140 pg/mL, with a 50-μg patch is 40-80 pg/mL, and with a 25-μg patch 30-45 pg/mL.[9] Reservoir patches deliver hormone through an alcohol gel, with estradiol levels peaking after approximately 30 hours and slowly declining over the course of 3.5 days.[9] The average maximal serum estradiol concentration with a 100-μg

patch is around 60-110 pg/mL, with a 50-μg patch is 40-60 pg/mL, and with a 25-μg patch is 30-40 pg/mL.[9]

Estradiol gel is also alcohol based and leads to rapid diffusion of estradiol into the stratum corneum until the gel has completely dried. The stored estradiol permeates the remaining skin layers and capillaries based on a concentration gradient over 2-14 hours.[9] There are 2 preparations of estradiol gel. The 0.06% estradiol pump system delivers 0.75 mg of estradiol per pump and should be applied to the abdomen, thigh, or upper arm. Serum estradiol peaks around 60-90 pg/mL with a daily dose of 1.5 mg and 100-120 pg/mL with a daily dose of 3 mg.[9] The 0.1% estradiol gel formulation delivers 0.25, 0.5, 0.75, 1, or 1.25 mg of estradiol per packet. Serum estradiol reaches a steady state around 80 pg/mL with a daily dose of 1.5 mg estradiol in 1.5 g of gel.[9]

Vaginal delivery also bypasses first-pass metabolism in the liver and allows for rapid absorption of estradiol through the vaginal mucosa. There are 2 doses of estradiol acetate in a silicone elastomer vaginal ring. The 12.4- and 24.8-mg estradiol acetate rings steadily release 0.05 and 0.10 mg of estradiol a day respectively. Serum estradiol rapidly increasea, reaching maximal concentrations within 1 hour. Estradiol then decreases after 24-48 hours and remains relatively constant over 3 months. It is important for prescribers to distinguish between the estradiol vaginal ring that delivers systemic estradiol doses (and thus necessitates the use of a progestogen in women with an intact uterus) and the low-dose estradiol vaginal ring intended for local treatment of vaginal atrophy (does not require concurrent progestogen therapy).

Side Effects

Common side effects of estrogen therapy include breast tenderness, headache, vaginal discharge, nausea, irregular bleeding, and local skin reactions with transdermal delivery.[6] Unopposed systemic estrogen therapy increases the risk of endometrial hyperplasia, thus necessitating the use of a progesterone in women with an intact uterus. In contrast, women using estrogen/progestogen therapy can experience bloating and worsening mood symptoms. Lowering the dose of estrogen therapy and using continuous estrogen/progestogen therapy versus cyclic dosing can reduce the incidence of side effects.[12] Data from the WHI demonstrated that estrogen therapy is also associated with an increased risk of venous thromboembolism with oral hormone therapy only (21 additional cases per 10 000 patient-years; 95%CI, 12-33 additional cases), gallbladder disease (21 additional cases per 10 000 patient-years; 95%CI, 10-34 additional cases), urinary incontinence (876 additional cases per 10 000 patient-years; 95%CI, 606-1168 additional cases), and stroke (9 additional cases per 10 000 patient-years; 95%CI, 2-19 addtiional cases).[13]

Drug-Drug Interactions

Estrogens are partially metabolized by cytochrome P450 (CYP) 3A enzymes. Inhibitors of CYP3A including medications like amiodarone, ketoconazole, verapamil, diltiazem, fluoxetine, and erythromycin can increase serum levels of estrogens. In contrast, CYP3A inducers such as rifampin and St. John's wort can decrease concentrations of estrogens. Because of first-pass metabolism in the liver, oral estrogen increases serum concentrations of thyroxine-binding globulin, leading to a higher percentage of protein-bound thyroxine (T4) and decreased serum levels of bioavailable T4.[14] Therefore, oral hormone therapy users with hypothyroidism may require higher doses of thyroxine; thus, the use of transdermal hormone therapy may be a better option in these women.

Clinical Data

Mortality Data. In the 18-year WHI follow-up, all-cause mortality in hormone therapy users was similar to those receiving a placebo. In the conjugated equine estrogen-only arm, all-cause mortality was 28.3% compared wotj 30.0% for the placebo (HR, 0.94; 95%CI, 0.88-1.01; $P = .11$). For women in the conjugated equine estrogen plus MPA arm, all-cause mortality was 26.4% in estrogen/progestogen therapy users versus 26.0% for the placebo (HR, 1.02; 95%CI, 0.96-1.08; $P = .51$).[15]

Cardiometabolic Data. Estrogen improves arterial function by increasing synthesis of the vasodilator nitric oxide, through endothelial nitric oxide synthase, and reducing the synthesis of potent vasoconstrictors.[16,17] Both oral and transdermal estrogens exhibit anti-inflammatory effects on blood vessels.[18] The Kronos Early Estrogen Prevention Study (KEEPS),[19] a large randomized, controlled trial (RCT), studied the progression of atherosclerosis in postmenopausal women following early initiation of oral estrogen therapy or transdermal estrogen therapy compared with placebo. KEEPS showed that after 4 years of therapy, estrogen therapy did not accelerate progression of atherosclerosis in healthy postmenopausal women.[20] Results also showed both oral and transdermal estrogen therapies reduce postmenopausal bone loss, bothersome vasomotor symptoms, and insomnia compared with placebo.[19] Oral formulations demonstrated greater beneficial effects on the mood, whereas transdermal preparations had greater effects on libido and insulin resistance.

The Early versus Late Intervention Trial with Estradiol (ELITE)[21] evaluated the progression of

atherosclerosis in relation to timing of hormone therapy. Women who were started on 17 β-estradiol within 6 years of menopause had slower progression of atherosclerosis compared with placebo (0.0044 mm/year with estradiol versus 0.0078 mm/year with placebo; $P = .008$). Women initiating hormone therapy $\geq$ 10 years after menopause had similar rates of progression as women taking placebo (0.01 mm/year in the estradiol group versus 0.0088 mm/year in the placebo group; $P = .29$). This study only evaluated 17 β -estradiol 1 mg per day (with or without 45 mg vaginal progesterone), and no comparisons with transdermal or other estrogen formulations were made.[13] As a follow-up to the ELITE trial, investigators studied the association between serum estradiol and the development of subclinical atherosclerosis. Serum estradiol concentrations were inversely proportional to atherosclerosis progression in early initiators of hormone therapy ($P = .041$).[22] Women starting hormone therapy 10 or more years from onset of menopause had greater atherosclerotic progression with increasing estradiol ($P = .006$) compared with placebo.[22] These data support the timing hypothesis, which suggests cardiovascular benefits for postmenopausal women initiating hormone therapy before age 60 and within 10 years of menopause.

Lipoprotein (a) (Lp[a]) is considered an independent cardiovascular risk factor because of its atherogenic and prothrombotic properties. Hormone therapy has been shown to reduce serum concentration of Lp(a). Anagnostis et al[23] conducted a meta-analysis reviewing the influence of hormone therapy on Lp(a) in postmenopausal women. Ten studies found that oral hormone therapy exerts greater reduction in Lp(a) than transdermal hormone therapy regardless of formulation (mean absolute difference, 9.90 mg/dL; 95%CI, 2.98-15.21 mg/dL, $P = .004$).[23]

A Finnish study identified close to 500 000 postmenopausal women who used estradiol-based hormone therapy and examined the risk of mortality from stroke, myocardial infarction, and all causes when compared with age-matched controls.[24] Duration of hormone therapy exposure was also assessed ($\leq$1, >1 to 3, >3 to 5, >5 to 10, or >10 years). Results showed significant reduction in all-cause mortality (absolute risk reduction, 8 to 60 fewer deaths per 10 000 follow-up years) and cardiovascular mortality (2 to 19 fewer deaths per 10 000 follow-up years) in hormone therapy users versus controls; the reduction in mortality was directly proportional to length of hormone therapy exposure. Similarly, mortality from stroke was also reduced (by 1 to 9 deaths per 10 000 follow-up years) in hormone therapy users with no relation to duration of exposure to hormone therapy.[25] The average age of women in the study was 52.2 years, with a mean of 6.7 years of hormone therapy use. A follow-up Finnish study revealed that both cardiovascular and stroke-related mortality increased (cardiovascular mortality: standard mortality ratio, 1.26; 95%CI, 1.16-1.37; stroke-related mortality: standard mortality ratio, 1.63; 95%CI, 1.47-1.79) within the first year after discontinuation of systemic hormone therapy in postmenopausal women < 60 years compared with age-matched controls.[26] Mortality was not increased in women older than age 60 years.

A recent 2-nested case-control study of 80 398 women with diagnosed venous thromboembolism (VTE) showed that oral estrogen is associated with greater VTE risk compared with no hormone therapy exposure (odds ratio, 1.58; 95%CI, 1.52-1.64).[27] Among estrogen formulations, VTE risk is greater with conjugated equine estrogen than 17 β-estradiol. The combination of conjugated equine estrogen and MPA conferred a higher VTE risk than other estrogen/progestogen combinations compared with no hormone therapy exposure. Higher doses of hormone therapy were associated with greater risk of VTE. In this study, transdermal estrogen was not associated with risk of VTE regardless of formulation (odds ratio, 0.93; 95%CI, 0.87-1.01).[27]

Transdermal administration avoids hepatic synthesis of inflammatory markers and clotting factors with neutral or beneficial effects on triglyceride production.[1] Conversely, first-pass liver metabolism of oral estrogens stimulates triglyceride synthesis with a more robust reduction in ratios of low-density to high-density lipoproteins and increase in insulin sensitivity.[1] Estrogen promotes these favorable effects on the metabolic profile in a dose-dependent fashion.[28] An improved metabolic profile could in part explain the reduction in mortality and cardiovascular events seen with patients on hormone therapy. Transdermal hormone therapy should be considered in women with elevated triglycerides and women who may have increased risk for venous thromboembolism.

Breast Cancer Data. Cancer risk associated with hormone therapy can differ based on hormone therapy formulation used, timing of initiation, and duration of hormone therapy use. Estrogen stimulates proliferation of breast tissue and breast cancer cells, yet high-dose estrogen can be used to treat breast cancer. Research shows that prolonged deprivation of estrogen makes cancer cells vulnerable to estrogen-induced apoptosis once estrogen is reintroduced.[29]

The WHI showed an increased risk of breast cancer diagnosis after 5.6 years of randomization to conjugated equine estrogen + MPA (HR, 1.24; 95%CI, 1.01-1.53).[6] Yet hysterectomized women receiving conjugated equine estrogen alone had an overall

nonsignificant reduction in breast cancer risk compared with placebo after 7.2 years (HR, 0.79; 95%CI, 0.61-1.02).[6] Among women who developed breast cancer, breast cancer-related mortality was reduced in those exposed to conjugated equine estrogen compared with placebo.[6] In an 18-year follow-up study, women using conjugated equine estrogen alone had decreased breast cancer-related mortality compared with placebo (HR, 0.55; 95%CI, 0.33-0.92).[15] A review of the WHI data suggests that the increased HR seen in the conjugated equine estrogen + MPA group is because of the lower incidence of breast cancer in women with a history of hormone therapy use who were randomized to placebo and not because of an increased risk of breast cancer in the conjugated equine estrogen + MPA treatment arm.[30]

A large prospective cohort evaluated the risk of invasive breast cancer based on dose, formulation, timing of administration, and route of administration in hysterectomized women on estrogen alone.[31] Transdermal estrogen was associated with nonsignificant reduction in breast cancer risk compared with conjugated equine estrogen (relative risk [RR], 0.75; 95%CI, 0.47-1.19).[31] There was no difference in breast cancer risk based on dose of conjugated equine estrogen (conjugated equine estrogen <0.625, 0.625, >0.625 mg). Compared with conjugated equine estrogen, oral estradiol was associated with a nonsignificant increase in breast cancer risk (HR, 1.20; 95%CI, 0.84-1.39).[31]

Mammography Effects. At the end of the first year of the WHI study, the incidence of abnormal mammograms was 9.4% in women taking conjugated equine estrogen/MPA versus 5.4% for placebo.[32] A recent study showed 1 year of combined 17 β-estradiol plus micronized progesterone resulted in similar rates of abnormal mammograms as placebo (3.7% versus 3.1%).[33]

Other Cancers. Eighteen years of follow-up from the WHI showed similar total cancer mortality rates in the pooled intervention group (8.2%) and the placebo (8.0%): HR, 1.03; 95%CI, 0.95-1.12.[15] Statistically significant reduction in colon cancer risk was observed for hormone therapy users compared with placebo. There were no significant differences in risk of cervical, ovarian, endometrial, and lung cancers.[15]

Bone Health. Several RCTs and observational studies have shown that conventional doses of postmenopausal hormone therapy reduce osteoporotic fractures at the spine and hip in women with or without a history of osteoporosis.[6] Hormone therapy reduces postmenopausal bone loss by inhibiting osteoclast-mediated bone resorption.[34,35] The WHI intervention groups (conjugated equine estrogen alone and conjugated equine estrogen + MPA) had a 33% reduction in hip fracture risk compared with placebo. Three years of treatment with conjugated equine estrogen + MPA was associated with a 3.7% increase in total hip bone mineral density (BMD) compared with 0.14% in the placebo group.[36] Although estrogen's protective effect on bone is dose dependent, an RCT showed that even low-dose daily 0.25 mg estradiol increases BMD (by 2.8% at the spine and 3.6% at the total hip) after 3 years of use.[34,37] According to the NAMS, estrogen-based hormone therapy can be considered for primary prevention of postmenopausal bone loss and fracture risk reduction when used in women 60 or younger or within 10 years of menopause.[6]

Bioidentical and Compounded Data. Diosgenin is extracted from plants, including soy and yams, and chemically modified to produce bioidentical androgens or estrogens.[38] Compounded hormone therapy mixes bioidentical hormones to create medications customized to individual patients.[38] Although there is a lack of efficacy and safety data, these compounded mixes are often marketed as more natural hormone therapy options. Consequently, many women have favored taking "bioidentical" compounded and unregulated hormone therapy because of a false sense of increased safety.[39] In fact, following the initial WHI publication, prescriptions for FDA-approved hormone therapy have significantly declined, and prescriptions for compounded hormone therapy have become more prominent.[40] A recent internet survey showed that women using compounded hormone regimens are more likely to use hormone therapy for unapproved indications.[41] The NAMS and the American Association of Clinical Endocrinologists caution against the use of compounded hormone therapy because of lack of safety data, inconsistent purity and potency standards, and lack of drug labeling.[6,42] With the plethora of options available and the wealth of safety and efficacy data for FDA-approved hormone therapy regimens, there is little need to compound menopausal hormone therapy.

The REPLENISH trial, a double-blind RCT, evaluated the safety and efficacy of oral bioidentical 17 β-estradiol and progesterone combined in a single soft gel.[39] The primary end points were incidence of endometrial hyperplasia and severity and frequency of bothersome vasomotor symptoms compared with placebo in healthy postmenopausal women. Four doses of the estradiol/progesterone soft gel were tested (1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, and 0.25 mg/50 mg). There were no cases of endometrial hyperplasia or cancer observed in any group over the 12-month trial. Rates of amenorrhea increased over time (90.2% with the highest dose, 96.2% with the

Table 1. Classification of Synthetic Progestogens[10]

Class	Progestogen	Characteristics
Pregnane derivatives	Acetylated: MPA Megestrol acetate Chlormadinone acetate Cyproterone acetate Segestrone Nonacetylated: Dydrogesterone Medrogestone	Structurally similar to progesterone
19-Norpregnane derivatives	Acetylated: Nomegestrol acetate Nesterone Non-acetylated: Demesgestone Promegestone Trimegestone	Structurally similar to progesterone
Ethinylated derivatives: estranes	Norethindrone Norethindrone acetate Tibolone Lynestrenol Norethynodrel Ethynodiol diacetate	Structurally similar to testosterone
Ethinylated derivatives: 13-ethylgonanes	Levonorgestrel Desogestrel Norgestimate Gestodene	Structurally similar to testosterone
Nonethinylated	Dienogest Drospirenone[a]	Structurally similar to testosterone or spironolactone[a]

[a] Reference 10.

Table 2. Lowest Effective Progestogen Dose Required for Endometrial Protection With Standard Postmenopausal Estrogen Dosing[a]

Progestogen Formulation	Daily Estrogen/Progestogen Therapy	Cyclic Estrogen/Progestogen Therapy[b]
Oral	200 mg	100 mg
Micronized progesterone	5 mg	2.5 mg
MPA	0.35-0.7 mg	0.35 mg
Norethindrone	2.5 mg	0.5-1 mg
Norethindrone acetate		
Transdermal	0.14 mg	—
Norethindrone acetate	0.015 mg	—
Levonorgestrel		
Intrauterine device		
Levonorgestrel	20 μg/d	20 μg/day
Vaginal		
p>Progesterone gel	45 mg	45 mg

[a] Standard doses of postmenopausal estrogen: 0.625 mg CE/esterified estrogen = 5 μg ethinyl estradiol = 1 mg oral 17 β-estradiol = 50 μg transdermal estradiol or other equivalent.
[b] Cyclic estrogen/progestogen therapy: daily estrogen therapy with 10-14 days of progestogen therapy per month.

lowest dose, and 97.8% with placebo).[39] Severity and frequency of baseline vasomotor symptoms were significantly improved in the estrogen/progesterone group (at doses of 1 mg/100 mg and 0.5 mg/100 mg) compared with placebo.[39] The combined estrogen/progesterone (1 mg/100 mg) soft gel (Bijuva, TherapeuticsMD, Boca Raton, Florida) is the first combination bioidentical estrogen–progesterone to be approved by the FDA.

Progestogens

Progestogens are indicated to prevent endometrial hyperplasia and reduce the risk of endometrial cancer in women with an intact uterus receiving estrogen-based hormone therapy. Progestogens are either natural or synthetic and are further classified by molecular characteristics (Table 1). The most common menopausal progestogen formulations include micronized progesterone (the only bioidentical progestogen), MPA, norethindrone acetate, levonorgestrel, and drospirenone. Progestogen therapy may be prescribed orally in combination with estrogen, as oral progestogen only, via transdermal patch in combination with estrogen, in an intrauterine device, as a vaginal gel, as a vaginal tablet, or as an injection. Progestogen dosing must provide sufficient endometrial protection for the amount of estrogen given (Table 2). Most topical progesterone creams contain diosgenin, a progesterone precursor. Conversion of diosgenin to progesterone can be carried out in the laboratory setting but not in the human body, making natural progesterone creams inadequate to provide uterine protection.[10]

Metabolism and Pharmacokinetics

Like oral estrogens, oral progesterone undergoes hepatic first-pass metabolism and is subject to hydroxylation by cytochrome P450 enzymes.[10] The metabolism of synthetic progestogens is not fully understood and may differ based on the class of progestogen.

In circulation, progestogens are either free or bound to albumin and/or other transport proteins. Progestogens have a low affinity and high binding capacity for albumin; therefore, these progestogens are considered biologically active. Some progestogens structurally similar to testosterone also have a high affinity and low-binding capacity for sex hormone-binding globulin or corticosteroid-binding globulin.[10]

Orally administered progesterone has 30 or more metabolites including 5α- and 5β-pregnanolone (has sedating effects), 20-dihydroprogesterone (potent progestogen), 11-deoxycorticosterone (potent mineralocorticoid), and pregnanediol (inactive).[9] Oral progesterone micronized in oil has high bioavailability. Oral progestogens reach maximal serum concentrations within 1-3 hours of administration; half-life varies based on progestogen type (shortest is 8 hours with norethindrone up to 32.5 hours with drospirenone).[10]

Like oral estrogens, bioavailability of oral progestogens is dependent on cytochrome P450 activity.

Progesterone administered vaginally leads to higher circulating progesterone than does oral progesterone.[9] Because of the bioadhesive properties of progesterone micronized in oil, vaginal administration leads to a sustained release of progesterone over 24-72 hours.[9] Studies have shown that maximal serum concentration rises rapidly with intramuscular administration and is reached gradually via transdermal routes.

Side Effects. Intracellularly, progestogens bind to progesterone receptors and have varying affinities to other steroid receptors based on molecular composition. These molecular differences can account for the clinical effects of each class of progestogen. Common side effects experienced include fluid retention, bloating, breast tenderness, headaches, mood changes, and nausea. Lowering the dose or switching to a different estrogen/progestogen therapy may help to relieve bothersome side effects.

Drug-Drug Interactions

Drug interactions are similar to those seen with estrogens. There is no firm evidence to suggest that progestogens concentrations are affected by concurrent antibiotic administration.[10]

Clinical Data

Cardiometabolic Data. Few studies have compared the cardiovascular effects of different progestogens. It has been well documented that estrogen therapy alone increases high-density lipoprotein cholesterol and triglycerides while lowering low-density lipoprotein cholesterol over time. Some studies have suggested that the addition of progestogens tends to blunt the beneficial effects of estrogen on metabolic profile.[28] A meta-analysis showed that the opposing effects of progestogens differ based on progestogen type. Commonly used progestogens listed from least to greatest opposing effect are progesterone, MPA, transdermal norethindrone acetate, and oral norethindrone acetate.[10] Drospirenone, a progestin structurally similar to spironolactone, has been shown to have antimineralocorticoid, antiandrogenic, and antialdosterone properties. An 8-week study of 750 postmenopausal women with hypertension investigated the effects of drospirenone (1, 2, and 3 mg) plus estradiol, estradiol alone, and placebo. Results showed that systolic blood pressure significantly improved in women taking the 2- and 3-mg doses of drospirenone.[10]

Breast Cancer Data. Laboratory studies in estrogen-deprived cells have been used to demonstrate breast cancer risk between synthetic progestins. It has been shown that MPA blunts estrogen's cellular apoptotic effects by increasing glucocorticoid receptor transcriptional activity, whereas norethindrone acetate at high doses upregulates target estrogen receptor genes, inducing cellular apoptosis.[43] Through this mechanism, MPA carries a higher risk of breast cancer diagnosis by promoting growth of breast cancer cells.[43,44]

Observational studies indicate that estrogen plus micronized progesterone carries a low risk of breast cancer compared with estrogen plus synthetic progestins (RR, 0.67; 95%CI, 0.55-0.81).[45] CECILE,[44] a population-based case-control study, investigated the effects of menopausal hormone therapy on breast cancer risk. In subgroup analysis, breast cancer risk was greater in women who were current estrogen/progestogen therapy users for 4 or more years compared with never-users (adjusted OR, 1.55; 95%CI, 1.02-2.36).[44] On further analysis, current users of estrogen with synthetic progestin had a greater risk of breast cancer compared with placebo (adjusted OR, 2.07; 95%CI, 1.26-3.39). The risk of breast cancer was not increased in women using estrogen plus micronized progesterone (adjusted OR, 0.79; 95%CI, 0.37-1.71).[44] In addition, early (within 1 year of menopause) estrogen/progestogen therapy use was associated with a greater risk of breast cancer compared with women who never used hormone therapy. Conversely, there was no increased risk of breast cancer in women who initiated early estrogen therapy alone. When hormone therapy was initiated after the first year of menopause, there was no increased risk of breast cancer.[44]

Bone. There are few studies that have evaluated the independent effects of progestogens on bone density and fracture risk in postmenopausal women, and results have been inconsistent. A 1985 study revealed that norethindrone acetate therapy alone prevents bone resorption in postmenopausal women.[10]

Estrogen Receptor Agonist-Antagonists

Estrogen receptor agonist-antagonists (ERAAs) selectively stimulate or inhibit estrogen receptors in target tissues. ERAAs can be used to treat vasomotor symptoms, osteoporosis, genitourinary symptoms, and breast cancer. The most commonly used ERAAs include tamoxifen, raloxifene, bazedoxifene, and ospemifene. All ERAAs are associated with increased risk of VTE. Here we will focus on ERAAs used to treat bothersome menopausal symptoms.

Bazedoxifene (BZA) acts as an estrogen agonist on the bones and vagina but antagonizes estrogen at the level of the breast and uterus. When combined with conjugated equine estrogen, BZA provides adequate

endometrial protection thereby eliminating the need for a progestogen. This is a good option for treating moderate to severe vasomotor symptoms in women who do not tolerate the side effects associated with progesterone. After oral administration, BZA reaches maximal serum concentrations at 1.2 hours and is converted to its major active metabolite (bazedoxifene-5-glucuronide) via glucuronidation.[46]

The Selective Estrogen Menopause and Response to Therapy (SMART) trials were double-blind, placebo-controlled RCTs evaluating the safety and efficacy of combined conjugated equine estrogen-BZA (0.625 or 0.45 mg of conjugated equine estrogen with 20 mg of BZA) in postmenopausal women.[47,48] The initial SMART trial showed that conjugated equine estrogen-BZA significantly improves bone mineral density at the spine and total hip at 12 and 24 months compared with placebo. SMART-2 showed that both doses of conjugated equine estrogen-BZA reduce the severity of hot flashes by 74% to 80% after 12 weeks.[47] In SMART-3 both doses of conjugated equine estrogen -BZA were more effective than placebo at increasing superficial vaginal cells and decreased parabasal cells at 12 weeks ($P < .01$).[49] Safety and side effect profiles were similar to placebo. Unlike common estrogen/progestogen therapy, conjugated equine estrogen -BZA is not associated with increased breast tenderness. In addition, conjugated equine estrogen -BZA protects the endometrium, has neutral effects on breast tissue, favorable effects on the lipid profile, and is not associated with adverse cardiovascular events.[50] In a 2-year multicenter RCT the incidence of VTE in women taking conjugated equine estrogen -BZA was 0.76 per 1000 women-years compared with 1.56 in placebo (RR, 0.48; 95%CI, 0.05-4.66).[50] The combination of conjugated equine estrogen 0.45 mg and BZA 20 mg (Duavee, Pfizer, New York, New York) is the only FDA-approved combination of estrogen with an ERAA.

Testosterone

There may be a select role for testosterone therapy in postmenopausal women with sexual dysfunction. However, there are currently no FDA-approved testosterone formulations for women.[51] Combination oral esterified estrogen (EE) with methyltestosterone (MT)—2 doses of EE 0.625 mg/MT 1.25 and EE 1.25 mg/MT 2.5 mg—was approved prior to the enactment of the FDA's current safety and efficacy regulations. Oral EEMT is indicated in postmenopausal women with bothersome vasomotor symptoms despite adequate treatment with estrogen-containing hormone therapy. Postmarketing surveillance studies have revealed few serious adverse events.[52] Our discussion will focus on menopausal hormone therapies approved by the FDA.

Local Hormone Therapy

When serum sex steroid levels decline, vaginal epithelial cells and genitourinary structures can revert to prepubescent states.[53] Genitourinary syndrome of menopause is an umbrella term describing multiple symptoms associated with decreased sex steroids in genitourinary tissues.[6] These symptoms include vaginal dryness or irritation, dyspareunia, impaired sexual function, dysuria, urinary urgency, and recurrent urinary tract infections (UTIs).[54] The Real Women's View of Treatment Options for Menopausal Vaginal Changes survey reported that 59% of women felt as though sexual activity is negatively impacted by genitourinary syndrome of menopause.[55,56] In another study of 3046 postmenopausal women, 55% reported vaginal dryness, 44% reported dyspareunia, and 37% reported vaginal irritation.[56] Although over-the-counter lubricants may temporarily decrease the discomfort related to genitourinary syndrome of menopause during intercourse, these options do not reverse vaginal atrophy. Systemic hormone therapy can be effective at treating genitourinary syndrome of menopause; however, meta-analyses have shown that local hormone therapy reverses vaginal atrophy and treats symptoms more effectively while avoiding first-pass liver metabolism.[57]

Vaginal Estrogen

There are multiple vaginal estrogen formulations that are FDA-approved for the treatment of symptoms of genitourinary syndrome of menopause. Vaginal estrogen can be prescribed in the form of vaginal creams (conjugated equine estrogen and 17 β-estradiol), rings (17 β-estradiol), tablets (estradiol hemihydrate), and soft gels (17 β-estradiol). In an 18-year follow-up of the Nurses' Health Study there were no differences in risk of cancer, cardiovascular events, VTE, or fracture between vaginal estrogen users and nonusers.[58] Compared with nonusers, vaginal estrogen users had lower risk of stroke (HR, 0.71; 95%CI, 0.47-1.09) and myocardial infarction (HR, 0.56; 95%CI, 0.36-0.87).[58] Because of potential systemic absorption, caution is advised with using vaginal estrogens in women with hormone-sensitive breast cancer on aromatase inhibitors, and treatment should be individualized.[59,60]

The newest FDA-approved vaginal estrogen product, Imvexxy (TherapeuticsMD), a vaginal soft gel, comes in 2 doses of vaginal 17 β-estradiol (10 and 4 μg) mixed in medium-chain triglycerides. In the randomized, controlled REJOICE trial, the safety and efficacy of Imvexxy was studied in 3 doses (4, 10, 25 μg) in postmenopausal women with moderate to severe dyspareunia.[61] After 12 weeks, each dose was shown to improve vaginal pH, severity of dyspareunia, and percent of parabasal and superficial cells compared

with placebo ($P < .0001$ for all, except dyspareunia with 4μg; $P = .0149$).[61] Treatment-related adverse events were similar to placebo.[61] Side effects include vaginal discharge.

A secondary study investigated the pharmacokinetics of each of the 3 doses given daily for 2 weeks, then twice weekly for 10 weeks. Serial serum concentrations were obtained and pharmacokinetics were analyzed. Systemic estradiol absorption was trivial to low. Pharmacokinetic parameters of the 25-μg vaginal estradiol dose were higher than placebo, but serum estradiol levels remained well within normal postmenopausal ranges.[62] This study also included a head-to-head comparison of 10 μg of estradiol vaginal insert (Imvexxy) with 10 μg of vaginal estradiol tablet (Vagifem, Novo Nordisk, Plainsboro, New Jersey). Compared with Vagifem, Imvexxy had significantly lower area under the concentration-time curve from 0 to 24 hours ($P < .0001$), lower maximum serum estradiol concentrations ($P = .0194$), and more rapid systemic absorption and return to baseline estradiol levels.[61] Although no randomized, controlled trials have been conducted, Imvexxy 4 μg may be an advantageous alternative treatment for estrogen-sensitive women (ie, women on aromatase inhibitors or with endometriosis) because of little to no systemic absorption.[59]

A silicone elastomer estradiol vaginal ring delivers 6.5-9.5 μg of estradiol per 24-hour period. Serum estradiol levels are sustained around 20-30 pmol/L for 3 months.[63] In clinical trials the vaginal estradiol ring was shown to lower vaginal pH, improve the vaginal maturation index, and reduce symptoms of genitourinary syndrome of menopause while having negligible effects on the endometrium.[63]

Vaginal Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA), a precursor adrenal hormone, is converted to estrogens and androgens in peripheral tissues possessing converting enzymes. Daily vaginal 0.5% DHEA (Prasterone/Intrarosa, Millicent Pharma, East Hanover, New Jersey) 6.5 mg has been shown to improve symptoms of genitourinary syndrome of menopause while having little systemic effects. In a 12-week prospective double-blind RCT, vaginal 0.5% DHEA 6.5 mg improved moderate to severe vaginal dryness by 1.44 severity score units from baseline compared with 0.27 units in placebo ($P = .004$).[64] Compared with placebo, vaginal DHEA increased superficial cells by 5.8-fold ($P < .0001$) and improved vaginal pH by 3.4-fold ($P < .0001$).[64] The most common adverse event, vaginal infection, was seen in 10.6% of placebo subjects and 14.2% of DHEA subjects.[64] The most common drug-related adverse event was vaginal discharge because of increased vaginal secretions and melting of the vehicle at body temperature. When administered daily for 52 weeks, vaginal DHEA was not shown to stimulate endometrial tissue.[65] From baseline to week 12, serum DHEA-S, testosterone, and estradiol concentrations remained within postmenopausal ranges.[64] When studied in postmenopausal women with history of gynecological or breast cancer, serum DHEA-S, testosterone, and estradiol increased (within postmenopausal ranges) after 12 weeks of 6.5 mg vaginal DHEA.[66] Serum estradiol did not increase in women on aromatase inhibitors.[66] In postmenopausal cancer survivors, there was no statistically significant difference in subjective vaginal dryness between 6.5 mg vaginal DHEA and plain moisturizer from baseline to 12 weeks ($P = .8$).[67] However, sexual health reported via the Female Sexual Function Index was significantly improved in the DHEA arm compared with plain moisturizer ($P < .001$).[67]

ERAAs for the Treatment of Genitourinary Syndrome of Menopause

Ospemifene acts as an ER agonist in the vaginal mucosa while antagonizing estrogen in the uterus, breast, and other sites. Ospemifene has agonistic ER effects on bone and suppresses bone turnover as well as raloxifene.[68] In animal models, ospemifene appears to decrease the incidence of breast cancer.[69]

Daily oral ospemifene (Osphena, Duchesnay USA, Rosemont, Pennsylvania) 60 mg is FDA-approved for the treatment of genitourinary syndrome of menopause. Ospemifene has a 26-hour half-life and is metabolized to active metabolites by cytochrome P450 enzymes. Three double-blind RCTs have shown superiority of ospemifene in treating genitourinary syndrome of menopause compared with placebo.[70] In a 52-week RCT, 426 women aged 40-80 years with genitourinary syndrome of menopause were randomized to daily ospemifene 60 mg or placebo.[71] Endometrial safety and efficacy were evaluated. Ospemifene showed significantly improved vaginal pH and maturation index at 12 and 52 weeks compared with placebo ($P < .0001$).[71] Eighty percent of subjects receiving ospemifene had no vaginal atrophy by week 52. There were no histologic endometrial changes between baseline and week 52 in the ospemifene group. The most common adverse event leading to study withdrawal was hot flashes, 2.2% in ospemifene compared with 0% in placebo.[71] Other adverse events included UTIs, nasopharyngitis, headache, back pain, muscle spasm, vaginal candidiasis, and insomnia. Overall, ospemifene is a good option for treating genitourinary syndrome of menopause in postmenopausal women who desire an oral alternative to vaginal therapy.

Conclusion

For postmenopausal women, the decision to initiate menopausal hormone therapy should be individualized. A thorough evaluation of the patient's cardiovascular, VTE, cancer, and fracture risk should be considered along with the patient's quality of life. Menopausal hormone therapy should not be used for the primary prevention of chronic disease. Hormone therapy exerts its therapeutic effects on vasomotor symptoms, the skeleton, and the genitourinary system independent of age because menopause and these benefits are lost once hormone therapy is stopped. The dose, formulation, mode of administration, timing of initiation, and duration of treatment should be optimized to provide the greatest benefit and minimize risk. Based on its potential vascular effects, it is optimal to start systemic hormone therapy within 10 years of menopause. After age 65, hormone therapy does not need to be stopped; rather, the dose may need to be lowered because of changes in metabolism and consideration to use a transdermal may be given. Vaginal estrogen and vaginal DHEA have few systemic effects and can be safely administered to postmenopausal women with genitourinary syndrome of menopause despite age.

With the plethora of efficacy and safety data of FDA-approved treatment options for postmenopausal women, there is little need to use compounded or unregulated hormone regimens. Using unregulated compounded hormone therapy is discouraged because of the potential increased risk of endometrial hyperplasia and other adverse events. When appropriate, combined estrogen plus progestogen/BZA formulations should be used to ensure adequate endometrial protection with each dose of estrogen; regimens that separate estrogen and progestogen administration increase the chance of user error and adverse endometrial effects.

Conflicts of Interest

Taryn Smith, MD, NCMP, has no disclosures. Sabrina Sahni, MD, NCMP, has no disclosures. Holly Thacker, MD, has a consulting or advisory role at TherapeuticsMD, and is on the speakers' bureau at TherapeuticsMD.

Author Contributions

Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountable for all aspects of the work: all authors.

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