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Bioidentical Oral 17β-Estradiol and Progesterone for the Treatment of Moderate to Severe Vasomotor Symptoms of Menopause

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Abstract

Objective: To review the efficacy, safety, and available literature regarding the novel combination bioidentical product Bijuva, or 17β-estradiol/progesterone (17β-E/P), for the treatment of moderate to severe menopausal symptoms in cisgender females with an intact uterus. **Data Sources:** Literature searches of both PubMed (1966 to October 2020) and Google Scholar were conducted using search terms including *bioidentical, estradiol, progesterone, menopause, E2/P4, TX-001HR*, and *Bijuva*. **Study Selection and Data Extraction:** All articles with studies conducted in cisgender human females and in the English language were considered for review; 18 publications were included. **Data Synthesis:** In 1 phase 3 clinical study, 17β-E/P was proven to be effective at reducing the frequency and severity of vasomotor symptoms (VMS) at 12 weeks compared with placebo, and no cases of endometrial hyperplasia were observed over the 52-week safety study period. Menopausal women with an intact uterus were included in the study population. **Relevance to Patient Care and Practice:** Concerns over content and safety of compounded bioidentical hormones have been raised by several professional societies. As women experience VMS of menopause, a desire for a Food and Drug Administration–regulated bioidentical combination product for the treatment of moderate to severe menopausal symptoms may be desirable. Given as a once-daily oral capsule at the dose of 1 mg estradiol/100 mg progesterone, 17β-E/P is approved for the treatment of VMS associated with menopause. **Conclusions:** 17β-E/P is a novel bioidentical product that is the first of its kind in the treatment of moderate to severe menopausal symptoms.

Keywords

bioidentical, estradiol, progesterone, menopause, E2/P4, TX-001HR, Bijuva

Introduction

The median age of natural menopause for cisgender women in the United States is currently 50 to 51 years, with a range of 40 to 60 years.[1,2] Twelve months of amenorrhea, which are not precipitated by secondary factors, has traditionally defined clinical menopause.[1] The International Society for the Study of Women's Sexual Health and the North American Menopause Society (NAMS) introduced the term *genitourinary syndrome of menopause* (GSM) in 2014 to encompass the syndrome of endocrine and physical changes associated with menopause caused by estrogen loss, including atrophic vaginitis, vulvovaginal atrophy, and urogenital atrophy. It has been reported that the majority of women will experience some aspect of GSM, most often vaginal dryness or dyspareunia.[3] Other GSM symptoms include physical changes involving the labia and clitoris, with additional genital symptoms such as urinary urgency and recurrent urinary tract infections.[4] Although menopausal symptoms are usually most severe within 5 years of menopause onset, vulvovaginal atrophy has been found to persist for more than 6

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years after menopause in some women.[4] In addition to GSM, vasomotor symptoms (VMS) such as hot flashes and night sweats are experienced by 50% to 80% of menopausal women.[5] Therefore, a need exists for effective treatment of menopausal symptoms whether it be short-term for VMS or longer term for GSM.

Estradiol, estrone, and estriol are the female body's endogenous estrogens. Estradiol is the predominant estrogen in premenopausal women, and estrone takes prevalence in menopause. As ovarian function declines leading to menopause, the serum level of estradiol continues to decrease and is predominantly responsible for the routinely reported vaginal and VMS associated with the menopausal transition.[3] Menopausal symptoms may, therefore, be improved through use of hormone therapy.

A number of treatment options are available to women depending on which bothersome symptoms of menopause are experienced.[4] Nonhormonal therapies include vaginal lubricants, vaginal moisturizers, and vaginal activity and are preferred for symptoms of GSM. Prescription therapies include both local and systemic estrogen preparations. Whereas local vaginal preparations are preferred for only GSM symptoms, systemic estrogen hormone therapy at the lowest dose for the shortest amount of time is the preferred treatment of choice for VMS per most recent recommendations.[6] Estrogen formulations that are most prescribed for menopausal symptoms include conjugated equine estrogens (CEEs), synthetic conjugated estrogens, micronized 17β-estradiol, and ethinyl estradiol.[6] Progestin formulations include micronized progesterone and synthetic progestins, such as medroxyprogesterone acetate (MPA), drosperinone, norethindrone, and norgestimate, and are used in combination with estrogens to prevent endometrial hyperplasia.[6] Bijuva or 17β-estradiol/progesterone (17β-E/P) was approved by the Food and Drug Administration (FDA) in October 2018 for oral treatment of moderate to severe VMS secondary to menopause.[7] The objective of this review is describe the efficacy, safety, and available literature regarding the novel combination bioidentical product 17β-E/P for the treatment of moderate to severe menopausal symptoms in cisgender females with an intact uterus.

Data Sources

PubMed (1966 to October 2020) as well as Google Scholar searches were conducted using the terms *bioidentical, estradiol, progesterone, menopause, E2/P4, TX-001HR*, and *Bijuva* to locate relevant clinical trials. Trials were eligible for inclusion if they were conducted in humans, conducted in cisgender females, and published in the English language. Additional articles were located utilizing the references of selected articles. Twelve studies were identified by PubMed, and 67 were found in Google Scholar. Duplicate reports from conference abstracts, animal studies, and those exclusively focused on compounded bioidentical therapy were excluded. One phase 3 trial was found with multiple publications describing outcomes. In all, 18 reports of the trial data were included for analysis. The prescribing information was obtained from the manufacturer's website.

Clinical Trial

17β-E/P was FDA approved based on results of "A 17b-Estradiol–Progesterone Oral Capsule for Vasomotor Symptoms in Postmenopausal Women" (REPLENISH) study.[8] REPLENISH was a phase 3, prospective, randomized, double-blind, double-dummy, placebo-controlled, multicenter clinical trial evaluating the safety and efficacy of the first single capsule bioidentical hormone (17β-E/P). Menopausal women (n = 1845, aged 40-65 years) with an intact uterus seeking treatment for VMS were randomly assigned 1:1:1:1 to 1 of 4 active doses of E/P (1 mg/100 mg, 0.5 mg/100 mg, 0.5/50 mg, and 0.25/50 mg) versus placebo for 52 weeks for the primary safety analysis (endometrial hyperplasia, assessed by biopsy read by 3 pathologists). Women with more VMS at baseline (7 or more per day or 50 or more per week) were stratified for the 12-week modified intention-to-treat (MITT) efficacy substudy; all study participants were included in the 52-week endometrial safety analysis evaluating amenorrhea, bleeding, spotting, and adverse events. The MITT efficacy analysis (n = 726) included 4 coprimary end points (mean change in frequency and severity of moderate to severe VMS from baseline to week 4 and week 12). Symptoms were assessed by daily diaries completed by the participants to include hot flush frequency and severity. A weekly hot flush severity score was calculated as

$$\left(\begin{array}{l}\left[\text{Number of mild hot flushes over 7 days} \times 1\right] + \\ \left[\text{Number of moderate hot flushes over 7 days} \times 2\right] + \\ \left[\text{Number of severe hot flushes over 7 days} \times 3\right]\end{array}\right) / \left(\text{Total number hot flushes over 7 days}\right).$$

Participants were not eligible for study inclusion with a body mass index (BMI) >34 kg/m^2; history of venous thromboembolism; melanoma; breast, uterine, or ovarian cancer; coronary artery disease; chronic kidney or liver disease; and diabetes. To account for multiple E/P dose comparisons, the highest dose was compared with placebo, and the next lowest dose was subsequently compared only if statistical significance was achieved for the primary end point.

At baseline, women were 54 to 55 years of age (average), with BMI 27 kg/m^2, and 5 to 6 years from the onset of menopause; two-thirds of the participants were White, whereas one-third were African American. The mean weekly number of VMS ranged from 72.1 to 77.0, and mean weekly severity scores ranged from 2.50 to 2.54. The participants were younger and closer to the time of menopause than those included in the Women's Health Initiative (WHI).[9]

The primary safety analysis included 1875 women who were initially randomized (10 participants took no doses of study drug and were excluded from the analysis). No cases of endometrial hyperplasia were observed in women receiving active treatment. No clinically important differences were noted in adverse events in active treatment versus placebo. The most common treatment-related adverse events were breast tenderness, headache, nausea, pelvic pain, vaginal bleeding, and vaginal discharge. At study completion, 1255 women remained on the study drug, with 7.3% to 11% of women in the active treatment groups discontinuing therapy as a result of adverse events, compared with 6.6% of women in the placebo group (n = 151).

In the MITT efficacy analysis, 89% of participants (n = 647) completed the subset study. Discontinuation as a result of lack of efficacy was higher in the placebo group; 89.5% of participants (n = 591) in the treatment groups completed the study compared with 87.4% of participants (n = 118) in the placebo group. All treatment doses were effective for reducing VMS frequency and severity by week 12; however, only the highest dose is currently available. VMS frequency significantly decreased from baseline at week 4 and week 12 compared with placebo in all groups except E/P 0.5/50 mg. In the 2 higher doses, frequency decreased from baseline by 40.6 and 35.1 compared with 26.4 with placebo. Symptom severity also improved from baseline, most significantly in the 2 highest doses by week 12 (by 1.12 and 0.90 points, compared with 0.56 with placebo).[8]

Amenorrhea was reported in 56% to 73% of women on active treatment and 79% in the placebo group ($P < 0.05$) for all doses except the lowest dose.[10] Women with amenorrhea were older, further from the last menstrual period, and on the lowest dose of 17β-E/P. Endometrial hyperplasia was seen in 0.36% on any dose with no cases of endometrial cancer. Vaginal bleeding was reported as an adverse effect in 1% to 4.6% of women on treatment compared with 0.7% of women in the placebo group. Bleeding led to discontinuation of treatment in 0.4% to 1.4% of women taking active treatment compared with 0% of those taking placebo. Bleeding is a noted adverse effect in women taking 17β-E/P; however, it may not lead to discontinuation for the majority of women. Bleeding risk decreases by 42% for every 5 years of age, by 39% for every 5 years from the last menstrual period, and by 33% in those with the least severe VMS ($P < 0.0001$).[11]

Effects on breast tissue of women enrolled in REPLENISH have been reported. Women included in REPLENISH must have had a normal or non–clinically significant breast exam and a normal mammogram (BI-RADS 1 or 2) performed at screening or within 6 months of the first dose of study drug. In addition to screening, breast exams were conducted at months 6 and 12 (end of treatment or early termination). Mammography was also performed at either screening or within 6 months before administration of the study drug and at study conclusion (month 12 or early termination). Mammograms of BI-RADS 1 (negative) or BI-RADS 2 (benign) of women were deemed appropriate for study inclusion. No statistically different rates of abnormal mammograms were observed across all E/P study arms, ranging from 1.7% to 3.7%, and 3.1% with placebo. Treatment-emergent adverse events in breast tenderness were seen across most treatment arms: 1/100 mg, n = 45 (10.8%), $P < 0.0001$; 0.5/100 mg, n = 19 (4.5%), $P = 0.0348$; 0.5/50 mg, n = 25 (5.9%), $P = 0.0052$; 0.25/50 mg, n = 10 (2.4%), P nonsignificant. However, only 8/502 (1.6%) women who prematurely discontinued E/P cited breast tenderness as the primary reason for study withdrawal.[12]

Participants in REPLENISH MITT also completed the Menopause-specific Quality of Life (MENQOL) 29-item questionnaire at baseline, week 12, and months 6 and 12 to assess the impact of 17β-E/P on vasomotor, psychosocial, physical, and sexual function.[13,14] A 7-item Likert scale was used for each question, ranging from not at all bothered to extremely bothered. A significant difference in total quality-of-life score was noted for all active doses versus placebo ($P < 0.05$) at all time points with the exception of the lowest dose at months 6 and 12, demonstrating that quality of life is improved throughout the course of treatment. Items evaluating hot flushes, night sweats, and sweating were all significantly reduced compared with placebo for all doses except the lowest dose at all time points ($P < 0.02$).[15]

Additionally, sleep changes were evaluated in all participants using the Medical Outcomes Study (MOS)–Sleep Scale questionnaire, a 12-item questionnaire using a 6-point Likert scale. At baseline, MOS-Sleep total scores were 43.2 to 48.1 and decreased to 27.5 to 29.4 with active treatment and 37.4 with placebo at 12 months ($P < 0.01$). Somnolence was reported in 0.2% to 1.2% of participants on active treatment versus 0% with placebo. 17β-E/P improves sleep scores throughout treatment, with minimal impact on somnolence.[16,17]

Although long-term safety studies have yet to be conducted, cardiovascular laboratory markers were obtained in REPLENISH. Total cholesterol increased 1% to 4% on active treatment versus 3% for placebo; triglycerides increased 6% to 11% versus 7%; and glucose increased 1% vs 2% at month 12.[18] Summary results without statistical comparison were reported, limiting interpretation of the

cardiovascular data, VMS, and sleep quality as compared with placebo in a post hoc analysis.[19] The REPLENISH study was limited by the 52-week study duration and a generally healthy patient population.[8] Future studies should compare 17β-E/P to approved hormone replacement therapy and should include longer-term safety monitoring.

Historical Hormone Therapy Safety

Although systemic oral estrogen preparations are currently recommended for severe menopausal symptoms, hesitancy to prescribe these medications has increased over the past 2 decades. A meta-analysis of 25 observational studies evaluating the effect of hormone therapy on the development of heart disease in women published in the late 1990s added support to the hypothesis that treatment with estrogen, predominantly CEEs, reduced the risk of coronary heart disease by 30%.[20] The WHI sought to confirm this hypothesis in a large, randomized controlled trial. More than 16 000 postmenopausal women with a uterus were randomized to CEE 0.625 mg/MPA 2.5 mg daily versus placebo. The trial was stopped early after 5 years because of a 26% increase in breast cancer and a 29% increase in coronary heart disease. Stroke and pulmonary embolism risk were also increased with active treatment compared with a reduction in colorectal cancer, endometrial cancer, and hip fracture.[9] Publication and reporting on the WHI led to a 66% decrease in prescriptions for CEE/MPA within 1 year.[21] Many critiques of the WHI have been noted since publication, including the age and time since menopause for women enrolled in the WHI, with younger women close to the time of menopause theoretically at lower risk of long-term risks, lack of low-dose comparison, and use of nonbioidentical hormones.[22,23]

Bioidentical Hormone Safety

Bioidentical hormones are either structurally or chemically similar to endogenous hormones produced in the body but are plant derived. Few studies have compared bioidentical estrogens with other estrogen formulations. Prior to publication of the WHI, transdermal estradiol (0.05 and 0.1 mg/d applied twice weekly) was compared with oral CEE (0.625 mg or 1.25 mg once daily) in 321 postmenopausal women with moderate to severe hot flashes over the course of 12 weeks. No difference was observed in efficacy between the formulations for reduction in frequency or severity of hot flashes. Although the trial duration was too short to evaluate long-term risks, adverse effects of breast tenderness and unexplained vaginal bleeding were similar in both treatment groups, with the lowest incidence for bleeding in the low-dose transdermal estradiol group.[24] A 2016 Cochrane Review evaluating randomized controlled trials comparing bioidentical hormones for treatment of hot flashes versus placebo or nonbioidentical hormones included 23 trials. Four trials compared bioidentical estrogen with placebo, whereas 1 study compared bioidentical estrogen with CEE. The authors determined that there is no evidence for a difference in efficacy or safety between formulations. Furthermore, they also found no data evaluating the long-term safety of bioidentical estrogen for heart attack, stroke, or breast cancer.[25]

In a systematic review and meta-analysis of studies evaluating the long-term risks of progesterone versus synthetic progestins, each in combination with estrogen, no data were found allowing comparison of cardiovascular benefits. However, progesterone was found to be 33% less likely to cause breast cancer over a period of 3 to 20 years (RR = 0.67; 95% CI = 0.55-0.81) than synthetic progestins, suggesting increased safety of bioidentical progesterone compared with synthetic preparations.[26]

Women desiring a combination of bioidentical estradiol and progesterone previously had 2 options: purchase FDA-approved oral formulations separately or seek out a compounding pharmacy that supplies oral and topical bioidentical products. In a survey of 184 women with VMS at an academic menopause center, 77% of women reported believing that bioidentical compounded hormone therapy is safer than conventional hormone therapy.[27] Despite being embraced by patients, compounded bioidentical hormone preparations have not been traditionally recommended by the NAMS, because of lack of FDA oversight, with conventional estrogen hormone therapy being preferred. Compounded products may have variable bioactivity and bioavailability, which could lead to possible overdosages or underdosages.[6] Therefore, NAMS recommends that prescribers only consider compounded products when patients experience adverse events with FDA-approved pharmacotherapy options. An FDA-regulated combination hormone product such as 17β-E/P is a novel therapy for the treatment of moderate to severe menopausal symptoms.

Prescribing Information and Counseling

17β-E/P is indicated for the treatment of moderate to severe VMS associated with menopause in cisgender females with an intact uterus. It is currently available in a fixed-dose capsule containing 1 mg of estradiol and 100 mg of progesterone. Contraindications include estrogen-dependent neoplasias, thrombophilic disorders, and history of deep-vein thrombosis, pulmonary embolus, or arterial thromboembolic disease.[7]

The capsule is recommended to be taken with food each evening and does not contain peanut oil (compared with micronized progesterone).[28] It is important to note that because both estrogens and progestins undergo partial metabolism by the cytochrome P450 3A4 isoenzymes,

inhibitors of CYP3A4 such as grapefruit juice could increase 17β-E/P concentrations, whereas CYP3A4 inducers (eg, St John's Wort) could induce the metabolism of 17β-E/P. The most common adverse effects include breast tenderness in 10.4% of women, whereas other adverse effects of headache, pelvic pain, vaginal bleeding, and vaginal discharge were seen in 3% to 4% of women. Recommended monitoring includes changes in VMS, annual breast exam, ongoing mammograms, endometrial cancer screening, thyroid function in women taking thyroid replacement, and for fluid retention in women with cardiac or renal dysfunction.[7]

Relevance to Patient Care and Clinical Practice

The menopausal transition can present both physical and mental challenges for cisgender women.[1,4] Following the premature discontinuations of both the estrogen-alone and estrogen plus progesterone arms of the WHI, traditional hormone therapies were widely rejected for the routine treatment of menopausal symptoms. This increasing hesitancy to both prescribe and use conventional hormone therapy precipitated women to search for alternative bioidentical therapies, which they considered "safer." Compounded preparations are not FDA regulated and may be involved in misleading advertisements and claims. 17β-E/P is the first bioidentical product that is FDA regulated and has, therefore, been evaluated for both endometrial safety and vasomotor, quality-of-life, and sleep efficacy in a randomized controlled trial design.[29]

Conclusion

Although efficacy and short-term safety is now established for a new FDA-approved, oral, fixed-dose combination, long-term safety with 17β-E/P is still unknown. 17β-E/P offers women with an intact uterus an option of a bioidentical, single-dose product that is accessible; however, the cost of the newly approved combination may be a deterrent for many patients. In line with current guidelines and recommendations for treatment of VMS, 17β-E/P may be utilized in younger women within 10 years of menopause for the shortest duration possible to avoid potential long-term risks.

Declaration of Conflicting Interests

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